

# 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, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.

## Linear Scleroderma en Coup de Sabre and Brain Calcification: Is There a Pathogenic Relationship?

To the Editor:

We read with interest the report by Flores-Alvarado, et al<sup>1</sup> describing a case of scleroderma en coup de sabre (SCS) and brain calcification. The authors note this condition is uncommon and there is no consensus on the association between the 2 conditions. We describe a child with similar clinical findings.

A 6-year-old girl was admitted to our clinic due to skin discoloration and depression on her right forehead and chin. She had been followed by the pediatric neurology department because of her epileptic seizures, and had been receiving carbamazepine and sodium valproate treatment for 2 years. Her family noted echymotic color change and a depression becoming progressively more prominent affecting her forehead and chin within one year. Her history revealed she had had seizures (secondary generalized tonic clonic, with right eye and head deviation) with onset 2 years before, which were controlled by antiepileptic therapy. She was the second child of non-consanguineous healthy parents and she had a healthy brother. No previous similar case was described in her family.

On physical examination her height was 112 cm (90–97th percentiles), weight was 26 kg (97th percentile), head circumference was 54.5 cm (2–50th percentile), and blood pressure was 90/65 mm Hg. There was skin thinning and darkening of the skin color on the right forehead starting from the brow through the scalp (2 × 3 cm area) and on the right chin under the lip commissure (1 × 3 cm). There was bone depression and atrophy beneath these affected skin regions (Figure 1). There was no glossal or buccal atrophy. Other systemic findings were ordinary.

Complete blood count, erythrocyte sedimentation rate, and biochemical findings of the serum were within normal ranges. Rheumatoid factor and antinuclear antibodies were negative. Bone scintigraphy was normal. She had had normal findings on her cranial magnetic resonance imaging examination 2 years before, but cranial computerized tomographic imaging demonstrated multiple intraparenchymal calcifications, predominantly in the left hemisphere localization, and there was thinning on her right mandible and right frontal calvarium (Figure 2). There were no sclerotic or



Figure 1. Scleroderma en coup de sabre lesion involving the right forehead.

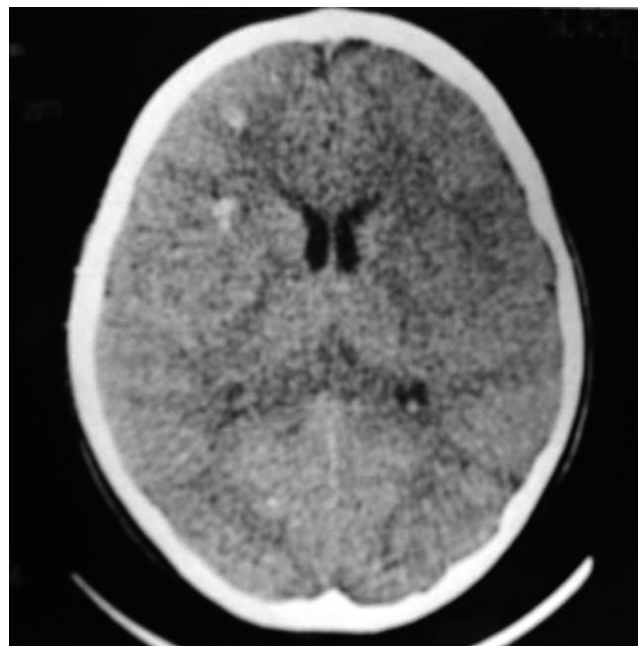


Figure 2. Axial computer tomography scan shows intracerebral calcifications.

lytic lesions of the bone structure. Bioelectrical disturbances were observed on the posterior region of the right hemisphere.

Prednisolone (10 mg/kg/day) and methotrexate (10 mg/m<sup>2</sup>/week) treatment was prescribed on a diagnosis of SCS with right facial progressive atrophy and linear scleroderma. After 6 months of treatment minimal fading of the skin lesions was observed.

Linear scleroderma is the most common subtype of localized scleroderma in children and adolescents, and is characterized by one or more linear streaks that typically involve an upper or lower extremity and may be associated with morphea plaques<sup>2</sup>. When a linear lesion involves the face or scalp, it is referred to as SCS<sup>2,5</sup>. Differential diagnosis of SCS should include the Parry-Romberg syndrome as stated by authors (1,4).

In most cases with SCS and Parry-Romberg syndrome, disorders such

as seizures, uveitis, dental abnormalities and ocular muscle dysfunction, loss of eyebrows or eyelashes, and atrophy of the iris have been described, in addition to the abnormalities noted above<sup>4,6-8</sup>. In adult cases having localized scleroderma, intracranial calcification together with seizures are reported rarely<sup>1</sup>. In 37 reported cases with systemic sclerosis, 16 (43%) had seizures, and 12 patients with seizures had intracerebral calcifications<sup>8</sup>. SCS having obscure etiology and pathogenesis may be observed in cases of childhood epilepsy, and seizures may occur before facial findings<sup>3,5</sup>. There is no intracranial pathology accompanying seizures<sup>4</sup>.

There are few reports of SCS cases in childhood. In the largest series consisting of 13 cases there was no intracerebral calcification (IC)<sup>4</sup>. In another study of SCS, despite the observation of seizures, no IC was reported<sup>3</sup>. Liu, et al<sup>5</sup> described IC in 2 SCS cases in a series of 23 cases of localized scleroderma. Thus, calcification is very rare in childhood SCS<sup>3,5</sup>.

The above data suggest that the coupling of SCS and IC may represent a new syndrome. In any case with SCS and seizure, cranial imaging studies should be performed.

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## Dr. Flores-Alvarado, et al, reply

To the Editor:

We appreciate the thoughtful comments of Kasapcopur, et al on our recent case report. From their review of the literature, they propose that the association of linear scleroderma en coup de sabre (SCS) and intracranial calcification represents a new syndrome or pathogenic coexistence, and further recommend cranial imaging studies in SCS and seizure<sup>1</sup>.

At present, however, there is limited evidence to support such a conclusion. SCS is an unusual disorder, and in contrast to adult scleroderma there are no available prospective imaging studies of SCS patients to detect intracranial calcification.

Regarding the study of Orozco-Covarrubias, et al<sup>2</sup> involving a fairly large number of SCS patients (n = 13), and also Parry-Romberg patients (n

= 9), it did not specifically address this issue, and it was not clear whether imaging studies were performed in all patients.

However, we agree with the second part of their conclusion, although we would expand it to include cranial imaging studies in all SCS patients exhibiting any type of clinical neurologic involvement.

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## Tumor Necrosis Factor- $\alpha$ Antagonists Induce Lupus-like Syndrome in Patients with Scleroderma Overlap/Mixed Connective Tissue Disease

To the Editor:

Novel biologic agents that attenuate inflammation by targeting tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) have gained acceptance in the treatment of rheumatoid arthritis (RA) and are being used in a variety of other inflammatory disorders, including Crohn's disease, adult onset Still's disease, uveitis, Wegener's granulomatosis, Behçet's disease, scleroderma, Sjögren's syndrome, sarcoidosis, pyoderma gangrenosum, and polymyositis/dermatomyositis<sup>1,2</sup>.

It now appears that although these therapies may suppress some autoimmune diseases, they may potentiate others. TNF- $\alpha$  clearly plays a deleterious role in the pathogenesis of RA; its role in lupus, however, is controversial. TNF- $\alpha$  blockade, in the form of either a soluble TNF- $\alpha$  receptor such as etanercept, or a monoclonal antibody directed against the TNF receptor such as infliximab, has been associated with the development of autoantibodies, and in some cases, a clinical lupus-like syndrome<sup>3,4</sup>. Patients treated with these agents for RA can develop subacute cutaneous lupus erythematosus or a drug-induced lupus syndrome<sup>5</sup>.

We describe 2 cases of patients with mixed connective tissue disease (MCTD) with prominent polyarthritis who developed clinical features consistent with a lupus-like syndrome and positive serological markers of lupus after treatment with a TNF- $\alpha$  antagonist. Discontinuation of the therapy in each case produced clinical remission, resolution of autoantibodies, and normalization of hypocomplementemia (Tables 1 and 2). Rechallenge with infliximab in the second case precipitated the recurrence of the lupus-like syndrome.

Case 1. A 44-year-old woman presented with Raynaud's phenomenon (RP), lymphadenopathy, constitutional symptoms, transient chest pain and arthralgias of her shoulders, knees, ankles, and small joints of the hands.

Table 1. Serial serologies of Patient 1.

	Before Etanercept	During Etanercept	One Month After Etanercept	One Year After Etanercept
ANA	+	+	+	+
DsDNA	-	+	+	-
Anti-Ro	-	+	+	-
Anti-La	-	-	-	-
Anti-Smith	-	-	-	-
UIRNP	+	+	+	+
C3, C4	Normal	Low	Normal	Normal
Arthritis	+	-	+	+
Lupus-like syndrome*	-	+	-	-

\* Fever, arthralgias, myalgias, and diffuse scaly eruption on face, arms, back, leg.

Table 2. Serial serologies of Patient 2.

	Before Infliximab	At Time of 3rd Infliximab Infusion	Between 3rd and 4th Infliximab Infusion	At Time of 4th Infliximab Infusion	One Year After Infliximab
ANA	+	+	+	+	+
DsDNA	-	NA	+	+	-
Anti-Ro	-	NA	-	-	-
Anti-La	-	-	-	-	-
Anti-Smith	-	NA	-	-	-
UIRNP	+	NA	+	+	+
C3, C4	Normal	NA	NA	Low	Normal
Arthritis	+	-	+	-	+ (episodic)
Lupus-like syndrome*	-	+	-	+	-

\* Fever, myalgias, abdominal pain. NA: data not available.

Studies revealed a positive antinuclear antibody (1:640), positive anti-RNP, but no anti-dsDNA, anti-Smith, anti-Ro, or anti-La antibodies (Table 1). Despite treatment with hydroxychloroquine (HCQ), she developed significant puffy hands and feet, morning stiffness, joint pain, and mild dysphagia for solids. Her examination disclosed cervical and axillary lymphadenopathy, mild sclerodactyly, and a symmetrical rheumatoid-like polyarthritis. She failed treatment for her arthritis with a combination of a non-steroidal antiinflammatory drug (NSAID), low dose prednisone, and weekly methotrexate (MTX). Etanercept was added in June 1999, and 9 months later she was able to discontinue prednisone and MTX. HCQ was reinstated in July 2000 for mild flare with synovitis in the metacarpophalangeal and proximal interphalangeal joints. In May 2001, a febrile illness developed with malaise, progressive anemia, and intense polyarthritis. The etanercept was stopped and then reintroduced in June 2001 after these symptoms resolved. However, new investigations showed anti-double-stranded DNA and anti-Ro and anti-RNP antibodies, whereas anti-Sm and anti-La remained negative. In July 2001, she developed periorbital edema, a malar rash, an erythematous nonpalpable rash on her legs and trunk and persistent, worsening polyarthralgia with active synovitis, including new bilateral knee effusions. A drug-induced lupus syndrome was suspected; the etanercept was discontinued and she was treated with corticosteroids. Her fever, constitutional symptoms, polyarthritis, and rash resolved. However, after one month without etanercept, her polyarthritis returned, requiring a combination of NSAID, prednisone, and mycophenolate mofetil for control. One year after etanercept, the dsDNA antibodies had disappeared, and complements remained normal.

Case 2. A 38-year-old man presented with RP and polyarthralgias. Laboratory data revealed normal complements and a positive antinuclear

antibody (1:640), positive anti-RNP, but no anti-dsDNA, anti-Smith, anti-Ro, or anti-La antibodies (Table 2). He was treated with amlodipine, HCQ, and prednisone. He then developed progressive shortness of breath, increasing myalgias and arthralgias, and dysphagia. Physical examination was remarkable for strikingly cyanotic fingers, diffuse lymphadenopathy, puffy fingers with synovitis, and sclerodactyly. He was treated with NSAID, HCQ, and MTX. Despite benefit, the MTX was discontinued after he developed persistent liver enzyme elevation. Active polyarthritis returned and infliximab therapy was instituted. Shortly after the third infliximab infusion, he developed a self-limited episode of flank pain, nausea, vomiting, and general arthralgias and myalgias that lasted about 24 hours. He received his fourth dose of infliximab 2 months later, and again he developed the same diffuse pain, chills, and vomiting. Hypocomplementemia and new anti-dsDNA antibodies were detected. He was switched to low dose prednisone and leflunomide, with good control. One year after discontinuing infliximab, the anti-dsDNA antibodies had disappeared, and complements normalized (Table 2).

This is the first report of the development of a lupus-like syndrome with specific autoantibodies and hypocomplementemia in MCTD treated with etanercept or infliximab. Although these agents are popular therapeutic options for RA, their use in the treatment of polyarthritis associated with MCTD is not reported. A subset of patients with scleroderma/MCTD will have RA-like polyarthritis requiring aggressive disease-modifying therapy to control the inflammatory process. Both these patients experienced excellent control of their arthritis, but developed an acute illness, in association with administration of a TNF- $\alpha$  antagonist. They both resolved their clinical syndrome, autoantibody production, and hypocomplementemia after discontinuing the drug. This temporal association strongly suggests a

causal relationship between the use of drug, the induction of autoantibodies, and the lupus-like syndrome.

TNF- $\alpha$  antagonists can be added to the more than 80 drugs that are thought to cause a lupus-like syndrome. It is of interest that both RA and systemic lupus erythematosus are associated with high serum concentrations of TNF- $\alpha$ . Studies in murine models of lupus provide conflicting explanations about whether TNF- $\alpha$  is pathogenic or protective<sup>6,7</sup>. In addition, in humans there is a correlation between higher serum levels of the soluble TNF- $\alpha$  receptors and increased lupus disease activity<sup>8</sup>. It is not clear why the use of a TNF- $\alpha$  antagonist in MCTD would trigger a lupus-like syndrome.

Although case reports have limitations in their interpretation, the temporal association of a lupus-like illness with serologic changes and hypocomplementemia in these 2 cases is compelling evidence of a causative relationship. TNF- $\alpha$  antagonists must be administered with caution if used to treat MCTD-associated polyarthritis.

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## Ocular Inflammatory Disease in Patients with Rheumatoid Arthritis Taking Etanercept: Is Discontinuation of Etanercept Necessary?

To the Editor:

Eye involvement is a frequent event in pediatric and adult rheumatologic patients. Tumor necrosis factor (TNF) may play a role in experimental uveo-retinitis. In scleritis, TNF and interleukin 1 released by the local inflammatory cell infiltrate may be associated with sclera destruction<sup>1,2</sup>. Treatment with anti-TNF, therefore, is a logical approach to this problem. Indeed, such treatment has been reported to be successful in intractable cases of juvenile rheumatoid arthritis (JRA) associated uveitis, seronegative spondyloarthropathies, rheumatoid scleritis, and Behçet's disease<sup>3-6</sup>.

There is one report, however, of anti-TNF treatment precipitating

inflammatory eye disease<sup>5</sup>. Clinicians may face the dilemma of whether discontinuation of etanercept is necessary. We describe 2 cases of anterior uveitis and severe scleritis occurring in patients undergoing chronic etanercept treatment. In our patients, local and systemic immunosuppressive treatment were curative without discontinuation of etanercept. The patients remained asymptomatic for one and 2 years, respectively.

The first patient was a 48-year-old white woman with seropositive RA and Sjögren's syndrome of 6 years' duration. She had been taking etanercept monotherapy (25 mg twice weekly) for 3 years, with remission of the arthritis. There were no extraarticular manifestations other than sicca syndrome. Eighteen months after the start of etanercept treatment, and while the disease remained in remission, she developed left eye scleritis, necessitating local and systemic steroids, local cyclosporine, and azathioprine treatment. HLA-B27 was absent and erythrocyte sedimentation rate (ESR) was 28 mm/h. There was resolution and nonrecurrence even after discontinuation of azathioprine. Etanercept was continued throughout the course of the illness.

The second case was a 58-year-old white woman with RA of 20 years' duration. She had been taking methotrexate (MTX) for 10 years, in combination with etanercept (25 mg twice weekly) for 3 years. Her RA was erosive, seropositive, and nodular with significant hand and feet deformities, but with no tender joints. She had no other extraarticular manifestations. Twenty months after the start of etanercept treatment, she developed severe anterior uveitis necessitating local and systemic steroids. HLA-B27 was absent, ESR was 30 mm/h, and there was no increase of synovitis or number of tender joints. There was resolution and nonrecurrence. Etanercept was continued throughout the course of the illness.

Our cases indicate that etanercept treatment, in the standard dosages, was selectively effective in improving the arthritis, but could not prevent ocular involvement. Perhaps the pathophysiologic process of ocular involvement is different, and TNF- $\alpha$  may not be the predominant responsible cytokine. It is of interest that infliximab rather than etanercept was found to be a more consistently beneficial treatment for patients with JRA with MTX-resistant uveitis and HLA-B27 associated chronic uveitis<sup>4,6</sup>. This may possibly indicate a different cytolytic mechanism. The data, however, are not sufficient to determine the superiority of infliximab over etanercept in the treatment of uveitis.

We believe that discontinuation of etanercept is not necessary in the management of ocular rheumatoid involvement in patients receiving etanercept.

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## Effect of Weather Exposure on Rheumatoid Arthritis

To the Editor:

Patients with arthritis often complain that certain weather conditions, in particular cold and dampness, aggravate their disease symptoms. However, studies on influences of weather on arthritis patients have reported conflicting results. In all studies, the extent to which the participating patients were actually exposed to the weather was not taken into account. This is a serious shortcoming since, except for barometric pressure, considerable differences will often exist between indoor and outdoor conditions. For example, outdoor frost will have little effect on patients staying indoors all day.

As I am myself a patient with rheumatoid arthritis (RA) [since 1979, male, 56 years old, fulfilling the American College of Rheumatology criteria<sup>1</sup>, positive rheumatoid factor (RF)] and live in the marine climate of The Netherlands, I looked for effects of the time I daily spent outdoors on subjective as well as objective variables of my RA. The beneficial effect of the time spent outdoors on joint pain score and erythrocyte sedimentation rate (ESR) has been reported<sup>2</sup>.

Over a period of 4 years (1999–2002), I daily recorded the time I spent outdoors (24 days excepted) and calculated the monthly means (Figure 1A). In addition to being outdoors for longer times, I undertook other measures in attempts to lower the 24 h ambient temperature and humidity: not wearing pyjamas<sup>3</sup>, keeping the bedroom window open<sup>3</sup>, not wearing a coat

outdoors at temperatures above 0°C, and sleeping on a ventilated spring mattress. These measures were all in effect during the study. Blood samples were taken regularly (n = 38, on Wednesdays between 11:00 AM and 12:00 noon) for determination of RF (latex-nephelometry, Figure 1B) and ESR as a measure of disease activity.

Based on the level of the monthly mean time spent outdoors, the study was subdivided into long outdoor periods ( $\geq 2.5$  h, shaded area in Figure 1) and short outdoor periods ( $< 2.5$  h, unshaded). Although at a clinically low level, the RF virtually always decreased during the long periods outdoors, and increased during the short periods (Figure 1). The percentage of change in RF in the interval between 2 successive determinations was negatively correlated with the mean 24 h time spent outdoors during the interval ( $r = -0.44$ ,  $p < 0.01$ ).

During the second half of the study (from January 1, 2001) the RF as well as ESR were negatively correlated with the mean 24 h time spent outdoors in the 4 weeks preceding each determination. The data from 1999 and 2000 were not used for these calculations because the medication was changed twice (horizontal bars in Figure 1C), with subsequent lowering of the ESR. For RF as well as the ESR, the negative correlation was maximal when the data were shifted back in time by 51 days with respect to the time-outdoors data ( $r = -0.57$ ,  $p < 0.01$  for the correlation with RF and with ESR). This indicates that an increase in weather exposure is followed 51 days later on average by a decrease in RF and ESR and vice versa. The similarity in the correlation of the time spent outdoors with the RF and ESR

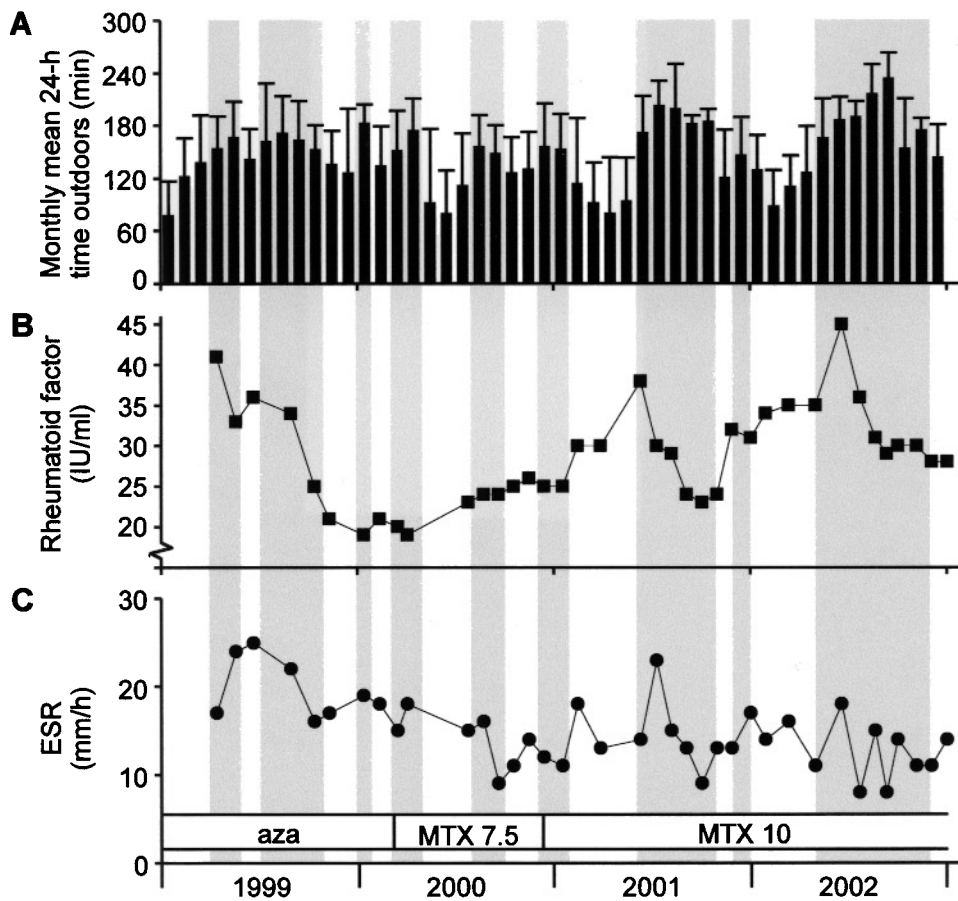


Figure 1. Monthly mean 24 h time outdoors (A), rheumatoid factor (B), and erythrocyte sedimentation rate (C) from January 1, 1999, to December 31, 2002, in a patient with RA. Shading indicates periods with monthly mean 24 h time outdoors  $\geq 2.5$  h. Error bars in A indicate standard SD. Horizontal bars in C indicate medication: azathioprine 125 mg daily (aza), MTX 7.5 mg, later 10 mg, weekly.

supports the conclusion of a recent study that RF concentrations reflect disease activity in RA<sup>4</sup>.

In general, outdoor activities were light (sitting and cycling, in the estimated ratio 1:1). Due to airy clothing with subsequent increased ventilation and cooling of the microclimate close to the skin, being outdoors was often a chilly experience. This observation shows that the beneficial effect of being outdoors is in agreement with the previously reported positive correlation between the meteorological temperature/humidity complex and pain in 88 patients with RA in The Netherlands<sup>5</sup>. The correlation of the RF as well as ESR with variations in weather exposure objectively illustrates linkage between weather and disease activity. Moreover, being outdoors seems to be a way to reduce the disease activity of my RA. The underlying mechanism is unclear. As described<sup>2</sup>, the effect might be related to skin vasoconstriction, or to increased production of cortisol.

For future investigations on weather effects on RA (or other disease), I recommend that the daily duration of weather exposure be taken into account. The results in this study justify similar research on a larger scale and in different climates. If the effects I found on myself can be reproduced in other patients with RA, being outdoors for longer times might be a valuable addition to the treatment of RA.

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### Polymyalgia Rheumatica and Biopsy-Proven Giant Cell Arteritis Exhibit Different HLA-DRB1\* Associations

To the Editor:

Jacobsen et al have confirmed the reported association between HLA-DRB1\*04 alleles and biopsy-proven giant cell arteritis (GCA). Moreover, they also found a lack of significant association between isolated polymyalgia rheumatica (PMR) and HLA-DRB1\*04 alleles in the Scandinavian population<sup>1</sup>.

Perhaps these authors were not aware of our observations reported 4 years ago<sup>2</sup>. In the Lugo region of Northwest Spain, temporal artery biopsy with histological examination is a general procedure for patients presenting with GCA manifestations. In addition, longterm followup of patients diagnosed with isolated PMR, without any clinical feature of GCA, is generally performed. This allows a rigorous distinction between biopsy-proven GCA, associated or not with PMR manifestations, and isolated PMR. In our

series of 86 isolated patients with PMR this condition was associated with HLA-DRB1\*13/14 (previously DR6), although HLA-DRB1\*0401 and \*0404 alleles were marginally increased in frequency compared with controls<sup>2</sup>. Unlike isolated PMR, in our series of 62 cases of biopsy-proven GCA an association with HLA-DRB1\*04 alleles, in particular with \*0401 and \*0404, was observed<sup>2</sup>. This association between GCA and HLA-DRB1\*04 alleles was independent of the presence or absence of associated PMR. Thus, our findings suggest that most of these associations with HLA-DRB1\*04 alleles are primary with biopsy-proven GCA, regardless of co-occurrence of PMR. As with isolated PMR, the associations of HLA with GCA in Northwest Spain were primarily with HLA-DRB1 and not HLA-DQA1 or HLA-DQB1 alleles<sup>2</sup>.

Further studies of our group have underlined the role of HLA-DRB1\*04 alleles as markers of disease severity in biopsy-proven GCA and PMR<sup>3,4</sup>. Indeed, patients with biopsy-proven GCA carrying HLA-DRB1\*04 alleles exhibited a significantly increased risk of ischemic visual manifestations<sup>3</sup>. Also, relapses of PMR in isolated PMR patients were more commonly observed in those carrying HLA-DRB1\*0401 alleles, in particular \*0401<sup>4</sup>. However, both GCA and PMR are polygenic diseases where other genes may play a role in both clinical expression and disease severity<sup>5,6</sup>. Due to this, besides a higher number of patients with biopsy-proven GCA and isolated PMR tested in our studies, the different expression of other genes may explain, at least in part, the differences in terms of disease severity observed between our series and the one of Jacobsen, *et al*<sup>1</sup>.

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### Biological and Clinical Markers of Disease Activity in Ankylosing Spondylitis

To the Editor:

The inflammatory response involved in ankylosing spondylitis (AS) involves special features<sup>1</sup> that distinguish it from other inflammatory rheumatic diseases: preferential location in the entheses<sup>2</sup> (which undergoes ossification) and sacroiliac joints, a prominent role of microorganisms in reactive arthritis, clear genetic predisposition regarding HLA-B27, and

exquisite sensitivity to nonsteroidal antiinflammatory drugs (NSAID). In patients with AS, clinical assessment of disease activity is difficult due, in part, to the relative inaccessibility of the body areas usually involved (i.e., the entheses and other rachial spinal structures) and overall because the correlation between the most frequently used serum markers, nonspecific biological indicators of inflammation<sup>4</sup>, and the activity of the disease are controversial (except in those clinical forms with peripheral involvement). While this has been widely documented<sup>5</sup>, no new biological measures allowing one to accurately discriminate the clinical activity of AS have been reported. Indeed, although some of these various inflammatory mediators may always be present, high concentrations of inflammation mediators are present in only 34–64% of patients with severe disease<sup>6</sup>.

We investigated whether biochemical variables are related to clinical features of disease activity in AS. Forty-two consecutive outpatients fulfilling the modified New York criteria for AS<sup>7</sup> were recruited. A single researcher examined all patients. Disease activity was assessed using visual analog scales (VAS) for night pain (NP), axial pain (AP) as rachialgia that was relieved with motion and increased by resting, and pain/swelling in peripheral joints (PP) during the week prior to the clinical visit. In addition, both the physician and the patients judged disease activity separately. Thus, the disease was considered to be active with a VAS measure  $\geq 40$  mm and inactive otherwise. AP and PP are 2 relevant components of the Bath AS Disease Activity Index (BASDAI)<sup>8,9</sup>.

On the same day, blood samples were collected for the determination of acute phase reactants: erythrocyte sedimentation rate (ESR), platelets, hemoglobin (Hb), serum concentrations of C-reactive protein (CRP), alpha-acid glycoprotein (AAG), and albumin (ALB).

We studied 42 patients (32 men/10 women) with mean age  $40 \pm 12$  years and disease duration  $16 \pm 11$  years. Thirty-six patients were HLA-B27 positive. All had bilateral sacroiliitis. All had axial involvement, either isolated (n = 12) or associated with peripheral involvement (n = 30). In spite of this, we analyzed the 2 groups (axial/mixed) separately, and the differences obtained were not statistically significant.

Comparisons of means between the active and inactive groups are shown in Table 1. Fifteen patients had AP; however, none of their biochemical indicators was significantly different from the patients without AP. Twenty patients had PP/swelling; their mean Hb levels were lower and their mean ESR, platelets, CRP, and AAG levels were significantly higher than in the other patients. Fifteen patients complained of NP; in these, only the mean AAG level ( $127.4 \pm 27.9$  mg/dl) was greater (p = 0.006) than in

those without NP ( $98.6 \pm 24.7$  mg/dl). Thirty patients judged that their disease was active at the time of the consultation; the mean AAG level ( $114.3 \pm 32.3$  mg/dl) was significantly (p = 0.048) higher than in the other 12 individuals ( $95.3 \pm 11.7$  mg/dl). After examining the patients, and in absence of information about their biochemical measures, the physician judged there was active disease in 21 patients; their mean Hb levels were lower and the mean levels of ESR, platelets, CRP, and AAG were significantly higher than in those with inactive disease.

Spearman's rho correlation coefficients between the clinical and biochemical disease activity measures are shown in Table 2.

The inflammatory clinical variables we evaluated (NP, inflammatory spinal pain, and peripheral arthritis) are all considered essential in assessment of clinical activity status in AS<sup>9,10</sup>. Presently, the BASDAI is a good instrument to measure disease activity in AS, but when we began our study it was not frequently used in our clinical practice; for this reason we use VAS to measure certain clinical disease activity variables. We combined the BASDAI components with additional information of special interest in clinical practice, i.e., NP and patient and physician global assessment. Specifically, NP is a good indicator of inflammatory status, as are morning stiffness and CRP serum levels<sup>11</sup>; in addition, NP, inflammatory spinal pain, peripheral arthritis, and the patient's global assessment are some of the specific indicators used for clinical record-keeping by the Assessments in AS Working Group<sup>12</sup>.

In our analysis, we assumed biological markers to be objective indicators, and each clinical symptom of VAS a subjective indicator of disease activity. From our results it follows that the presence of pain (particularly NP or PP) and patient global assessment and physician assessment of the activity status are correlated with the mean increase in AAG levels. Dougados, *et al*<sup>11</sup> also consider NP to be an accurate indicator of inflammation. According to Taylor, *et al*<sup>13</sup>, NP is positively correlated with sacroiliac sclerosis, but negatively with ankylosis. On the other hand, we found assessment of activity status by the physician and PP to be the clinical variable most strongly correlated with the objective biological elements. Our results reveal that PP (a component of BASDAI) is associated with the biochemical markers of inflammation in patients with AS. Similarly, subjective assessments of disease by a physician correlate well with biological markers of disease activity.

The acute phase reactants most frequently used as indicators of inflammatory activity in AS are CRP and ESR. Some investigators have reported increased ESR and CRP values in patients with active AS and markedly

Table 1. Comparisons of means between active and inactive disease groups.

	ESR, mm/h		Platelets, x 1000/ $\mu$ l		Acute Phase Reactants (normal values)				AAG, mg/dl		Albumin, g/dl	
	mean $\pm$ SD	p*	mean $\pm$ SD	p*	Hb, g/dl (12–18g/dl)	CRP, mg/dl (up to 8 mg/dl)	AAG, mg/dl (33–88 mg/dl)	Albumin, g/dl (3.5–5.5 g/dl)	mean $\pm$ SD	p*	mean $\pm$ SD	p*
Axial pain												
Active, n = 15	20.1 $\pm$ 15.6	0.9	276.9 $\pm$ 64.6	0.9	13.2 $\pm$ 2.1	0.30	10.2 $\pm$ 8.3	0.9	109.8 $\pm$ 25.6	0.88	4.1 $\pm$ 0.3	0.9
Inactive, n = 27	21.2 $\pm$ 22.2		263.4 $\pm$ 65.4		14.5 $\pm$ 1.9		11.0 $\pm$ 17.3		108.4 $\pm$ 31.4		4.0 $\pm$ 0.5	
Peripheral pain												
Active, n = 20	30.0 $\pm$ 22.5	0.012	292.5 $\pm$ 70.5	0.038	13.2 $\pm$ 2.3	0.033	16.0 $\pm$ 19.2	0.012	123.0 $\pm$ 28.9	0.012	3.9 $\pm$ 0.5	0.12
Inactive, n = 22	12.4 $\pm$ 12.8		246.2 $\pm$ 50.9		14.8 $\pm$ 1.5		5.9 $\pm$ 5.7		96.0 $\pm$ 23.3		4.2 $\pm$ 0.3	
Night pain												
Active, n = 15	24.4 $\pm$ 22.3	0.70	270.5 $\pm$ 63.4	0.87	13.1 $\pm$ 2.4	0.20	15.4 $\pm$ 21.8	0.30	127.4 $\pm$ 27.9	0.006	3.9 $\pm$ 0.5	0.29
Inactive, n = 27	18.8 $\pm$ 18.6		267.0 $\pm$ 66.5		14.5 $\pm$ 1.7		8.1 $\pm$ 7.8		98.6 $\pm$ 24.7		4.1 $\pm$ 0.4	
Patient assessment												
Active, n = 30	24.1 $\pm$ 21.0	0.30	277.9 $\pm$ 68.0	0.26	13.6 $\pm$ 2.2	0.26	12.6 $\pm$ 16.7	0.35	114.3 $\pm$ 32.0	0.048	4.0 $\pm$ 0.4	0.21
Inactive, n = 12	12.5 $\pm$ 12.8		244.2 $\pm$ 50.0		15.0 $\pm$ 1.4		5.9 $\pm$ 4.9		95.3 $\pm$ 12.0		4.2 $\pm$ 0.4	
Physician assessment												
Active, n = 21	30.6 $\pm$ 22.1	0.003	287.3 $\pm$ 64.0	0.036	12.9 $\pm$ 2.0	0.001	16.3 $\pm$ 18.7	0.002	128.7 $\pm$ 23.8	0.001	3.9 $\pm$ 0.5	0.054
Inactive, n = 21	11.0 $\pm$ 11.2		249.2 $\pm$ 60.9		15.1 $\pm$ 1.4		5.1 $\pm$ 4.5		89.0 $\pm$ 18.7		4.2 $\pm$ 0.3	

\* Legendre and Legendre corrections. ESR: Erythrocyte sedimentation rate; Hb: hemoglobin; CRP: C-reactive protein; AAG: alpha-acid glycoprotein.

Table 2. Correlations between clinical and biochemical disease activity measures.

	Night Pain	Axial Pain	Peripheral Pain	Physician Assessment	Patient Assessment	ESR, mm/h	Platelets, x 1000/ml	Hb, g/dl	CRP, mg/dl	AAG, mg/dl
Axial pain										
rho	0.378									
p	0.014									
Peripheral pain										
rho	0.284	-0.014								
p	0.068	0.929								
Physician assessment										
rho	0.646	0.248	0.572							
p	0.000	0.113	0.000							
Patient assessment										
rho	0.471	0.251	0.603	0.632						
p	0.002	0.108	0.000	0.000						
ESR, mm/h										
rho	0.146	0.058	0.467	0.532	0.279					
p	0.357	0.717	0.002	0.000	0.074					
Platelets, x 1000/ml										
rho	0.059	0.129	0.338	0.328	0.207	0.488				
p	0.708	0.415	0.028	0.034	0.189	0.001				
Hb, g/dl										
rho	-0.262	-0.306	-0.338	-0.556	-0.289	-0.751	-0.429			
p	0.093	0.049	0.028	0.000	0.063	0.000	0.005			
CRP, mg/dl										
rho	0.279	0.144	0.466	0.544	0.246	0.706	0.324	-0.382		
p	0.074	0.365	0.002	0.000	0.117	0.000	0.037	0.012		
AAG, mg/dl										
rho	0.482	0.076	0.500	0.741	0.328	0.639	0.141	-0.417	0.763	
p	0.001	0.633	0.001	0.000	0.034	0.000	0.374	0.006	0.000	
Albumin, g/dl										
rho	-0.259	-0.029	-0.240	-0.346	-0.196	-0.372	-0.282	0.300	-0.378	-0.317
p	0.098	0.857	0.125	0.025	0.214	0.015	0.070	0.054	0.014	0.041

ESR: erythrocyte sedimentation rate; Hb: hemoglobin; CRP: C-reactive protein; AAG: alpha-acid glycoprotein; rho: Spearman's rho correlation coefficient; p: significance level (2-tailed).

increased levels in cases of peripheral arthritis relative to axial forms<sup>14</sup>. By contrast, other authors have found increased ESR and CRP values only in peripheral forms of AS<sup>15,16</sup>. Our results reveal that alpha-acid glycoprotein concentration might be an additional, very useful disease activity marker because of its good correlation with NP, PP, physician assessment, ESR values, and CRP serum levels.

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## Ceiling Effects and the Schober Test

To the Editor:

In patients with ankylosing spondylitis (AS), assessments of restrictions in lumbar range of motion most often measure lumbar flexion, using the Schober test or one of its modifications. Lumbar extension is rarely measured, despite evidence indicating that lumbar extension is restricted earlier in the course of AS than lumbar flexion<sup>1,2</sup>. If extension is restricted before flexion, some patients who have a normal Schober test may have limited spinal extension. These patients may have little ability to demonstrate further improvement in lumbar flexion, but would be able to demonstrate improvement in lumbar range of motion if extension was measured. The inability of a measure to indicate further improvement is known as a ceiling effect<sup>3</sup>. We examined the extent to which measurement of lumbar flexibility was subject to a ceiling effect because these measures included only the Schober test and not measurement of lumbar extension. To do so, we determined the prevalence of restrictions in lumbar extension among patients with AS who had a normal or mildly restricted Schober test.

We measured the Schober test of lumbar flexion and Smythe's test of lumbar extension in 230 patients with AS on their enrollment in a prospective cohort study<sup>4,5</sup>. The Schober test was measured as the increase with forward flexion of a 10-centimeter segment marked on the patient's back with the inferior mark at the level of the posterior superior iliac spines<sup>6</sup>. Smythe's test was recorded as the contraction of three 10-cm segments marked on the patient's back, with the inferior mark at the level of the posterior superior iliac spines, measured while the patient pushed up from a prone position and arched his back<sup>7</sup>. For this analysis, we used the contraction of the lowest 10-cm segment. The mean of 2 attempts of each maneuver was recorded. One rheumatologist (SK) performed 85% of the examinations, and the remainder were performed by a second examiner (MMW).

Twenty patients were examined by both examiners, and intraclass correlations (> 0.80) showed good interobserver agreement.

Of the 230 patients, 22 patients (9.5%; mean age 43.2 ± 11.7 yrs; mean duration of AS 16.1 ± 11.3 yrs; 73% men) had a normal Schober test with an increase of 5.0 cm or more, and 43 patients (18.7%; mean age 42.4 ± 12.6 yrs; mean duration of AS 12.3 ± 11.4 yrs; 70% men) had a Schober test of 4.0–4.9 cm (Table 1). Among 22 patients with a normal Schober test, 2 patients (9%) had markedly limited spinal extension (< 1.5 cm contraction), while an additional 3 patients (13%) had limited extension of lesser degrees. Among 43 patients with a mildly restricted Schober test, 3 (7%) had marked limited spinal extension, and another 25 patients (58%) had limited extension of lesser degrees.

We chose to focus our analysis on contraction of the lower segment of the Smythe test, as this region corresponds with that measured in the Schober test and because it has a greater ability to indicate contraction than the middle or upper segments of the Smythe test. However, extension was also limited in the middle and upper segments of the Smythe test, with contraction of less than 1.5 cm in the upper segment in 5 of the 22 patients with a normal Schober test, and contraction of less than 1.5 cm in the middle segment in 2 of the 22 patients with a normal Schober test.

Our findings support studies that indicate that lumbar extension can be limited in patients with AS who have normal lumbar flexion. This distinction may be present in more than 20% of patients who have a normal Schober test, and in more than one-half of patients with a mildly limited Schober test. In these patients, the Schober test may not be able to detect much further improvement in lumbar flexibility, but improvement could potentially be detected by measuring changes in lumbar extension. In intervention studies, reliance on the Schober test alone may underestimate the effect of treatment in these patients, while measuring both lumbar flexion and extension would provide greater opportunity to detect improvement in lumbar flexibility.

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Table 1. Contraction with lumbar extension of the lowest 10-cm segment of Smythe's test in patients with AS who had a normal Schober test (increase of ≥ 5.0 cm) or mildly restricted Schober test (increase of 4.0–4.9 cm).

	Mean Contraction (Standard deviation)	Median Contraction (Range)	Distribution of Contraction, n (%)			
			< 1.5 cm	1.5–2.9 cm	3.0–3.9 cm	≥ 4.0 cm
Normal Schober test, n = 22	4.0 (1.1)	4.4 (1.0–5.25)	2 (9.1)	1 (4.5)	2 (9.1)	17 (77.3)
Mildly restricted Schober test, n = 43	3.5 (1.1)	3.8 (0–5.0)	3 (7.0)	6 (14.0)	19 (44.2)	15 (34.8)

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## Fibromyalgia and Pramipexole: Promise and Precaution

To the Editor:

Despite 13 years of research after the establishment of criteria<sup>1</sup>, fibromyalgia syndrome (FM) remains difficult to understand and even more difficult to treat effectively. However, 2 articles provide important insight into pathogenesis and lead to a new treatment paradigm involving pramipexole.

First, Moldofsky and colleagues describe FM symptoms in healthy controls after an auditory arousal from stage IV sleep over 4 nights<sup>2</sup>. Second, Yunus and Aldag identified restless legs syndrome (RLS) disproportionately in subjects with FM versus healthy controls (31 % vs 2%, respectively)<sup>3</sup>. Therefore, FM could be the predictable consequence of prolonged and intense stage IV sleep deprivation, but reduction of the arousal (perhaps RLS as one example) was more important than induction of stage IV sleep with antidepressants.

Lorazepam and clonazepam (2 mg qhs) reduce RLS<sup>4</sup>. In a retrospective chart review, they also reduced FM tenderness scores for 82% of 202 patients at 2 weeks<sup>5</sup> and for 62% of 174 patients at one year<sup>6</sup> when added to nighttime antidepressants. By intention-to-treat (ITT) analysis at one year, 54% had  $\geq$  50% decrease in tenderness score using either clonazepam or lorazepam 2 mg qhs.

Pramipexole is a second-generation dopamine 2 (D2) receptor agonist, approved by the US Food and Drug Administration in 1997 for Parkinson's disease, that is remarkably effective treatment for RLS<sup>7</sup>. It has strong affinity for the dopamine 3 receptor subtype in the D2 family, mild affinity for the central alpha-2 adrenoreceptor (target of clonidine), and no affinity for other dopamine, benzodiazepine, norepinephrine, or serotonin receptors.

A retrospective chart review of pramipexole for 166 patients with FM revealed encouraging results<sup>8</sup>. Patients added pramipexole to their best regimen to date and increased by 0.125–0.25 mg weekly, similar to its use for RLS. For those who continued pramipexole for more than 7 days (n = 127), the tenderness score decreased 54% at a mean dose of 1.55 mg qhs for 2–12 months (mean 4 mo). Inefficacy correlated with seeing a psychiatrist (p < 0.05, chi-square test), but not with age, pretreatment tenderness score, or disability. Twenty-three percent quickly discontinued for non-serious intolerances, usually nausea or anxiety. There were no serious adverse events even with doses up to 6.0 mg qhs. By ITT analysis (n = 166), 58% achieved  $\geq$  50% decrease in tenderness score, even though 22 (13%) discontinued pramipexole before they could be evaluated. Other measures of FM activity were not collected. Further, for 19 patients unresponsive or intolerant to pramipexole, ITT analysis showed that 74% achieved  $\geq$  50% decreased tenderness score after adding the other known dopamine 3-specific agonist, ropinirole, for a mean of 4 months<sup>9</sup>. Unfortunately, 13 of 19 also eventually discontinued for non-serious intolerances, especially nausea.

Since then, a strategy to decrease gastrointestinal intolerance has been very helpful. Of 89 consecutive patients given pramipexole scheduled to increase by 0.25 mg weekly to 2.0 mg qhs, 57 (75%) noted some nausea when interviewed at 3 weeks (0.75 mg dose). However, 39 of 57 continued treatment and controlled nausea by using one of 4 branded proton pump inhibitors (PPI) qhs at supratherapeutic doses (3 tablets). Of 16 who discontinued pramipexole, 8 refused the PPI and 6 took < 3 tablets qhs. Diarrhea and other PPI intolerances were infrequent. At 8 weeks (pramipexole 2.0 mg qhs), PPI use was not different from pretreatment use (16% vs 15%, respectively). Individual PPI success was unpredictable, ranging from 33% to 54%.

Finally, much higher pramipexole doses have been prescribed, as the most therapeutic dosage for FM appears to be 4.5 mg qhs achieved over 12

weeks. With careful monitoring, doses have been increased up to 10.5 mg qhs in select, previously injured, narcotic-dependent patients. A retrospective chart review of usual clinical practice for consecutive patients taking  $\geq$  2.25 mg qhs (2.25–10.5 mg qhs) revealed 195 patients taking a mean dose of 4.2 mg for 7.6 months (range 2–25 mo). Patients discontinued because of cost (0.5%), inefficacy (5%), and intolerance (4%), including nausea (1.6%), daytime somnolence (1.1%), anxiety (0.8%), headache (0.2%), and dizziness (0.2%). Certainly, more patients had intolerances, but discontinuation rates were unexpectedly low, possibly because the patients were a select group (already tolerating  $\geq$  2.25 mg qhs) or because the efficacy of pramipexole outweighed the degree of intolerance.

In summary, pramipexole may become an important option for patients with FM, but further studies are required to confirm these results and improve its application. Nevertheless, manipulating dopamine-related central nervous system regulatory mechanisms must be gradual, and initial nausea prevented whenever possible. These preliminary safety data are incomplete, but to date, there are no published data at single pramipexole doses > 2.25 mg for any condition. Until more sophisticated, randomized, blinded, placebo-controlled studies are completed, these data may illustrate potential benefits and important precautions when considering pramipexole for FM.

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## Book review

### Skeletal Muscle Pathology, Diagnosis and Management of Disease

Victor Preedy and Timothy Peters, Editors, Greenwich Medical Media: London, 2002, 716 pages, price \$199.00 US.

This is a multiauthor, up-to-date review of the different skeletal muscle disorders. The book brings together several investigators, 100 in total, with

expertise and research focus in the various aspects of muscle disease. The text is, on the whole, well written, richly illustrated and thoroughly documented. The book is divided into 58 chapters covering a medley of diagnostic studies (including biochemical markers, histological, ultrastructural, histochemical and immunohistochemical assessment of muscle biopsies, electrophysiologic studies, skeletal muscle imaging, and assessment of muscle function by isometric tests) and the various skeletal muscle diseases (including mechanism of muscle pain, inflammatory myositis, genetic and congenital myopathies, metabolic diseases, infections, and muscle injuries). The chapters on steroid misuse in athletes, alcoholic myopathy, HIV myopathy, inclusion body myositis, AMP deaminase (myoadenylate deaminase) deficiency, biochemical markers of skeletal muscle disease, and immunomodulation in skeletal muscle disease are of particular interest.

It would have been useful to include an introductory section outlining the book's theme and objectives, a broad classification of muscle disorders in children and adults, and a chapter dedicated to the structure, metabolism, physiology and function of normal skeletal muscle.

In the chapter on inflammatory myositis (a better term than "inflammatory myopathies"), the clinical presentation, natural history, prognosis, pathogenesis, diagnostic studies, myositis-specific antibodies and differential diagnosis of proximal muscle weakness and of elevated serum creatine phosphokinase are briefly discussed; to be truly useful to the clinician, however, these require further expansion. The question of management was not addressed. Another concern is the duplication of related chapters, (e.g., chapters 34 and 42, and 19 and 54), which could have been combined into single, cohesive, comprehensive sections.

Notwithstanding these caveats and inequities of content, *Skeletal Muscle Pathology* is a useful, well researched reference textbook. Its greatest strength lies in the quality of some individual chapters. The book provides a valuable, user friendly, easy-to-read resource, not only for pathologists but also for rheumatologists, neurologists, internists, pediatricians, and physiatrists.

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## Correction

Minh Hoa TT, Damarwan J, Shun Le C, et al. Prevalence of the rheumatic diseases in urban Vietnam: a WHO-ILAR COPCORD study. *J Rheumatol* 2003;30:2252-6. The second and third authors' names are John Darmawan and Shun Le Chen, respectively. We regret the error.