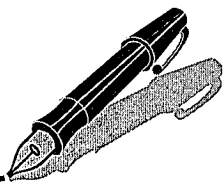


Correspondence



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.

Women in Rheumatology

To the Editor:

I find it fascinating to have observed the increase in numbers of women in medicine in the United States since I first arrived in the US as a Fellow in late 1959. I remember my first American Rheumatism Association (ARA) meeting and I think one of the only senior women rheumatologists present was Dr. Marian Ropes from Boston. Gradually, there has been an increase, as Dr. Clark¹ and others have noted, in the percentage of women in rheumatology. However, I think there is still a relatively small proportion in academic medicine in the US.

I wonder if the very large number of women in rheumatology in Mexico may not reflect to some extent the culture of the country. In the US as you are probably aware, there is an increasing number of women in every branch of medicine, including surgery, orthopedic surgery, and other surgical subspecialties. It would be of interest to know that percentage in Mexico and other Central and South American countries and of considerable interest to do comparative studies with rheumatology, for example, in Great Britain or the Scandinavian countries.

Although Clark, *et al*'s data were not totally clear cut, the implication was that women physicians might choose rheumatology because of their ability to be more empathic and sensitive. It has been my observation over the years that in academic medicine there are relatively few women in power positions; could this be due to a lack of assertiveness, to not being resolute, determined, and ambitious! The reasons often given for this lack of leadership include being married, and having families and many other responsibilities. However, I wonder if it may not indicate that the lack of the characteristics mentioned and the dominance of the ones listed by Clark, *et al* might not result in the lack of women in leadership positions in rheumatology and academic medicine. I think that this is an interesting topic for further study and discussion.

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Dr. Alarcón replies

To the Editor:

Dr. Hess's comments are pertinent and thought provoking. I would prefer that Dr. Clark address the issue regarding the large number of women in rheumatology in Mexico, since she practices there¹. I would point out, however, that throughout my visits to different Latin American countries over the last 20 years, I have witnessed the growing numbers of women physicians not only in rheumatology but in medicine in general (well over 50% in some places). More women are seeking higher education and perceive medicine within their reach; proportionally, fewer men appear to be interested in medicine. My informal assessment of this trend is that it is the result of, among other things, changes in the labor market. Physicians are not well paid in Latin America, despite their many years of graduate and postgraduate education. Women may be more willing to accept this economic reality than men.

Whether there is a "glass ceiling" effect for women in academic medicine and in professional organizations or, on the contrary, whether women actually choose not to occupy positions of leadership is unclear. My view is that both factors may play a role. The effect of temperamental dispositions as suggested by Dr. Hess is an intriguing, but debatable possibility. Another scenario is that of women who went to medical school and entered into academic medicine several years (if not decades) ago, who may have developed a seemingly self-imposed, passive attitude as a result of their earlier experiences in an environment dominated by men. I should only add that data from the Mayo Clinic² have shown that only a proactive plan to recruit, retain, and promote women in academic institutions will shift the demographic composition of the faculties in US medical schools as we know it today³. Unfortunately, most medical schools do not seem to be willing to implement such a strategy.

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Dr. Clark, *et al* reply

To the Editor:

Dr. Hess is concerned about whether the relatively high percentage of women in rheumatology in our country reflects a cultural trend; this is difficult to answer since there have not been specific studies in the area, but it is important to mention that there are less than 400 board certified rheumatologists throughout Mexico, and rheumatology is not a widely distributed specialty and only one-third of them are women. For her second question about the preferences in specialty choices compared to other countries, as well as the US and Canada have a lower proportion of women going to surgical specialties, for example, in orthopedic surgery only 7% are women, urology 5%, and general surgery 11%, whereas in family medicine 38% are women, dermatology 37%, and internal medicine 24%¹. We do not

have information about other countries in Latin America, and we agree that it would be interesting to compare our data with those from European countries.

The study² was done to evaluate the female rheumatologist's perception about career choice and performance from a gender point of view. We did not specifically explore issues regarding power positions, but it was not a thematic topic during interviews. We agree with Dr. Hess that currently there are fewer women in power positions, not only in medicine but also in other professional areas. This has been extensively studied in medical and non-medical literature and the two main reasons that explain this imbalance might be first the so-called "glass ceiling effect" that refers to the scarcity of women at the top levels of organizations due to invisible factors as much as or more than overt discrimination that keep women from rising to the top³ in which several gender biases operate; and second, the genuine female decision of not searching for power positions due to the need of a balanced life working through "support nets."

Last but not the least, it has been described that a great proportion of persons (both male and female) chose their profession and working schedules according to the accepted cultural patterns for their sex³.

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Do Antifilaggrin Antibodies Within the "Normal" Range Predict Rheumatoid Arthritis?

To the Editor:

In a large scale, prospective, nested case control study, Aho, *et al*¹ investigated antifilaggrin antibody (AFA) concentrations in pre-illness serum specimens to determine their ability to predict rheumatoid arthritis (RA). Also, they examined the association of baseline AFA levels with the rheumatoid factor (RF) status of study subjects at baseline and of the cases at the time of diagnosis. The main conclusions were, first, that AFA within the normal range (i.e., to 95th percentile of controls) can predict the development of RF positive RA, and second, that this antibody is closely associated with RF¹. Given the strong ability of elevated RF titers to predict RA^{2,5}, another relevant issue is whether AFA might be either an independent or a correlated predictor of RA. This letter further analyzes the data available within the valuable report of Aho, *et al*¹, in order to explore these issues relevant to the development of RA.

Did AFA levels within the "normal" range (i.e., to 95th percentile) predict RA? (Table 1). From data in Tables 1 and 3 of Aho, *et al*¹, the baseline serum AFA levels in the highest quintile distribution of control subject values (i.e., 0.074 to 2.348 optical density units) were further stratified. The 46 RA cases and 73 controls were divided into their upper normal (i.e., 80th to 95th percentiles) versus elevated (95th plus percentiles) levels (Table 1). Assuming that the serum AFA levels ≥ 0.074 units reported in Table 3 of Aho, *et al*¹ include all higher values (i.e., the elevated 95th plus percentiles), then the AFA values within the upper normal range, i.e., from 0.074 (defines the 80th percentile) up to but not including ≥ 0.138 units (defines the 95th plus percentiles), do not predict RA (Table 1). Only the elevated levels of AFA of ≥ 0.138 units (95th plus percentiles) significantly predict RA with an odds ratio (OR) of 6.37 and 95% confidence intervals of 2.67 to 15.41, using the unmatched cross products analysis method⁶.

Table 1. Odds ratios with 95% confidence intervals for predicting RA. Cases versus controls by percentile levels of baseline serum antifilaggrin antibodies (AFA)*.

	Numbers of Subjects		OR [†]	95% CI [†]
	Cases	Controls		
Percentiles of control AFA levels				
< 20	18	75	1.00	—
20–39	15	73	0.86	0.38–1.95
40–59	20	70	1.19	0.55–2.58
60–79	25	74	1.30	0.76–2.23
80–94*	20	56	1.36	0.78–2.38
95+*	26	17	6.37	2.67–15.41
Total	124	365		

*Modified from Table 1 of Aho, *et al*¹ by stratifying the highest quintile of AFA levels into its upper normal (80 to 95 percentile) and elevated (95 plus percentiles) ranges.

[†]OR within the data set are based upon estimates derived from the unmatched cross products method⁶.

Chi-square 2-tailed p for linear trends: 0 up to only the 95th percentile (5 levels) = 0.1174; 0 through the 95th plus percentiles (6 levels) < 0.0001.

In this study design that employed 3 matched controls per case¹, more precise analyses would need to be performed by the conditional logistic model to estimate OR of RA for fractiles of AFA concentrations⁷, but those data were not published.

Did heterogeneity occur within the highest quintile of AFA levels for predicting RA? The elevated AFA levels predicted RA to a significantly greater extent than did the upper normal 80th to 95th percentile values, both included within the highest quintile (Fisher's exact 2 tailed test of levels 6 vs 5 in Table 1, $p = 0.00037$, OR 4.28, 95% CI 1.80–10.32). A linear trend for the relationship of AFA levels to the prediction of RA is significant only when the data for elevated values are included in analysis (Table 1). Although the available data in the report¹ are detailed, they did not permit the analyses presented in Table 1 to be stratified into the 89 RF positive versus 35 RF negative RA cases and their respective controls. Possibly a subgroup (e.g., RF positive RA) might show a significant relationship between normal ranges of AFA levels and the prediction of RA?

Did baseline AFA levels within the normal range associate with RF status (Table 2)? At baseline, only the elevated levels of AFA (95th plus percentiles) significantly associated with a positive RF status among the future RA cases (OR 4.97). Significant associations also occurred in the controls (7.50) and the total study subjects (8.97). When the predictions of cases and controls are analyzed according to baseline RF status (Table 2), again only the elevated baseline AFA levels (95th plus percentiles) associated with the development of RA. The OR is 2.81 in RF+ and 4.24 in RF– subjects, being significant in the latter subgroup and in the total subjects, with an OR of 5.78.

Further analyses are needed to clarify the relationships of AFA to RA. Critical analyses of prospective data promise to reveal essential insights into the complex pathways of RA^{1,5}. Further analyses of the total 124 future RA patients stratified by their RF status at both baseline and diagnosis also was not permitted by the data presented¹. The 4 subgroups of cases (and their respective controls) would be: (1) RF positive at both times ($n = 36$); (2) RF negative at both times ($n = 32$); (3) cases who converted from RF negative to positive ($n = 53$); and (4) the few cases ($n = 3$) who converted from RF positive to negative¹. Relationships of normal or elevated AFA levels to RA may be particularly strong in one versus another subgroup, which deserves further exploration.

An open question remains whether AFA levels, within either the normal or the elevated ranges, can independently predict the development of RA,

Table 2. Association of baseline levels of AFA and RF status within outcome groups and the predictability of AFA levels for RA by baseline RF status.

Subjects' Outcomes	Baseline RF Status								
	< 0.074 units (< 80 percentile)		0.074 to 0.138 units (80 to 95 percentiles)			0.138 + units (95 + percentiles)			Total AFA N
	N	OR	N	OR	(95% CI)	N	OR	(95% CI)	
Baseline RF in outcomes									
Future RA									
RF+	19		4			16			39
RF-	59	1.00	16	0.78	(0.19-2.91)	10	4.97	(1.76-14.30)	85
Future CN									
RF+	20		7			6			33
RF-	275	1.00	49	1.96	(0.71-5.25)	11	7.50	(2.19-25.10)	335
Total Subjects									
RF+	39		11			22			72
RF-	334	1.00	65	1.45	(0.66-3.12)	21	8.97	(4.29-18.81)	420
Outcomes in baseline RF									
Baseline RF+									
RA	19		4			16			39
CN	20	1.00	7	0.60	(0.12-2.84)	6	2.81	(0.80-10.18)	33
Baseline RF-									
RA	59		16			10			85
CN	275	1.00	49	1.52	(0.77-2.98)	11	4.24	(1.58-11.35)	335
All baseline RF									
RA	78		20			26			124
CN	295	1.00	56	1.35	(0.73-2.47)	17	5.78	(2.85-11.80)	368

*OR within the data sets are based upon estimates derived from the unmatched cross products method⁶. CN: controls.

among the total study subjects or any of its subgroup categories. Given the significant associations observed with elevated AFA levels, multivariable analyses would be indicated to determine if they can independently predict the development of RA (or any of its subgroups), after adjusting for baseline RF status⁵, intervals from sampling to clinical onset¹, and other appropriate correlative variables⁵.

The mechanisms of origin of the AFA system are biologically interesting, whether or not these autoantibodies independently predict RA or contribute to its susceptibility. The report of Aho, *et al*¹ is a welcome contribution to defining complex relationships in the development of RA, and future analyses will hopefully provide further clarifications and insights.

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Drs. Aho, *et al* reply

To the Editor:

We thank Drs. Masi and Aldag for their interest in our paper¹. We tried to be concise in writing; our approach would have been different if we had been presenting a paper intended for an epidemiological journal.

We reanalyzed our material with the conditional logistic model by dividing the highest quintile of antifilaggrin antibody (AFA) distribution into the percentiles from 80 to 94 and from 95 to 100, as Masi and Aldag proposed (Table 1). Of note is that we had also analyzed our data both by quintiles and by entering AFA as a continuous variable to test linearity of the relation. We maintain our conclusion that AFA already within "normal" range predicts RA.

In contrast to rheumatoid factor (RF), AFA in our study series did not correlate significantly with age, sex, smoking, or coffee drinking. Adjustments for these and additional variables would of course be technically possible but we might face problems concerning statistical power and the true significance of the findings. Although there was a close correlation between AFA and RF, the linear relation between baseline AFA and risk of RF positive RA remained statistically significant after adjustment for baseline RF status ($p = 0.02$), but not after adjustment for Waaler-Rose titer ($p = 0.11$). One problem in the current study was the lack of RF values covering the whole range. In our earlier series of patients with recent onset arthritis a proportion of RF negative but AFA positive nonerosive cases devel-

Table 1. OR with 95% CI of rheumatoid factor (RF) positive RA and RA in total between percentiles* of serum antifilaggrin (AFA) concentrations**.

Percentiles of AFA*	No. of Cases	RF+ RA			No. of Cases	RA in Total		
		No. Controls	OR	95% CI		No. Controls	OR	95% CI
< 20	11	56	1.00		18	75	1.00	
20–39	9	54	0.88	0.30–2.54	15	73	0.87	0.39–1.93
40–59	14	50	1.78	0.69–4.65	20	70	1.35	0.63–2.90
60–79	20	52	2.74	1.05–7.16	25	74	1.75	0.81–3.78
80–94	15	33	3.60	1.29–10.04	20	51	2.21	0.98–5.02
95+	20	15	8.12	2.93–22.52	26	22	5.78	2.52–13.23

*The percentiles are based on the distribution of concentrations among controls. Percentile divisions are 0.004–0.027, 0.028–0.039, 0.04–0.051, 0.052–0.073, 0.074–0.128, and 0.129–2.348 optical density units.

**Modified from Table 1 of Aho, *et al.*

oped an erosive disease in due course². Nevertheless, whether AFA has any independent role remains an open question, as Masi and Aldag state.

We would like finally to point out that our study was on Finnish patients with RA. Much information is available on RF but data concerning the occurrence of other marker antibodies of RA are from a rather limited geographical area. According to a number of studies, anti-RA 33 is present in some 30–40% of Central European patients with RA. Yet in a recent study this antibody proved to be virtually absent in a large patient series collected from the Bethesda area in the United States³. Thus, much additional information is needed on the occurrence of marker antibodies of RA.

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Temporal Arteritis Associated with *Chlamydia pneumoniae* DNA Detected in an Artery Specimen

To the Editor:

We read with interest the case report by Rimenti, *et al.*¹ on temporal arteritis associated with *Chlamydia pneumoniae*. The authors suggest a possible association between *C. pneumoniae* infection and giant cell arteritis (GCA). Using a touchdown polymerase chain reaction (PCR) technique on a paraffin embedded temporal artery with GCA, they detected DNA from *C. pneumoniae*. To our knowledge the first report suggesting *C. pneumoniae* to play a pathogenetic role in temporal arteritis using the PCR technique was by Wagner, *et al.* at the annual meeting of the American College of Rheumatology in 1998². In their study examining paraffin embedded temporal artery biopsies using both immunohistochemistry and PCR technique, *C. pneumoniae* was detected in 7 of the 9 examined patients with GCA.

In our own study examining 20 paraffin embedded temporal arteries with proven vasculitis in the artery (giant cells present in 12 biopsies) using a sensitive PCR technique, *C. pneumoniae* could not be detected in any of the examined biopsies³. The patients in our study were recruited from an

area with the highest incidence of temporal arteritis reported worldwide⁴ and IgG antibodies against *C. pneumoniae* are frequently found in the Norwegian population⁵.

C. pneumoniae has been suggested to play a pathogenetic role in other autoimmune diseases like reactive arthritis⁶ and multiple sclerosis (MS)⁷. In the latter contradictory results have also been reported⁸. As in the present discussion rather convincing primary data on the role of *C. pneumoniae* in the pathogenesis of MS was published⁷. However, in other studies the results could not be confirmed⁸. This may reflect the lack of standardization of methods used to diagnose *C. pneumoniae* infections or differences in epidemiology.

The poor correlation between serological results, culture, and PCR for diagnosis of this agent in respiratory infections has been documented by Verkooyen, *et al.*⁹. In their case report Rimenti, *et al.*¹ used a PCR method described by Blasi, *et al.*¹⁰. The very high number of cycles (40 plus 35) may yield unspecific PCR products at the same size as the specific amplicons, and the specificity should therefore be proved by probing or sequencing. We have tried this method, and experienced that some respiratory specimens can yield an apparently positive band on the gel, but are negative by retesting using other primers and probes. Infection caused by *C. pneumoniae* is common, and the rise in specific IgG titer by microimmunofluorescence may have been coincidental. Further, the authors do not present any immunohistochemical investigations with monoclonal antibodies that could support their findings.

The results of studies examining the etiologic role of microbes should be interpreted with great care until the findings are confirmed in other studies.

Our finding stands in a sharp contrast to the case report by Rimenti, *et al.*¹ and the study by Wagner, *et al.*². We are therefore not convinced that *C. pneumoniae* has a pathogenetic role in temporal arteritis. Further research in this field is needed before any conclusions can be made.

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Dr. Blasi, et al reply

To the Editor:

We are grateful to Haugeberg, et al for their comments regarding our case report on *Chlamydia pneumoniae* DNA detection in a temporal artery specimen of a patient with giant cell arteritis¹. Our patient had persistent fever nonresponsive to multiple antibiotic treatment (cephalosporin, teicoplanin, and pefloxacin) and signs and symptoms of histologically confirmed temporal arteritis. Antibiotic treatment with a macrolide was associated with fever remission; *C. pneumoniae* serology showed a more than 4-fold increase in antibody titers, and evidence of *C. pneumoniae* DNA was found on both the arterial specimen and peripheral blood mononuclear cells.

Haugeberg, et al suggest that the high number of cycles required for the PCR technique we employed favors the yield of nonspecific PCR products, and that the use of probing or sequencing would have confirmed the specificity of our findings. However, a report by Boman, et al² shows that nested PCR techniques are roughly 10 times more sensitive than single-step PCR, with specificity ranging between 95% and 100% compared to culture and enzyme immunoassay tests. Moreover, as in previous studies³, we repeated testing twice on the arterial specimen, and in both cases results were positive for *C. pneumoniae* DNA, reducing the probability that the finding was due to unspecific PCR products. As the authors point out, immunohistochemical investigations were not performed, but a previous report by our group shows that the specificity of nested PCR is equal to that of immunohistochemistry⁴.

The purpose of our case report was to describe the observation of an association between *C. pneumoniae* DNA detection and the presence of giant cell temporal arteritis. As noted by Haugeberg, et al, our finding is not unique, and agrees with the recent report by Wagner, et al⁵.

We agree that further research is needed before any conclusions can be drawn, and for this reason we cannot completely rule out a possible pathogenetic role of *C. pneumoniae*.

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Incidence of Elbow Involvement in Rheumatoid Arthritis

To the Editor:

As I have always considered elbow flexion contracture a pathognomonic and diagnostic feature of rheumatoid arthritis, I read the recent prospective 15 year endpoint study¹ with great interest. While it focuses chiefly on the erosive lesions of the bones, the paper yields insights into the progression of joint involvement at the elbow. However, I was disappointed to find no mention of concomitant soft tissue changes; in particular, the lesions described by Lehtinen and co-authors lend themselves to the development of antecubital cysts^{2,3}, corollaries to the popliteal cysts of the knees. Were these looked for, found, recorded, or treated?

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Drs. Lehtinen, et al reply

To the Editor:

The study is based on the Heinola Follow-up Survey of Arthritis and the prospectively followed cohort of rheumatoid patients in which only radiographic changes are evaluated. Unfortunately no detailed data on soft tissue changes or the range of motion exist. No excisions of antecubital cysts were recorded in patient documents in this series. According to our clinical experience antecubital cysts occur occasionally and some of these are excised separately by elbow synovectomy. In elbow replacement, cysts are usually left undisturbed unless careful synovectomy is performed as a part of the procedure. In the course of elbow destruction, flexion contracture occurs regularly, except in some totally damaged and unstable elbows.

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The Use of Botulinum Toxin-A in the Treatment of Patients with Fibromyalgia

To the Editor:

Botulinum toxin-A (BTX-A), one of 3 subtypes of the toxin produced by *Clostridium botulinum*, causes weakness or paralysis of skeletal muscle. It blocks the release of acetylcholine from motor nerve endings. Although its main effect is on the motor neuron function, it may also affect gamma motor neurones, resulting in lowering of resting muscle tone, thus alleviating spasm¹.

Although long used by neurologists primarily for the treatment of blepharospasm², spasmodic torticollis³, and strabismus⁴, for which its use has been approved in the USA, it is also used extensively by plastic surgeons for the treatment of facial lines (wrinkles).

Recently several publications have documented its efficacy in whiplash injury associated with neck pain⁵ or cervicogenic headaches⁶, and investigators have even extrapolated its use to the treatment of tension-type headaches⁷ as well as myofascial pain syndromes⁸⁻¹⁰. Following on the publication of the recent pilot study by Freund and Schwartz⁵, we describe our initial experience with BTX-A in the treatment of patients with fibromyalgia (FM) "trigger points" who have been resistant to other forms of local and systemic therapy for this ailment.

The resistant patients we have treated with BTX-A injections into local "trigger points" all had the following characteristics: They either did not respond, or responded for only one to 2 days following local lidocaine injections into these "trigger" points. They often experienced enhanced pain following these injections. They frequently stated that they had to spend at least 24 hours in bed following these injections because of "side effects." FM had been present for up to 10 to 15 years. They all had numerous FM "trigger" points affecting the cervical area, upper shoulders, borders of the scapulae, and lower back, as well as medial aspect of knees (these often predominated).

Sixteen patients were included in the study. Five had one course, 7 had 2 courses, 3 had 3 courses, and one had 4 courses of BTX-A therapy. Repeated courses were given within one to 2 months when "trigger" points at the initial injection session were too numerous to inject at one time.

In several patients, pain intensified in areas that had not been injected, or new "trigger" points appeared in areas previously unaffected, requiring repeated courses. Relief from symptoms after BTX-A injections lasted a minimum of 16 weeks, in all patients.

No patient was injected with more than 100 u (diluted in 10 cc saline) at any one time, thus limiting possible side effects from the medication.

It is concluded that BTX-A injections into FM "trigger" points offer more prolonged relief without any discernible side effects in a "pilot" study in 16 patients and is superior to local saline or anesthetic injections. Its use is limited by the cost of treatment and, in the USA, by lack of US Food and Drug Administration approval for its use in fibromyalgia. This should be remedied.

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Dr. Freund replies

To the Editor:

I read with interest the experiences reported by Asherson and Pascoe. Patients with fibromyalgia (FM), as noted by the authors, are difficult to treat. The specific pathology of this condition is elusive and the patients are often complex, presenting with several chronic pain conditions. Commonly these include chronic tension headache, neck pain, temporomandibular and back pain. As pointed out, these latter conditions are also responsive to botulinum toxin-A (BTX-A) and may, as in Asherson and Pascoe's patients, require more than one set of injections to control the pain. This technique of reinjecting patients in a short time frame has raised concerns about antibody production and the eventual immunity of patients to a potentially effective method of controlling chronic pain conditions. At this time there is little evidence that the new low protein formulations induce high antibody titers in the doses used in non-spasticity applications.

As BTX-A has shown clinical effectiveness in a number of seemingly unrelated non-spastic painful conditions such as FM, skeptics have argued that the effect of the toxin is primarily psychological, since its accepted primary mechanism of action is to relax muscle. However, new animal work using rat jaw joint, rat paw, and guinea pig cornea has shown that BTX-A can effectively inhibit second phase inflammatory responses in these provocation model systems. Evidence is also accumulating from clinical work by ourselves and others that BTX-A is efficacious in obtunding neurogenic inflammation. This is significant for 2 reasons, one that botulinum toxins appear to have pharmacologic properties that are far from fully understood. The second is that many clinically defined painful conditions such as FM may have an underlying common pathology, which these toxins can modify. This makes BTX-A a useful therapeutic tool as well as a possible diagnostic tool. I agree with Asherson and Pascoe that further work defining the role of BTX-A in FM is warranted and should be encouraged.

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Tolosa-Hunt Syndrome Mimicking Giant Cell Arteritis

To the Editor:

Tolosa-Hunt syndrome is a rare disorder consisting of unilateral orbital and facial pain and multiple cranial neuropathies on the same side as the pain.

The erythrocyte sedimentation rate (ESR) is elevated in about 45% of cases. Pain decreases promptly and dramatically in response to glucocorticoid therapy⁴. We bring this entity to the attention of rheumatologists because it shares some characteristics with giant cell arteritis.

A 70-year-old man was evaluated for nasal congestion, right ear ache, right side headache, and numbness on the right side of his neck. Examination by an otolaryngologist, an audiogram, and a computerized tomography (CT) scan of the neck were normal. One year later, he reported sharp and boring episodic facial pain and a sensation resembling pin-pricks over the right scalp. Neurological examination and CT scans of the brain and the base of the skull were normal. He then developed palsies of the right 5th, 7th, and 12th cranial nerves. ESR was 48 mm/h (normal 0–15) and a magnetic resonance image (MRI) study showed moderate cerebral atrophy. Reevaluation by a neurologist showed no cranial nerve palsies. Serial ESR values over the following 4 months were 95, 72, 67, and 56 mm/h. There was no evidence of giant cell arteritis in a temporal artery biopsy. A second MRI of the brain was interpreted as showing moderate cortical atrophy.

In 1999, a 3rd neurological examination showed decreased sensation in the distribution of the right 5th cranial nerve and diminished right corneal reflex. ESR values were 98 and 85 mm/h, and right 6th cranial nerve palsy appeared. One month later, he complained of diplopia and right side headache, right side orbital and facial pain, decreased taste, and drooling from the right side of the mouth. Abduction of the right eye was impaired and sensation was diminished in the distribution of the ophthalmic and maxillary divisions of the right 5th cranial nerve. He had right 7th cranial nerve palsy and the tongue was deviated to the right. A tentative diagnosis of Tolosa-Hunt syndrome was made on the basis of periorbital pain, the episodic nature of the disease, involvement of multiple cranial nerves on the same side as the pain, and imaging studies that did not show an intracranial lesion as a cause of his symptoms. Treatment was started with prednisone, 60 mg/day. Two weeks later the pain had resolved almost completely. After 5 weeks of treatment, the 5th and 7th cranial nerve palsies had resolved, but the 6th cranial nerve palsy remained. Retrospective review of pretreatment MRI studies showed subtle changes consistent with inflammation in the superior aspect of the right side of the cavernous sinus (Figure 1).

Tolosa-Hunt syndrome is characterized by painful ophthalmoplegia due to granulomatous inflammation involving the cavernous sinus and superior

orbital fissure. In 1954, Tolosa² described painful left ophthalmoplegia in a patient with paralysis of the left 3rd, 4th, and 6th cranial nerves. Angiography showed narrowing of the carotid siphon just distal to the cavernous sinus. At necropsy, the intracavernous portion of the left carotid artery and the adjacent carotid sinus were surrounded by "a cuff of non-specific granulation tissue including the adjoining nervous trunks." Hunt, *et al*³ reported 3 additional cases in which remitting and relapsing pain and ophthalmoplegia were believed to result from an inflammatory lesion of the cavernous sinus. One of these cases remitted spontaneously and the other 2 responded to treatment with oral prednisone. In 1966, Smith and Taxdal⁴ described 5 additional cases and introduced the eponym Tolosa-Hunt syndrome for the triad of unilateral periorbital pain, accompanying cranial nerve palsies, and dramatic response to systemic corticosteroids. The International Headache Society⁵ defined diagnostic criteria for the Tolosa-Hunt syndrome: (1) Episode or episodes of unilateral orbital pain for an average of 8 weeks if untreated; (2) association with paralysis of one or more of 3rd, 4th, and 6th cranial nerves that may coincide with the onset of the pain or follow it by a period of up to 2 weeks; (3) pain relieved within 72 hours after initiation of corticosteroid therapy; (4) exclusion of other causative lesions by neuroimaging and (not compulsory) carotid angiography. Some cases may have additional involvement of the 2nd, 5th, 7th, or 8th cranial nerves⁵.

The classic angiographic finding in Tolosa-Hunt syndrome was segmental narrowing in the intracavernous carotid artery, thought to represent inflammatory changes in the space between the carotid artery and adjacent nerves². Six of 9 patients in the series of Miwa, *et al*⁶ had poor filling of the cavernous sinus with orbital venography. CT scans and MRI studies showed asymmetric shape of the cavernous sinus in about one-half of patients¹⁶. Goto, *et al*⁷ reported unremarkable CT scans in 2 of 3 affected patients. In all 3 cases, however, T1 and intermediate weighted MRI revealed an abnormal soft tissue area with intermediate signal intensity in the cavernous sinus. The abnormal areas became smaller and in 2 cases, the signal intensity dropped after corticosteroid treatment.

Tolosa-Hunt syndrome has a wide differential diagnosis. It may be difficult to differentiate cranial pain in Tolosa-Hunt syndrome from giant cell arteritis if Tolosa-Hunt pain occurs before cranial nerve involvement. On the other hand, eye pain, diplopia, and oculomotor disorders are rare in giant cell arteritis^{8,9}. Tolosa-Hunt syndrome should be considered in a case

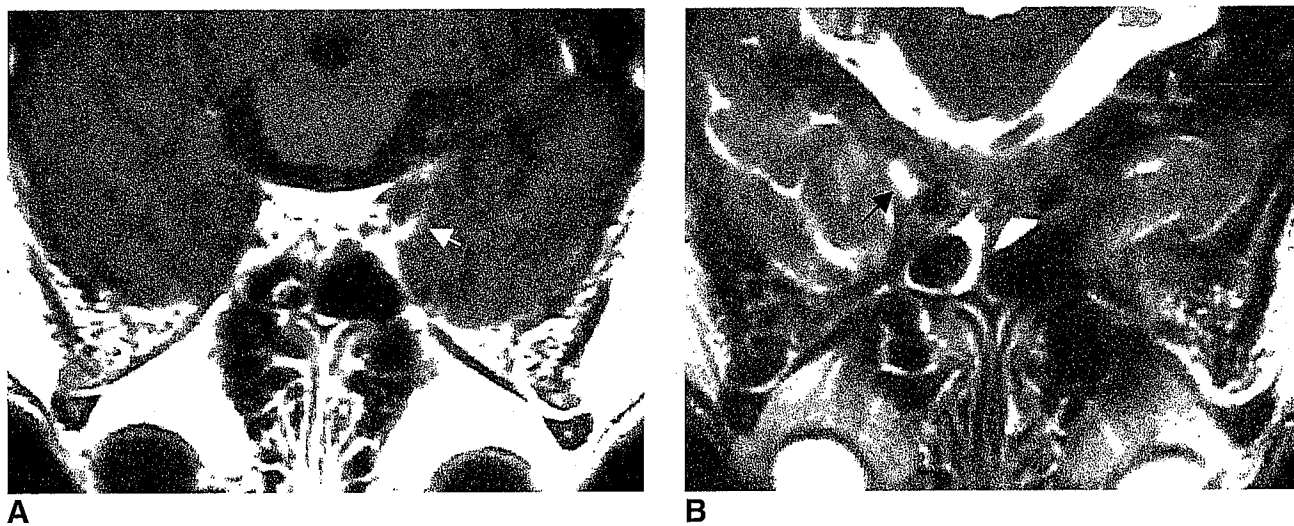


Figure 1. Coronal views from the second brain MRI (April 1999) show changes consistent with inflammation in the right side of the cavernous sinus. A. T2 weighted sequence with gadolinium contrast. On the left side of the brain, white arrow points to the cavum trigeminale (trigeminal cave of Meckel), a cleft-like recess between the endosteal and meningeal dural layers in the middle cranial fossa¹⁰. This area is normal and is filled with cerebrospinal fluid, which is white. The corresponding area on the opposite side of the brain shows changes consistent with an inflammatory process. There is no cerebrospinal fluid in the right cavum trigeminale. B. T1 weighted sequence with gadolinium contrast. The abnormal cavum trigeminale on the right of the brain shows enhancement with gadolinium contrast (black arrow) indicating abnormal tissue. The high signal intensity is consistent with inflammation. This lesion is not seen on the normal left side of the brain.

with recurring and remitting cranial pain, especially if pain is localized to the orbit and associated with cranial neuropathy. A negative temporal artery biopsy, failure to observe a space-occupying brain lesion, imaging studies that show narrowing in the intracavernous carotid artery or evidence of soft tissue inflammation in the cavernous sinus, and prompt response of pain to corticosteroids support the diagnosis of Tolosa-Hunt syndrome.

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Effect of Antimalarial Agents on Fasting Lipid Profile in Systemic Lupus Erythematosus

To the Editor:

We were interested to read the report by Dr. Tam and colleagues¹. We reported this effect in RA in 1997, and given the premature cardiovascular morbidity seen in patients with RA, as well as that occurring in the SLE population, this effect is potentially valuable².

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Book Reviews

Kelley's Textbook of Rheumatology, 6th Edition

S. Ruddy, E.D. Harris, C.B. Sledge, editors, R.C. Budd, and J.S. Sergent, associate editors. Philadelphia: W.B. Saunders, 2000, 1788 pages, price \$399.00 US.

"Never write a textbook, if it is a failure it is time thrown away and worse than wasted; if it is a success it is a millstone around your neck for the rest of your life"

— Michael Foster (1836–1907). In: Rolleston HD. *The Cambridge Medical School: a Biographical History*. Cambridge: Cambridge University Press, 1932:87–8.

It is fortunate for rheumatology that Dr. William N. Kelley and his co-editors did not take this advice when they published the first edition of their famous textbook of rheumatology in 1977. It was the intention of the editors to produce a textbook that was "the best of its genre," and this they have achieved with each successive edition. It was also the policy of the editors to bring in new talent with each new edition, so providing both "vigor and freshness." They have maintained this policy and in this, the 6th edition, roughly 70% of the 162 contributions are new, with some 15% from outside the United States. The senior editor, Dr. William N. Kelley, has now retired, but in appreciation of his contribution his co-editors have generously used his eponym, the book now being known as *Kelley's Textbook of Rheumatology*.

The first of the 2 volumes begins with 21 chapters on the scientific basis of rheumatology. There are 5 chapters on the biology of the normal joint, few of which have been updated from previous editions, and a new one on proteinases and matrix degeneration, which provides new insight into the biochemical factors involved in joint destruction. All these chapters are "heavy going," but well written. For an aging reviewer, like myself, however, some of the concepts are difficult to follow: for example Figure 6.1 on the molecular genetic aspects of cartilage morphogenesis.

The 2nd series, on the scientific basis of immune and inflammatory responses, runs to no less than 22 chapters, 2 of which, on apoptosis and autoimmunity, are entirely new. Apoptosis, I rejoice to say, is the 2nd Scottish concept with a Greek name, the first being isotope. There is a much enlarged discussion on dendritic cells in the chapter on macrophages; T and B cells, immune complexes and complement now enjoy chapters of their own. The discussion on the messenger molecule, nitric oxide and its effects on vasculature, cells of the nervous system and immune cells, I found particularly interesting. But what is surprisingly missing from the section is a chapter on Celsus' first cardinal feature of inflammation, namely pain. There has been much recent research on this topic that would seem to warrant an updated account.

The 8 chapters on evaluation of the patient and the 6 on diagnostic procedures and tests provide all the information and references that a reader would want. I am not entirely in agreement that "strict adherence to aseptic procedures is required while performing arthrocentesis or soft tissue injections," as the author of the chapter on joint aspiration and injections would have us believe. The bacterial load injected into a joint with a sterile needle through normal skin is insufficient to cause a septic arthritis. The wearing of surgical gloves is necessary to protect the doctor, not the patient. The role of arthroscopy and arthroscopic surgery is fully discussed, but since the authors maintain that the former procedure can now be office based, a full description of the technique would be helpful.

Community physicians will find the 7 chapters on special issues, such as nutrition and various forms of alternative care, particularly helpful. Antirheumatic drugs and biologic agents occupy 9 chapters, together with an introductory chapter on the design of clinical trials. The fact that nonacetylated salicylate does not inhibit cyclooxygenases explains why it is equipotent with aspirin as an antiinflammatory analgesic, but much less toxic to the gastrointestinal tract.

Volume II begins with a breathtaking review of the etiopathogenesis of rheumatoid arthritis, complete with 371 references. This is followed by several excellent chapters on the clinical features and treatment of the disease, with separate sections on Felty's and Sjögren's syndrome. The problem of fatigue is discussed in relation to Sjögren's syndrome; this in my experience often responds to treatment with hydroxychloroquine. The chapters on spondyloarthropathies, systemic lupus erythematosus and related antiphospholipid syndrome, vasculitic disorders, systemic sclerosis, and mixed connective tissue diseases provide extensive coverage of these problems. Inflammatory disorders of muscles and other myopathies are well covered, as are diseases of bone. In the chapter dealing with Paget's disease it might have been worth emphasizing that although fractures are the most common complication, it was the only one not described by Sir James Paget (1814–99). Sarcomatous change is, as the author indicated, rare in Paget's disease, but it might have been useful to emphasize that it only occurs in severe and extensive disease. The first patient Paget described had a tumor in a bone not affected with the disease, and was almost certainly a secondary form of bronchial neoplasm. The problems of rheumatic disease in childhood (2 chapters by the same author) and 2 chapters on crystal induced synovitis all provide excellent reviews of these problems. Osteoarthritis, the commonest form of arthritis, occupies 3 separate chapters written by internationally recognized experts. It is gratifying that in the treatment of osteoarthritis, due emphasis is given to non-drug remedies. Acute rheumatic fever is dealt with fully in the last of 6 chapters dealing with arthritis related to infections. Most rheumatologists are unlikely to encounter a classical case of acute rheumatic fever, but may see adult patients with the so-called post-streptococcal reactive arthritis, which may last more than a year and, in my experience, may respond to sulfasalazine.

There are extremely useful chapters on the rheumatic problems associated with acquired immunodeficiency syndrome and sarcoidosis. *Mycobacterium tuberculosis* has long been considered a causative agent in sarcoidosis, and it is of interest that cell wall deficient mycobacteria, L-forms in culture media, have recently been identified. It might have been worth noting that synovial histology may reveal only nonspecific inflammatory changes, and not typical noncaseating granulomas. The different forms of amyloidosis are particularly well reviewed, as are iron storage disorders, and hemoglobinopathies. The author of the chapter on rheumatic manifestations of diabetes mellitus omits to mention other rarer forms of collagen disorders, namely, Lederhosen disease (nodular thickening of the plantar fascia) and Buschke's scleroderma. The latter consists of a massive skin thickening of "woody" consistency, often at the back of the neck, where it can be mistaken for a "buffalo hump," and often resolving spontaneously within a year. There are reports of Peyronie's disease in diabetic patients, but the association has yet to be proven. Other systemic disorders associated with arthritis, including hemophilia, various endocrine disorders, and malignancy, are all thoroughly dealt with, as are tumors involving joints and joint reconstructive surgery.

A comment should be made on the illustrations. The line drawings are nothing short of superb, but some of the clinical photographs would have been better in color; for instance, the figures of ocular complications in rheumatic disease (Chapter 29, Volume I), the different patterns of antinuclear immunofluorescence (Figures 11–1 and 11–2), and immune complex deposition in tissues (Figures 12–4 and 12–5). Some of the radiographs are not as clear as one would expect. One radiograph (Figure 8, Chapter 5) is reported as showing the principal tensile and compressive groups of trabeculae in the femoral head, but to my eye it does not.

Having read through the 115 chapters of the 2 volumes I have to say that I have been unable to find a poor chapter. The editors are once again to be congratulated on excellent work. It was Sir Francis Bacon (1561–1626) in his essay "Of Studies" who stated, "Some Bookes are to be Tasted, Others to be Swallowed, and Some Few to be Chewed and Digested: That is, some Bookes are to be read onely in Parts; Others to be read but not Curiously" [i.e., carefully]. I would certainly agree with the editors that this text book should not be read from cover to cover, but it will enable the reader to readily obtain information on a problem in rheumatic disease. This

now well established international textbook is a must for all whose clinical practice or laboratory research includes management and study of the rheumatic diseases. The cost is high but well worth the price.

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Rheumatoid Arthritis. New Frontiers in Pathogenesis and Treatment

G.S. Firestein, G.S. Panayi, and F.A. Wollheim, editors. Oxford, New York: Oxford University Press, 2000, 581 pages, price \$362.50 CDN.

This is the first comprehensive text dedicated to rheumatoid arthritis (RA) encompassing topics ranging from basic to clinical science and therapeutics. The 77 contributors provide an understanding of the genetics, immunopathogenesis and epidemiology of RA, pertinent clinical trial design, physical manifestations, and current therapies of rheumatoid disease. In the last 4 of the 44 chapters the authors also review the latest concepts in anticytokine therapies and future targets of therapy.

The text is divided into 7 sections. Section 1 outlines perspectives on the genetics and possible infectious agents that may play a role in the pathogenesis of RA. The chapter on experimental models provides an excellent overview of the strength and limitations of various animal models of inflammatory arthritis. Section 2, which constitutes the bulk of the text, reviews cellular and molecular mechanisms of inflammation, including the role of adhesion molecules in cell migration, cytokine networks, apoptosis, and rheumatoid factors in mediating the inflammatory response.

Sections 3 to 6 address the clinical manifestations of RA including imaging modalities, DMARD therapy, non-drug therapy, and surgical interventions. They also explore the role of the neuroendocrine axis in this disease.

The final section is entitled "Frontiers in Therapy." It outlines the requirements of appropriate clinical trial design. Each subsequent chapter is dedicated to the specific targets of cytokines, T-lymphocytes, macrophages, matrix metalloproteinases, and small molecule inhibitors of signal transduction. These chapters provide a current review of the status and limitations of therapeutic agents in development.

This text is well written and easily understood. It serves as a sound resource for clinician and scientist alike, and will be a valuable addition to the library of those interested in enhancing their understanding of RA. Future editions are welcomed to maintain a current perspective in this rapidly expanding field of rheumatology.

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Atlas of Pain Management Injection Techniques

Steven D. Waldman, MD, JD, Philadelphia: W.B. Saunders Company, March 2000, 400 pages, price \$140.00 US.

Beautifully illustrated, methodically and simply organized and presented, this atlas will prove to be a very useful tool for the management of musculoskeletal pain for the neophyte and the accomplished. The author reviews the indications and clinical considerations, the pathophysiology and functional anatomy, the step-by-step injection technique, side effects and complications and "clinical pearls" for each site under consideration. Missing, however, is an introduction with general principles such as preparation of the skin, size of syringe and needle, amount and kind of local anesthetic, amount and kind of corticosteroid, and the justification for use of corticosteroid when performing nerve blocks. Experienced physicians prefer to

mark the injection site with a finger nail and use proper skin preparation and not use gloves rather than find the proper injection site with the gloved finger, as recommended here. The author uses 40 mg methylprednisolone for most sites including large joints such as the hip and tiny joints such as the finger or toe interphalangeal joints. Missing is a discussion of the use of other frequently used corticosteroids and the incompatibility of some with local anesthetics. The local anesthetic of choice seems to be 0.25% preservative-free bupivacaine or occasionally 0.5% preservative-free lidocaine. The author mixes the anesthetic and corticosteroid together and does not discuss the merits of going to the site, i.e., nerve or tendon sheath or joint with local only, removing the syringe, leaving the needle in place, and then mixing the remaining local with steroid for the final injection. Missing is a mention of the side effects of corticosteroid such as depigmentation of skin, especially in dark skinned people, 24–48 hour worsening of diabetes, and rare systemic side effects. The inclusion of Relative Value Guides and billing codes for each injection technique as an aid to billing are of value only in the United States.

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