INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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Renal Amyloidosis in Rheumatoid Arthritis

To the Editor:

Dr. Uda, *et al* reported 2 distinct clinical courses of renal AA amyloidosis in patients with rheumatoid arthritis (RA)[1]. Their findings are of considerable interest; however, a few comments regarding the selection of patients and the authors' conclusions may be important. The authors performed duodenal biopsy in patients with RA who did not present with renal manifestations. Those patients who had positive duodenal biopsies for amyloidosis had renal biopsies. Those who were positive for amyloid renal biopsies have been followed for up to 5 years and the survival was estimated. According to the authors, 53 of 524 patients with RA (~10%) had renal biopsies positive for amyloid. Thirty-eight of 53 patients (72%) were followed up. In the abstract, the authors stated that in 27 patients, amyloid was found exclusively in the glomeruli, and in 11, in the blood vessels only. However, in the Results section (page 1483, last paragraph on the left) they stated that among 27 patients, the amyloid was exclusively found in the glomeruli in 7 cases only, and in the other 20, a mixed pattern (glomerular/vascular) was found. This statement seems to contradict the abstract. In Figure 3, it was not clear whether the curves apply to 7 and 11 patients or to 27 and 11. If the curves apply to 7 and 11 patients, then another (third) curve showing a mixed pattern in 20 patients would be appropriate.

It would be of interest to know if some control patients with RA with negative duodenal biopsy had renal biopsy. AA amyloid does not necessarily have to be present simultaneously in the duodenum and the kidney.

It would also be appropriate to state in the Methods what was the minimal number of glomeruli in the biopsy that the authors considered sufficient for diagnosis. Nephropathologists require minimum of 5 or even 10 glomeruli for correct diagnosis. Regarding the diagnosis of AA amyloid, it would be of interest to stain renal biopsies for kappa, lambda, and immunoglobulin chains and to do serum immunofixation electrophoresis, since in some cases mixed AL and AA amyloidosis can be present. Finally, perhaps in some patients, renal biopsies were performed at the end of the followup. If so, it would be of interest to know whether the initial pattern persisted.

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Dr. Saiki replies

To the Editor:

We thank Prof. Pruzanski for his kind comments on our report about renal amyloidosis in patients with RA.

As written in our abstract, we followed 38 patients with renal amyloidosis, and in 27 patients amyloid deposition was found exclusively in the glomerulus (type 1) and in 11 in the blood vessels only (type 2). However, in the Results we stated that among 27 patients the amyloid was "exclusively" found in the glomeruli in 7 cases only, as suggested by the comment. The word "exclusively" was inadequate and we should have used "selectively" in its place. That is why the statement is not contradicting the abstract.

Of 27 patients with type 1 who had amyloid in the glomerulus, 20 had amyloid deposition in the blood vessels simultaneously, but the other 7 had no amyloid deposition in the blood vessels. Therefore, in Figure 3, the survival curves apply to 27 patients with glomerular involvement (type 1) and 11 without glomerular involvement (type 2).

We also agree that it would be of interest to know if some control patients with RA and negative duodenal biopsy have renal amyloidosis. In our center, however, it was not easy to carry out renal biopsy in all patients with RA who had no renal involvement.

We are sorry for not stating the number of glomeruli in the biopsy. We examined more than 10 glomeruli for the diagnosis of type 1, but more than 20 glomeruli were examined for type 2. In the text, we show few glomeruli because of space limitations.

In some cases we stained renal biopsies for kappa, lambda, and immunoglobulin chains, but we found no case of mixed AL and AA amyloidosis.

We also examined renal biopsy at the end of the followup study, especially in the patients with type 2 disease. We are now preparing a manuscript describing these results.

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Seasonal Variations in Onset of Wegener's Granulomatosis: Increased in Summer?

To the Editor:

We read with interest the article by Mahr, *et al* reporting an excess of Wegener's granulomatosis (WG) presenting in summer months[1]. This contrasts with several previous reports of a winter predominance. The preponderance of onset of WG in the winter and reported cyclical fluctuations in incidence has led to the hypothesis that an infection may trigger disease. Possible explanations for the observed differences between studies include: a real heterogeneity in trigger factors between geographical areas; methodological discrepancies including case ascertainment; and the uncertainty in establishing an accurate date of onset of the disease process.

As part of an epidemiological study of primary systemic vasculitis, investigating possible environmental factors involved in pathogenesis, we

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reviewed all patients diagnosed with WG (American College of Rheumatology 1990 criteria) within a well-defined population[2,3]. The date of the first symptom of WG and the date of diagnosis were established for 55 patients with WG diagnosed between January 1989 and July 2000 by case-note review and interview of 47 surviving patients. Details of the 51 patients whose symptoms of vasculitis began between January 1989 and December 1998 only were included in analysis to optimize case ascertainment, which could otherwise be underestimated due to delay between first symptom and diagnosis. Details of the annual fluctuation of influenza, mycoplasma pneumonia, parvovirus, and chlamydia for the Eastern Region of the UK were obtained from the public health laboratory services. Annual fluctuations in each infection were compared to annual fluctuations in the onset of WG using the Poisson distribution. Seasonal fluctuations were assessed by the chi-square test where seasons were defined as winter (December–February), spring (March–May), summer (June–August), and autumn (September–November).

There was a nonsignificant trend ($p < 0.5$) towards a higher onset of WG in autumn (35.3% cases), winter (25.5%), and spring (23.5%), with a trough in summer (15.7%). Findings were similar for 37 patients diagnosed with microscopic polyangiitis ($p < 0.1$) or Churg-Strauss syndrome ($p > 0.5$). We also failed to find any significant associations between the first symptom of vasculitis and season of onset, although it was interesting to note a high number of patients whose first manifestation of vasculitis were ear, nose, and throat symptoms presented in November, December, and January. There were also no significant annual peaks or troughs in the onset of WG, microscopic polyangiitis, or Churg-Strauss syndrome, and annual fluctuations in infection rates did not correspond with nonsignificant fluctuations in vasculitis.

Thus, in a well-defined population we have been unable to confirm the occurrence of a seasonal onset for WG or other types of primary systemic vasculitis. Unfortunately, although analysis of temporal variations in the onset of vasculitis offers a tantalizing insight into potential pathogenic trigger factors, studies are limited by methodological problems, especially full case ascertainment within well-defined populations, difficulty in establishing the actual onset of vasculitis, and small numbers of cases.

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Dr. Mahr, *et al* reply

To the Editor:

Lane, *et al* raise a number of methodological concerns inherent to the study of seasonality in the onset of Wegener's granulomatosis (WG); most of these issues were also discussed in our article. Although complex to study, this question merits examination for several reasons, including the need to address the hypothesis that WG preferentially starts during the winter. Notably, one of the first surveys to provide "evidence for a seasonal variation in the onset of symptoms (highest in winter)" was based on the same background population, and an extensively overlapping observation period (1988–94)[1], as those for the data given in Lane's letter that no longer support the initial finding.

Our study was designed to bypass as much as possible the methodological pitfalls to which Lane, *et al* refer. As opposed to their now reported investigation, our study was entirely devoted to the assessment of the season of disease onset. Patient interviews took place at most 4 years after diagnosis of WG to attempt to accurately discern its season of onset. We acknowledge that, similar to Lane's study, our results may have suffered from statistical fluctuation due to the small sample size. Conversely, we respectfully disagree with the implication that investigating seasonality of WG onset requires a population-based study design. That reasoning would imply that patients seen at a referral center or participating in a clinical trial are non-random with respect to the season of disease onset, an assumption that appears unlikely, both in general and in the setting of our specific study.

The conflicting findings of our, Lane's, and another recently published study[2] add to the uncertainty about whether the onset of WG is influenced by a particular seasonal pattern. However, we may have to wait for more data on WG epidemiology to decide if these divergent conclusions are solely attributable to methodological flaws.

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Preanalytical Biases in Measurement of Matrix Metalloproteinases and Their Tissue Inhibitors in Peripheral Blood

To the Editor:

Fiedorczyk, *et al*[1] recently analyzed serum concentrations of the matrix metalloproteinases (MMP) MMP-1, MMP-3, MMP-9, and MMP-13 and their tissue inhibitors (TIMP) TIMP-1 and TIMP-2 in patients with early rheumatoid arthritis (RA) before and after treatment with methotrexate. They found elevated concentrations in comparison with patients with osteoarthritis and reduced levels and ratios of MMP to TIMP after therapy. Since these results strongly correlated with clinical signs of disease activity and laboratory data such as C-reactive protein, the authors concluded that the determination of serum MMP and TIMP would be helpful to characterize the disease activity of RA. In previous reports, the authors also used serum as samples for the measurements of MMP and TIMP[2,3], but did not clearly describe what type of collection system, either with or without clot activator, they used. On the other hand, the influence of the kind of blood sample, either collected as serum with or without clot activator or as plasma with different types of anticoagulants like heparin, citrate, or EDTA, on the measurement of these analytes was discussed in detail in analytical and clinical journals[4-9]. As yet no information on the effect of

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blood sampling on circulating MMP-1 and MMP-3 is available in the literature. However, since the reasons for that effect do not seem to be restricted to only MMP-9 and TIMP-1, I believe the clinical readership should be aware of that general problem. I should like to demonstrate it by summarizing some of my own experiments.

Briefly, blood samples from 8–10 healthy adults were simultaneously prepared in plastic tubes (Monovette Systems, Sarstedt GmbH, Nümbrecht, Germany) without additives or with kaolin-coated plastic granulate as coagulation accelerator to prepare native serum or serum after enhanced coagulation and in respective devices coated with lithium heparin to obtain plasma. Within 30 min after venipuncture, the blood samples were centrifuged at 1600 × g for 15 min; the collected supernatants were recentrifuged and stored at –80°C until analysis. ELISA kits from Amersham (Little Chalfont, Buckinghamshire, UK) were used for the measurements of MMP-1, MMP-3, TIMP-1, and TIMP-2; MMP-9 was determined with a kit from Medac Diagnostika, Wedel, Germany.

Data are summarized in Figure 1. The following conclusions can be drawn: (1) Concentrations of MMP-1, MMP-3, MMP-9, and TIMP-1 are several-fold higher in serum than in plasma (means of 6 for MMP-1, 2.3 for MMP-3, 5.3 and 20.3 for MMP-9, and 6.9 for TIMP-1). (2) Serum samples collected with clot activator as the conventional way to prepare serum for routine use show higher concentrations of MMP, for example, MMP-9.

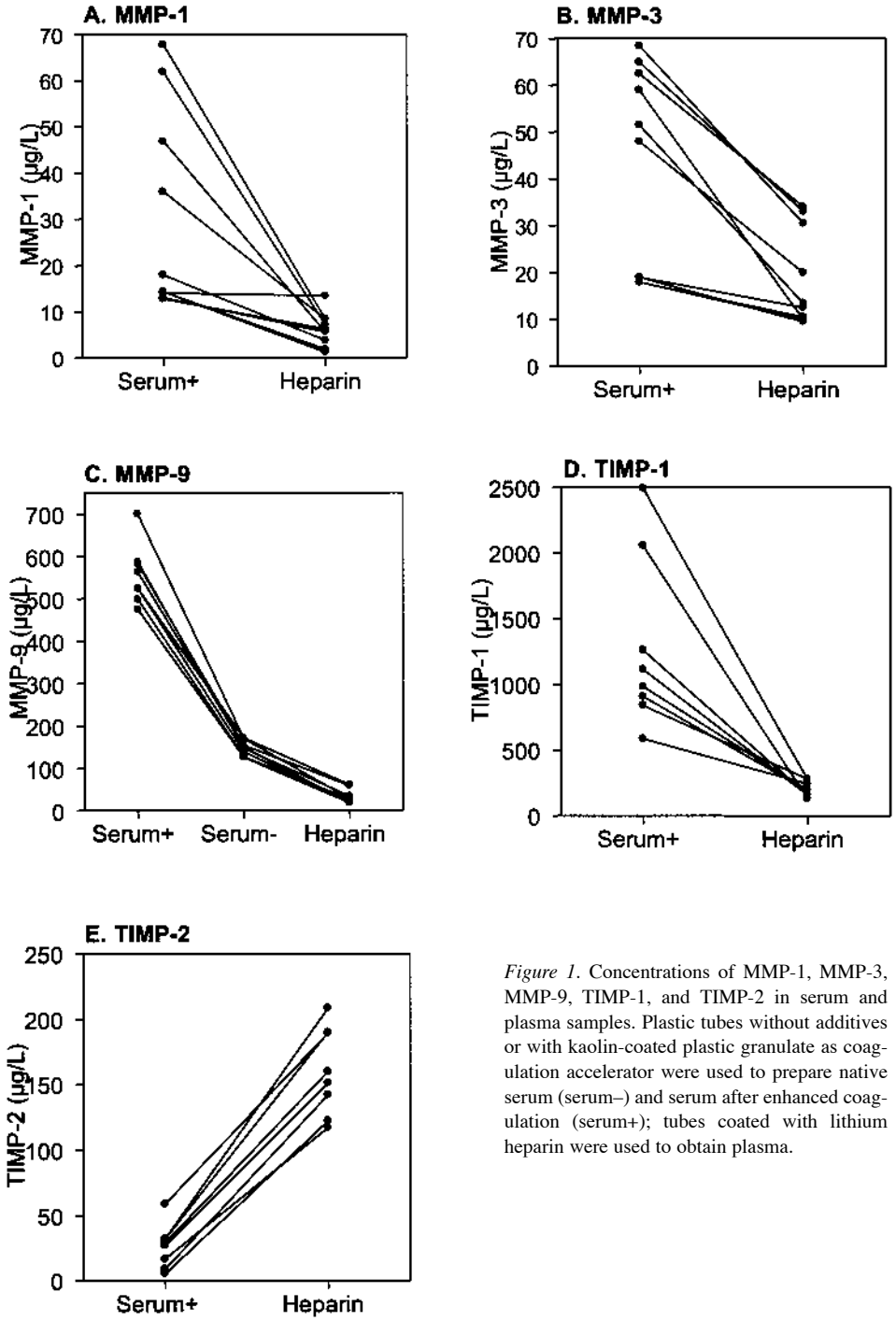

Figure 1. Concentrations of MMP-1, MMP-3, MMP-9, TIMP-1, and TIMP-2 in serum and plasma samples. Plastic tubes without additives or with kaolin-coated plastic granulate as coagulation accelerator were used to prepare native serum (serum–) and serum after enhanced coagulation (serum+); tubes coated with lithium heparin were used to obtain plasma.

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(3) In contrast, TIMP-2 concentrations are about 9-fold higher measured in heparin plasma than in serum.

The reason for these different concentrations of MMP-1, MMP-3, MMP-9, and TIMP-1 in serum and plasma is very likely the variable release of these components from platelets and leukocytes depending on the different blood collection procedures, as these blood cells contain high concentrations of these analytes[7]. TIMP-2 increased with increasing heparin concentration, probably because of the interaction of heparin with the proMMP-2-TIMP-2-complex[5].

These data illustrate the problem: to measure true concentrations of MMP and TIMP in peripheral blood and to come to trustworthy conclusions with samples collected under different conditions. Recently, citrate has been suggested to be the best anticoagulant to prepare blood samples for measuring MMP-2 and MMP-9 in peripheral blood[6,8], while recommendations for TIMP and other MMP have not been provided yet. However, the high unspecific background found in serum due to the release of the MMP or TIMP from blood cells during sample preparation may hamper the actual diagnostic or prognostic information of MMP and TIMP. Since white blood cell count and release of the analytes from blood cells may additionally change during treatment[10], the usefulness of MMP and TIMP as monitoring markers may be rather limited, despite a consistent use of serum collected under identical conditions.

Thus, the clinician should be aware of these preanalytical pitfalls to avoid misinterpretation of data when MMP and TIMP should be used for clinical purposes.

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Dr. Fiedorczyk, *et al* reply

To the Editor:

We agree with Jung that several factors may influence measurements of matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) in peripheral blood. Therefore our assessments were performed always under the same conditions. Blood specimens were clotted for 30 minutes without clot activator, and then centrifuged for 5 minutes at 2000 × g. Serum aliquots were frozen at –80°C immediately after sample collection. Aliquots for the serum MMP and TIMP measurements were thawed only once. The analysis of serum concentrations of MMP-1, MMP-3, MMP-9, MMP-13, TIMP-1, and TIMP-2 was based on a quantitative sandwich ELISA (Amersham Biosciences UK, Little Chalfont, Buckinghamshire, UK) strictly according to the manufacturer's instructions.

In our patients white blood cell count before and after methotrexate treatment did not change significantly. Therefore we presume that possible release of the MMP or TIMP from white blood cells during sample preparation could not significantly hamper prognostic information of MMP and TIMP. However, we agree with Jung that interpretation of serum MMP and TIMP measurements should be performed with special caution.

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Interleukin 1 Receptor Antagonist Therapy-Induced Thrombocytopenia in Adult Onset Still's Disease

To the Editor:

Anakinra is a recombinant nonglycosylated form of the human interleukin 1 receptor antagonist (IL-1Ra) that prevents IL-1 signaling[1-3]. It has been proposed as an effective and safe treatment for adult onset Still's disease (AOSD) refractory to standard therapy[4,5].

We describe a 57-year-old man with AOSD[6] characterized by fever, sore throat, pleuritis, pericarditis, nonerosive arthritis, splenomegaly, and aminotransferase elevation at onset (January 2004), who was treated with high-dose steroids (1 mg/kg/day), slowly tapered to low doses (prednisone 5 mg/day) and then suspended in 6 months, and methotrexate (MTX) 20 mg/week, achieving a complete remission. The disease then relapsed in September 2005, after a 9-month period of remission. He was treated with adalimumab 40 mg every other week and MTX 15 mg/week for 6 months,

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with improvement but without achieving a complete clinical and laboratory remission. After 6 months the disease relapsed with fever, arthritis, and aminotransferase elevation and a marked increase of C-reactive protein (306.7 mg/l; normal value 0–5 mg/l), serum ferritin level (3645 μg/l; normal 27–300 μg/l), and erythrocyte sedimentation rate (79 mm/h; normal 1-15 mm/h).

Anakinra 100 mg/day without MTX (discontinued due to aminotransferase elevation) was initiated with prednisone 0.5 mg/kg/day, tapered to 0.3 mg/kg/day in 15 days. Two weeks after the first anakinra administration, while the disease was responding to the treatment, the platelet count started to decrease from 250,000/mm^3 (baseline) to 127,000/mm^3 and to 100,000/mm^3 (the platelet count was confirmed also in citrate tube to exclude pseudothrombocytopenia) after 8 and 10 days from baseline, respectively (Figure 1). Disseminated intravascular coagulation, which can rarely complicate the course of AOSD, was excluded through laboratory test and peripheral blood smear analysis. Antiphospholipid and antiplatelet antibodies were absent. No clinical or laboratory evidence of recent infection was noticed. He was taking no other drugs except prednisone and anakinra. Anakinra was stopped, and the steroid dose was left unchanged (0.3 mg/kg/day). Platelet count remained stable and then increased to 145,000/mm^3 6 days after anakinra discontinuation. Afterwards, steroids were increased to 0.5 mg/kg/day to prevent flare (Figure 1). Platelet count was 235,000/mm^3 at the last followup, 11 days after anakinra discontinuation.

This is the first case of AOSD in which the patient experienced thrombocytopenia under IL-1Ra treatment. Our case highlights an uncommon side effect related to IL-1Ra therapy, potentially leading to treatment dropout. An observational study in 146 patients with rheumatoid arthritis reported only one episode of thrombocytopenia related to IL-1Ra treatment, where thrombocytopenia resolved soon after IL-1Ra discontinuation[7]. In our case there was a temporal relationship between institution of anakinra and development of thrombocytopenia, even if the causality was not confirmed by a rechallenge. However, discontinuation of IL-1Ra, without increasing the steroid dose, led to rapid increase of the platelet count. The putative mechanism involved in the IL-1Ra–related thrombocytopenia might be the inhibition of megakaryocytopoiesis, where IL-1 seems to play a central role together with other cytokines[8]. However, an idiosyncratic reaction may likely be the cause, as suggested for the thrombocytopenia rarely induced by tumor necrosis factor-α blocking[9].

Thrombocytopenia is a rare side effect related to IL-1 blockade. The short drug half-life could explain the rapid resolution after drug interruption. Based on previous experience[7], the anakinra rechallenge is not advisable in our opinion. Since thrombocytopenia in AOSD may represent a diagnostic and clinical challenge due to several possible causes, and since anakinra seems very promising in AOSD, this possible drug side effect deserves particular attention. We also suggest that patients' hematological measures should be known and then strictly monitored before and after starting anakinra treatment.

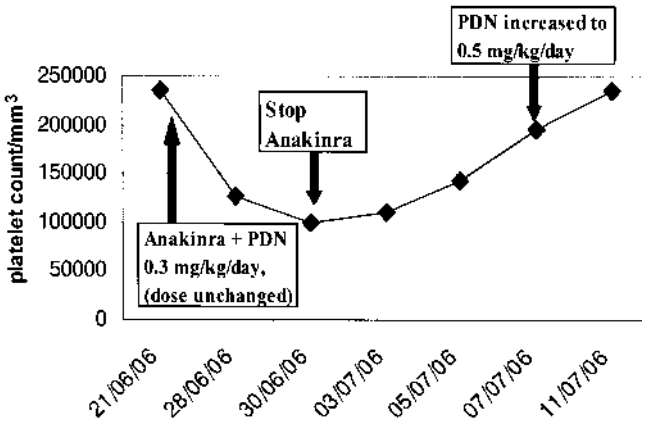

Figure 1. Platelet count course. PDN: prednisone.

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Systemic Lupus Erythematosus with Major Organ Involvement in a Patient with Systemic-Onset Juvenile Idiopathic Arthritis

To the Editor:

Our patient, now 18 years old, presented initially as an 11-year-old girl with high-grade quotidian fever, sore throat, and bilateral symmetrical polyarthritis along with cervical spine involvement. Based on her presentations and supported by investigations [including rheumatoid factor and antinuclear antibodies (ANA), both of which were negative], a diagnosis of systemic-onset juvenile idiopathic arthritis (JIA) was made. She was treated with nonsteroidal antiinflammatory drugs, oral corticosteroids, and methotrexate with which her fever subsided in 2 months; however, arthritis continued later, resulting in deformity of the right little finger along with ankylosis of the right wrist joint. After one year, she went into remission and remained so for the next 6 years, when there was recurrence of fever accompanied by maculopapular erythematous rash. Over the following few months, she developed pedal edema with periorbital puffiness. There was

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no history of hematuria, oliguria, nocturia, frequency of micturition, or frothy urine. Examination revealed moderate pallor and solitary, nontender left axillary lymph node. Systemic examination was normal. Arthritis resolved, although there was limitation of movement of temporomandibular joints, cervical spine, and wrists. Investigations revealed anemia [hemoglobin 8.1 g/dl, lymphopenia (980/μl), and hypoalbuminemia (2.1 g/dl)]. Serum creatinine and liver function tests were normal. However, urinalysis showed proteinuria (2+), leukocytes (5–6/hpf) with hyaline and granular casts; 24 h urinary protein was 540 mg. Abdominal fat-pad evaluation for amyloid was negative. In view of recent problems, the possibility of lupus was considered, and ANA was found to be 4+ speckled with rim pattern. Diagnosis of lupus was further supported by markedly raised anti-dsDNA antibody (336.4 IU/dl), low C3 (26.4 mg/dl) and C4 (< 5.4 mg/dl), and C-reactive protein (0.79 mg/dl). She was treated with immunosuppressive drugs, with which she has improved. Later she developed neuropsychiatric manifestations, which were managed successfully with antidepressants and immunosuppressive drugs.

There are few case reports of patients initially diagnosed with JIA but later developing features of lupus on followup[1-3]. Ragsdale, *et al*[3] described 10 patients with juvenile rheumatoid arthritis (JRA) who developed clinical manifestations of systemic lupus erythematosus (SLE) in 2.5 to 21 years. Itzkowitch, *et al*[4] reported 2 patients with features of SLE, scleroderma, and JRA. Martini, *et al*[5] described a girl who presented at 5 years of age with Jaccoud's arthropathy, developing typical symptoms of SLE at the age of 11.

However, systemic-onset JIA and SLE occurring in the same patient is rare. Our patient developed systemic-onset JIA at the age of 11 years; this diagnosis was made after ruling out other conditions including lupus (ANA was negative), and supported by the presence of cervical and wrist joint fusion. Six years later, she developed typical clinical and serological evidences of lupus including seroconversion from an ANA-negative to ANA-positive state, high-titer anti-dsDNA antibody positivity, and nephritis. Therefore, there may an important subgroup of patients with JIA who ultimately go on to develop connective tissue diseases. At onset, there is little to distinguish these patients from other children with JIA[4]; chronic arthritis develops in all and is not different from that seen in JIA; onset of SLE follows a flare of arthritis, development of serositis, fever, and rash. A high index of suspicion is necessary when a patient diagnosed with systemic-onset JIA has recurrence of symptoms so that diagnoses like SLE are not missed.

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The Impact of IL-1Ra and MBL Gene Polymorphisms on Joint Damage After 5 and 10 Years in Patients with Early Rheumatoid Arthritis

To the Editor:

Most studies investigating the relationship between genetic markers and susceptibility and severity of rheumatoid arthritis (RA) have so far focused on HLA-DRB1 gene polymorphism[1]. Apart from those of the HLA system, candidate genes suggested to be of prognostic value are those encoding for mannan-binding lectin (MBL) and interleukin 1 receptor antagonist (IL-1Ra). However, previous studies have not been conclusive[2-7].

The *IL-1Ra* gene is located on chromosome 2 as a part of the *IL-1* gene complex. A variable-length polymorphism in intron 2 of the *IL-1Ra* gene caused by a variable number of an 86-base pair tandem repeat stretch of DNA has been described[6]. There are 5 different alleles but allele 1, consisting of 4 copies of the repeat sequences (IL-1RN*1) and allele 2, consisting of 2 repeats (IL-1RN*2) are most common.

MBL is derived from a single gene on chromosome 10 (*MBL-2*). Three structural mutations are found within exon 1 of the *MBL* gene. The normal MBL allele is commonly named A, and the mutant alleles (B, C, and D) are often pooled as 0[5,7]. MBL expression is also influenced by promoter polymorphisms upstream of the gene (H/L allele) and (X/Y allele).

We investigated the impact of IL-1Ra and MBL gene polymorphisms on progression of joint damage during the first 10 years in an early RA cohort.

In total, 183 patients with RA and disease duration less than 2 years were enrolled in a prospective study in 1985-1989[8]. Of these, 148 patients (49 men and 99 women) included in our study were available for DNA analysis and radiographic examinations. All were Caucasians. The mean age and disease duration at inclusion were 50.6 years and 11.1 months, respectively. Seventy-two percent were rheumatoid factor positive. There were no significant differences in any disease state variable at study start between cohort patients included or not. During the study time patients with active disease were offered treatment with disease modifying antirheumatic drugs: in the early years mostly D-penicillamine or antimalarials and in the last years mostly methotrexate.

Controls consisted of 200 blood donors (100 women and 100 men). Approval from the Ethical Review Board at Lund University (LU 525-02) and informed consent from each patient were obtained. The radiographic changes in hands and feet at inclusion and after 5 and 10 years were evaluated according to Larsen, *et al*[9]. Larsen scores [median (range)] at inclusion, 5 and 10 years were 6 (0–42), 43 (0–152), and 52 (0–162), respectively. The differences were significant ($p < 0.001$, Wilcoxon's test for paired data).

Gene polymorphisms were determined using polymerase chain reaction as described[10]. Distribution of allotypes was in concordance with Hardy-Weinberg expectations in both patients and controls. The frequencies of different alleles did not differ between patients and controls.

IL1-Ra gene polymorphisms and MBL gene polymorphisms were not related.

The correlations between different alleles and radiographic changes dichotomized at the 3rd quartile for the group were analyzed.

Patients carrying at least one IL-1RN*2 allele had a significantly higher risk to develop the worst radiographic changes (Table 1). The number of patients homozygous for allele IL-1RN*2 were too few (n = 8) to allow a separate analysis. The stratification of patients as MBL-deficient and MBL-sufficient was done according to MBL genotype (Table 2)[7]. MBL genotypes were not linked to radiographic outcome.

Our main finding was that patients carrying the allele IL-1RN*2 showed the most pronounced joint damage progression during the first 10 years. This finding might have practical implications as only about 40% of the patients carried the risk factor. In contrast, some other possible predictive factors such as shared epitope or rheumatoid factor are present in the majority of patients with RA[1].

The mechanism explaining association between allele IL-1RN*2 and joint damage in RA is unknown. Our finding is probably not directly relat-

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Table 1. Carriage rate of IL-1RN*1 and IL-1RN*2 alleles in patients with early RA and controls. Patients carrying allele 2 (IL-1RN*2) had significantly higher risk to develop extensive radiographic changes (Larsen score ≥ 75% for the group; ≥ 62 and ≥ 80, respectively).

Carriage rate	RA (N = 148)	Controls (N = 200)	p
IL-1RN*1	140/148 (95%)	184/200 (92%)	NS
IL-1RN*2	64/148 (43%)	88/200 (44%)	NS

Odds ratio (955 CI) to develop most extensive radiographic changes (Larsen score ≥ 75% for the group; ≥ 62 and ≥ 80, respectively) for patients carrying allele 2 (IL1RN*2)

	OR	95% CI
5 yrs	2.5	1.2–5.4
10 yrs	2.4	1.1–5.0

NS: nonsignificant.

Table 2. Distribution of MBL genotypes in the early RA cohort and controls.

	MBL Genotype*	Patients** (n = 147)	Controls (n = 200)	p
MBL-sufficient genotypes	A/A	79 (54%)	116 (58%)	NS
	YA/0	44 (20%)	56 (28%)	NS
MBL-deficient genotypes	XA/0	18 (12%)	14 (7%)	NS
	0/0	6 (4%)	14 (&%)	NS

* The normal (wild type) MBL allele is called A, the structural gene mutant alleles B, C, and D are referred to as 0. X/Y allele = promoter polymorphisms upstream of the gene at position-221. ** Data for one of the 148 patients is missing.

ed to the encoded gene product (IL-1Ra) as there is no established relationship between IL-1RN genotypes and IL-1Ra levels in serum[2,3]. A more likely explanation is linkage disequilibrium with as yet unknown promoter variants in the *IL-1* gene complex responsible for the observed differences in joint damage progression.

Our findings are in contrast to some other studies[2,3]. One explanation for the diverging results may be different radiographic scoring methods. MBL genotypes conferring MBL deficiency were not found to be a risk factor for worse outcome. This is in accordance with a study where appearance of erosive changes after 5 years was evaluated[5]. By contrast, a Danish study has reported an association between MBL gene polymorphism and radiographic progression after the first year in patients with early polyarthritis[4]. A different study population may have contributed to the conflicting result.

In conclusion, our findings suggest an association between IL-1Ra gene polymorphism but not MBL gene polymorphism and development of joint damage in RA.

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Obituary for an Organization

To the Editor:

The American Rheumatism Association (ARA) was founded in the 1930s, and its initial meetings featured many clinical papers. By the 1970s, scientific papers predominated, and from a few hundred attendees, the organization drew thousands from all over the world, and became the preeminent rheumatologic association. In fact, a subspecialty board in rheumatology was added to the other subspecialties of internal medicine.

Through the agency of Dr. Sanford Roth, and the late Dr. John Harter of the Food and Drug Administration (FDA), informal get-togethers were held in Phoenix, Arizona. Dr. Roth decided to formalize these meetings, bringing together rheumatologists, FDA officers, regulatory personnel from abroad, and representatives from the pharmaceutical industry for an exchange of ideas, and so the International Society for Rheumatic Therapy

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(ISRT) met for the first time in 1988, in Dr. Roth's home town, Phoenix. Thereafter, the meetings were held every other year, alternating between the United States and foreign cities.

Frank Dudley Hart and Andrei Calin chaired the next meeting, in London in 1990, and brought together FDA and European regulators to discuss guidelines for therapeutic trials. The long doldrums that had afflicted rheumatology, with few new advances in therapeutics, were at an end, and ISRT's clinical emphases, especially the rules for clinical trials, were important to usher in the new era of advances in treatment, applying basic science to clinical aims. In 1992, the meeting in Mannheim, Germany, was chaired by Gerhard Bach, with a spillover to the Czech meetings and closer relations with colleagues from Eastern European countries. The next meeting, in Washington, DC, added pediatric rheumatology to the mix, and resulted in clinical guidelines under the leadership of Daniel Lovell and Anne-Marie Prieur (who later helped establish a collaborative pediatric rheumatology study group).

Kenneth Wilske and Daniel Furst then established a drug evaluation resource alliance, including Michael Weinblatt, Harold Paulus, and Theodore Pincus, under John Harter's leadership. The Paris meeting in 1996 was chaired by David Trentham. This was also the first meeting in which the World Health Organization (WHO) participated, to standardize quality control in the developing world, so that studies done there could be used in the industrialized nations. Followup meetings to coordinate the process were held in Geneva, the base of WHO. Subsequent meetings, in Boston, Washington, and Lisbon, coordinated international guidelines, but the ARA, now the American College of Rheumatology (ACR), expanded its meetings to include some of these issues, and the European League of Associations for Rheumatology (EULAR) began to meet annually and covered similar topics.

ISRT had obviously addressed an interest of many rheumatologists and, with the international community willing to consider the issues, no longer needed to exist as a separate organization Thus, at the end of 2006, after 2 decades of seminal input, ISRT's job was done. As a final act, ISRT, through its founder, Sanford Roth, spawned the Arizona State University's interdisciplinary conferences on the future of healthcare in the US.

The close coordination of ideas and guidelines that ISRT furthered in regulatory, pharmaceutical, academic, and practice circles has helped to lead the way to better and safer clinical trials and better relations of the various groups, without compromising any of them. ISRT provided a bridge from the bench to the office and permitted regulators to monitor all aspects of therapeutic development. The ACR has taken over some of the tasks of ISRT, and some of the sponsored programs at ACR congresses also address the questions. A sea change in responsibilities has changed the role of other organizations of rheumatology, with the demise or downgrading of some and the ascendancy of the Bone and Joint Decade, an internationally recognized campaign that was launched at WHO in Geneva, and is predominantly orthopedic-oriented. ACR and EULAR have incorporated many of ISRT's ideas and programs. Thus, ISRT's task as a catalyst to promote an interface among the clinical, regulatory, and scientific disciplines is complete, but its contributions will not soon be forgotten. *Requiescat in pacem*.

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DAVID TRENTHAM, MD, Beth Israel-Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ROSELYNN DYNESIUS-TRENTHAM, MS; SANFORD ROTH, MD, Arizona Research and Education, Phoenix, Arizona, USA. Address reprint requests to Dr. G. Ehrlich, 241 South Sixth Street #1506, Philadelphia, PA 19106-3733.

Ivory Vertebra and Palmoplantar Pustulosis

To the Editor:

The term "ivory vertebra" can be defined as a solitary, homogenously-radiodense vertebral body, with normal size and contours with no concomitant changes in adjacent intervertebral disks. The incidental finding of such a vertebral body presents a diagnostic challenge given the numerous potential etiologies. We report the radiological and pathological findings of an ivory vertebra in a patient with palmoplantar pustulosis.

A 46-year-old woman with a history of smoking and inactive palmoplantar pustulosis presented with back pain in September 2003. The pain was located in the dorsal area. Examination was normal. Plain radiographs of the spine were obtained and were unremarkable except for the finding of a normally-shaped, homogenously-radiodense or "ivory" vertebra at the level of T10 (Figure 1).

Blood tests ordered included acute phase reactant levels, protein electrophoresis, and bone metabolism markers to investigate the possible existence of Paget's disease, which occurs commonly in our region. Serum tests for tumor markers were also ordered. All blood tests were normal.

Further imaging included a computerized tomography (CT) scan of T10, magnetic resonance imaging (MRI) of the spine (Figure 2), technetium bone scan, thoraco-abdominal CT scan, and mammogram. The CT scan of the thoracic spine revealed diffuse sclerosis of the vertebral body of T10 with an associated left paravertebral soft tissue mass (Figure 3).

The MRI showed on T1-weighted images a diffuse decreased signal intensity of the body of T10 with detachment of the anterior longitudinal ligament, and an increase in signal intensity in T2 in left pre- and paravertebral soft tissues. Diffuse uptake in the body of T10 and the pre- and paravertebral soft tissues occurred upon the administration of intravenous contrast. An increase in signal intensity was found on short-tau inversion recovery (STIR) sequences. The technetium bone scan showed isolated uptake in the body of T10.

Given the suspicion for a malignant lesion, a transpedicular biopsy was performed; the procedure revealed a slightly higher consistency than normal bone tissue, but bone histopathology was normal. Six months later, the MRI was repeated. Given the persistence of soft tissue abnormalities, an additional biopsy of the vertebral body of T10 was obtained by right mini-thoracotomy. This also revealed normal tissue. Two years after presentation, the patient's back pain has disappeared and there is no further pathological evidence to explain the lesion found.

The finding of a radiodense vertebral body, or "ivory vertebra," presents a diagnostic challenge given the number of possible etiologies[1]. These include serious conditions such as tumor metastases and lymphomas[2,3]. This raises concern for the patient and doctor.

An idiopathic ivory vertebra usually is an incidental and benign finding that appears in the spine in adult patients. There is a slightly higher incidence in females[2]. Given that it commonly presents in our area, Paget's disease was presumptively diagnosed. However, this was not confirmed by laboratory tests or by later biopsy. Some authors have postulated that this type of vertebral body corresponds to the initial phase of Paget's disease[4].

In our case, the patient's only medical history of interest was that of palmar pustulosis, which makes it necessary to include in the differential the syndrome called "SAPHO" (synovitis, acne, pustulosis, hyperostosis, and osteitis)[5,6]. The spine is the second most common site of bony disease in adults and is involved in 33% of cases. This preferentially affects the thoracic spine and usually manifests itself with sclerosis of one or more vertebral bodies[7].

This diagnostic possibility not entertained in some previous publications should be kept in mind even when, as in the present case, the skin lesions are inactive. The lesions described as "ivory vertebrae" in the setting of palmoplantar pustulosis correspond to sclerotic areas with either variable involvement of the vertebral body[8].

In general, the diagnosis of an ivory vertebra is made by exclusion, primarily after ruling out malignant etiologies. This requires, as in the

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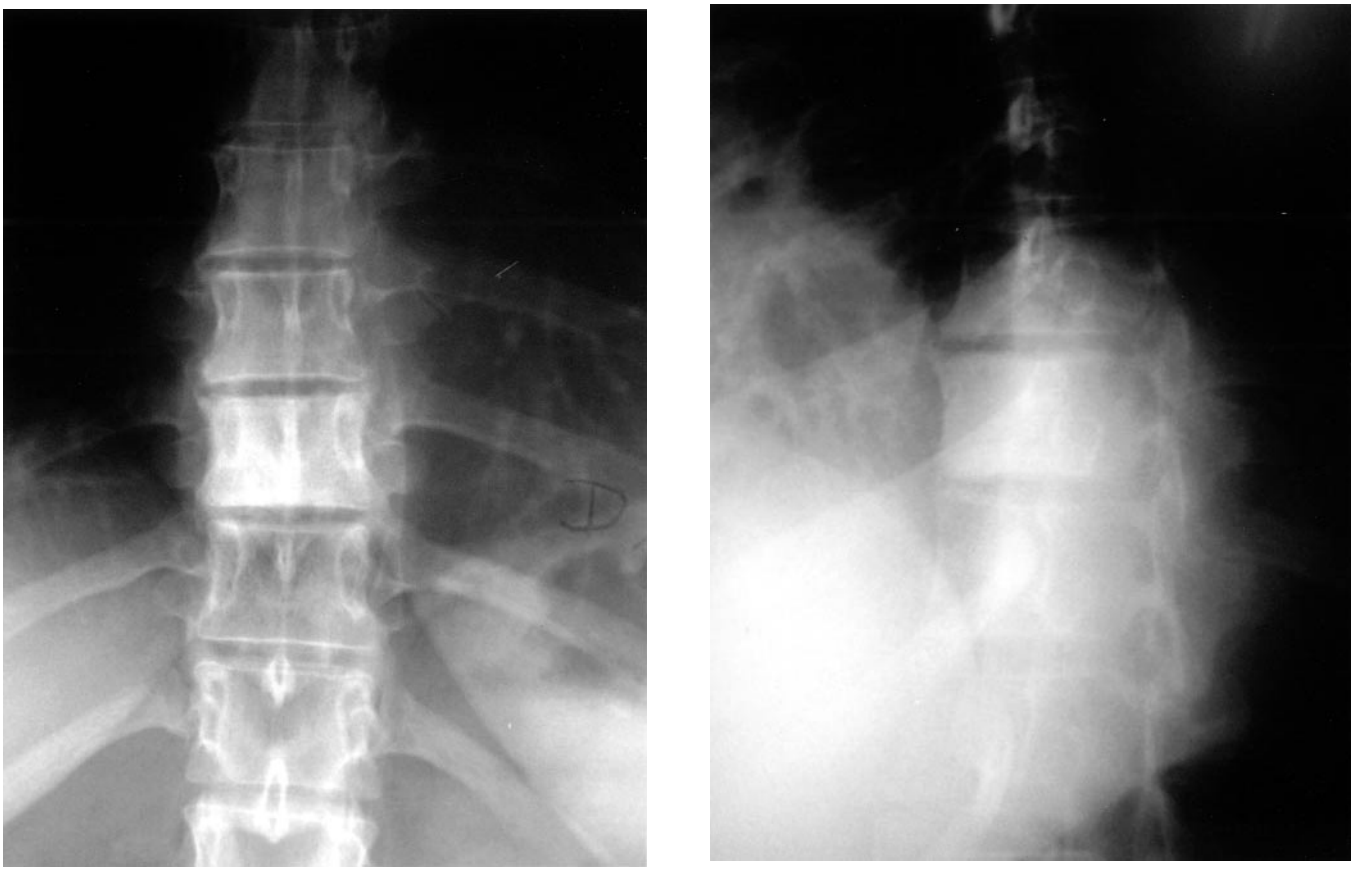

Figure 1. Normally-shaped, homogenously-radiodense or "ivory" vertebrae at the level of T10.

case at hand, carrying out a number of costly diagnostic tests. Recently, Carpineta and Gagné[1] have proposed an algorithm to help guide the investigations of those patients presenting with the finding of an isolated ivory vertebra.

In conclusion, an ivory vertebra presents a diagnostic challenge, given the multitude of possible and alarming conditions that may be the underlying cause.

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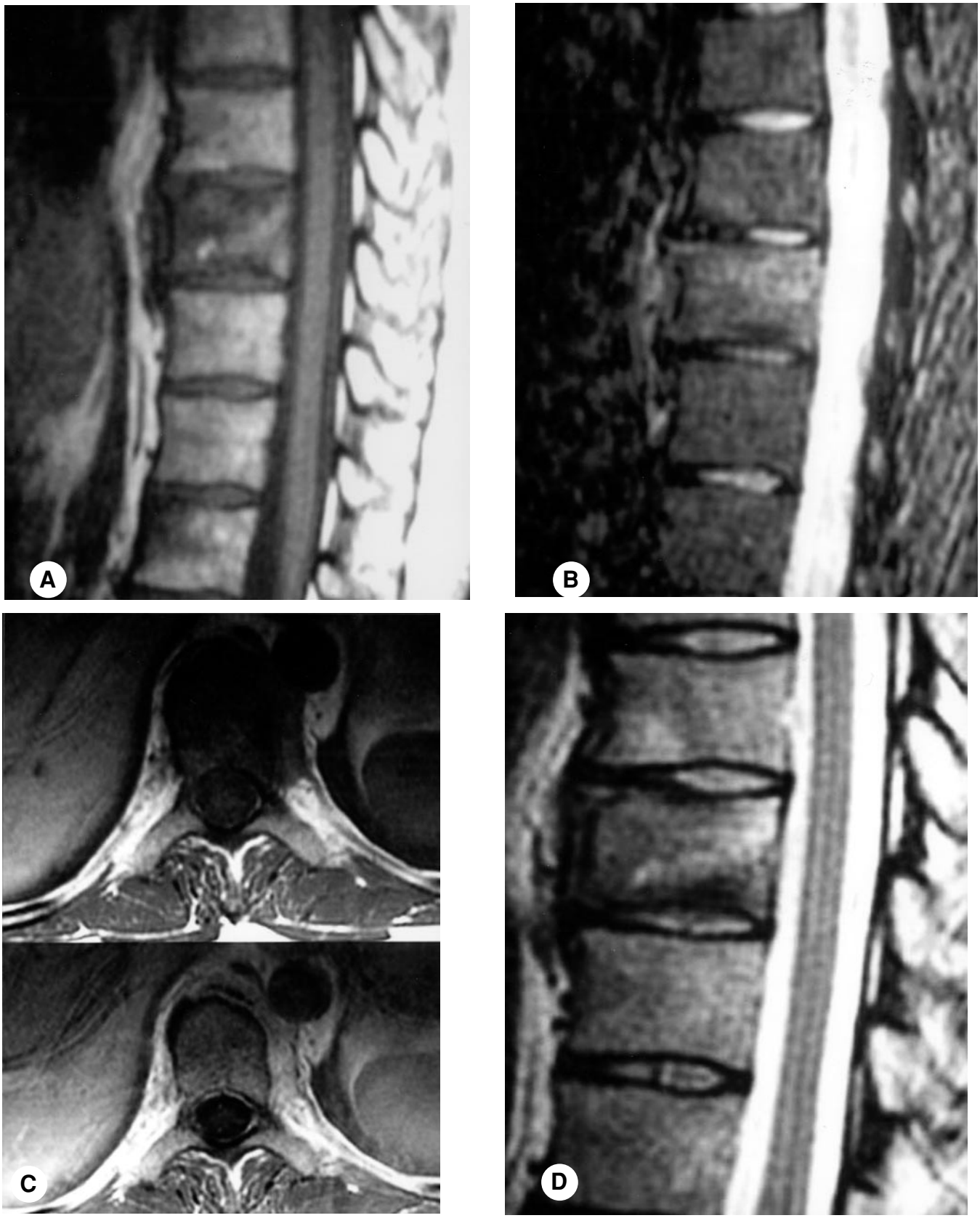

Figure 2. MR images. A. SE T1-weighted images a diffuse decreased signal intensity of the body of T10 with detachment of the anterior longitudinal ligament. B. Increase in signal intensity on STIR sequence. C and D: increase in signal intensity in FSE T2 in left pre- and paravertebral soft tissues.

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Figure 3. CT image. Sagittal view showing a dense and organized trabecular bone.

Antineutrophil Cytoplasmic Antibodies in Nonsystemic Vasculitic Neuropathy

To the Editor:

It was recently brought to my attention that my editorial on nonsystemic vasculitic neuropathy (NSVN)[1] received comment by Peer Aries and Wolfgang Gross[2]. I thank them for their interest and appreciate this opportunity to address their concerns.

Aries and Gross were "amazed" that the importance of antineutrophil cytoplasmic autoantibody (ANCA) testing in NSVN and, for that matter, any "undefined neuropathy" was not emphasized. However, NSVN is not an ANCA-associated vasculitis (AAV), which is why I elected to discuss more pertinent issues in my editorial.

For the record, in our own series of 48 patients with NSVN encountered at Ohio State University[3], only one of 14 patients assessed for ANCA was positive [anti-myeloperoxidase (MPO) pANCA]. For a 2004 review article, I combined this data with the available literature to obtain an 11% (3/28) prevalence of ANCA in NSVN[4]. In the intervening 2 years, an additional 40 patients with NSVN tested for ANCA have appeared, all with negative results[2,5-7]. Therefore, the current cumulative percentage of published NSVN cases positive for ANCA is 4% (3/68), implying that NSVN is not an AAV.

I agree with Aries and Gross that peripheral nerve involvement is common in Churg-Strauss syndrome[8], but ANCA occur in less than 40% of patients with this condition[9-11], an observation that has prompted some experts to doubt their pathogenic significance[9]. The "classic example" of an AAV, Wegener's granulomatosis, is rare in series dedicated to pathologically proven vasculitic neuropathy[12-15]. I also agree that every patient diagnosed with a vasculitic neuropathy should undergo surveillance for additional vasculitic manifestations, but this is true irrespective of ANCA status.

Patients who develop an unexplained multifocal or asymmetric neuropathy suspicious for vasculitis deserve to undergo ANCA testing as part of their "systemic" workup. However, Aries and Gross go further and recommend similar testing for all patients with an unexplained neuropathy, irrespective of tempo or pattern. I disagree. For the type of neuropathy most commonly encountered by practicing neurologists and primary care physicians — a late-onset, indolent, slowly progressive, distal, symmetric polyneuropathy — the diagnostic specificity of ANCA testing is quite low. In the only study of its kind, Chalk, *et al* obtained ANCA in 166 consecutive patients referred to a peripheral neuropathy center[16]. Although 4/6 patients with a vasculitic neuropathy (none of them nonsystemic) did, in fact, have pANCA or MPO-ANCA, MPO-ANCA were also identified in 5/44 patients with other types of inflammatory neuropathy, 1/8 with motor neuron disease, 13/69 with other types of noninflammatory neuropathy, 5/22 with central nervous system or muscle diseases, and 7/17 with symptoms but no signs or laboratory abnormalities. None of the patients had cANCA or PR3-ANCA. The authors concluded that "in patients being evaluated for peripheral neuropathy, the utility of ANCA as a simple serologic test for vasculitic neuropathy is limited by nonspecificity"[16]. By inference, if every patient with an unexplained neuropathy is tested for ANCA, false positives will outnumber true positives, engendering many unnecessary nerve biopsies. A more cost-effective approach is to tailor ANCA testing and nerve biopsy to the neuropathic profile.

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Refractory Wegener's Meningitis Treated with Rituximab

To the Editor:

A 36-year-old woman presented to our rheumatology department in 1995 with arthralgia, sinusitis, early morning stiffness, fatigue, weight loss, vasculitic rash, and a leg ulcer, with associated proteinuria and hematuria. Initial blood tests showed erythrocyte sedimentation rate (ESR) 89 mm/h; C-reactive protein (CRP) 25 mg/dl; positive cytoplasmic antineutrophil antibodies (cANCA) 1:160; hemoglobin 8.9 g/dl; platelets 618×10^9/l. A diagnosis of Wegener's granulomatosis (WG) was made and she was treated with 9 intravenous pulses of cyclophosphamide 10 mg/kg over 6 months. With this regime she went into remission and was then maintained taking oral prednisolone 7.5 mg/day and azathiaprine 150 mg/day. Her ANCA subsequently became negative. She relapsed 2 years later, and remission was induced with monthly intravenous pulses of cyclophosphamide for 3 months followed by monthly oral pulses (3 days of 300 mg/day) for 3 months. For the next 5 years she was maintained taking low-dose oral prednisolone as she started a family. She remained asymptomatic and her ANCA remained negative.

In 2004, her disease relapsed, with symptoms of arthralgia, headaches, and vomiting and a vasculitic leg ulcer proven on biopsy. She developed chondritis of her ear as well as inflammation of her eye. Her cANCA was positive at 1/320 and CRP 47 mg/dl. Magnetic resonance imaging (MRI) of her brain was unremarkable. She started taking monthly intravenous pulses of cyclophosphamide 750 mg and methylprednisolone 500 mg over 6 months. Over the subsequent few months she had several recurrences of her headache, vomiting, visual disturbance, and anorexia. Lumbar puncture and chest radiograph excluded mycobacterium, cryptococcus, syphilis, Lyme disease, cytomegalovirus, malignancy, and sarcoidosis. She was treated with an intravenous pulse of 1 g methylprednisolone on each occasion. In spite of this she remained symptomatic, with distressing headache, nausea, and vomiting. A repeat T1 weighted MRI brain scan with gadolinium enhancement revealed widespread meningeal enhancement over the tentorium (Figure 1) and both hemispheres (Figure 2). Neurological examination revealed florid papilledema and a XIIth nerve palsy. Her cANCA remained positive at 1/160, with a proteinase-3 titer of 327 and CRP 111 mg/dl.

She was treated with 2 intravenous infusions of rituximab 1 g, 2 weeks apart, together with 250 mg intravenous methylprednisolone. The day after the rituximab infusion she received 750 mg intravenous cyclophosphamide. She subsequently had complete resolution of her symptoms. At the time of writing, she has been in remission for 6 months, maintained successfully with a reducing dose of prednisolone, currently 12.5 mg daily. Her ANCA is negative, inflammatory markers have normalized (CRP 14 mg/dl, ESR 13 mm/h), and CD19+ B cell count has dropped to zero.

The diagnosis of WG was made on the basis of fulfilling the modified American College of Rheumatology criteria[1]. Studies have shown the diagnostic value of biopsies to be variable, with fewer than 20% of cases showing a full picture of necrotizing vasculitis and granulomatosis in cutaneous examples of WG[2]. A meningeal biopsy was not performed, as an infectious

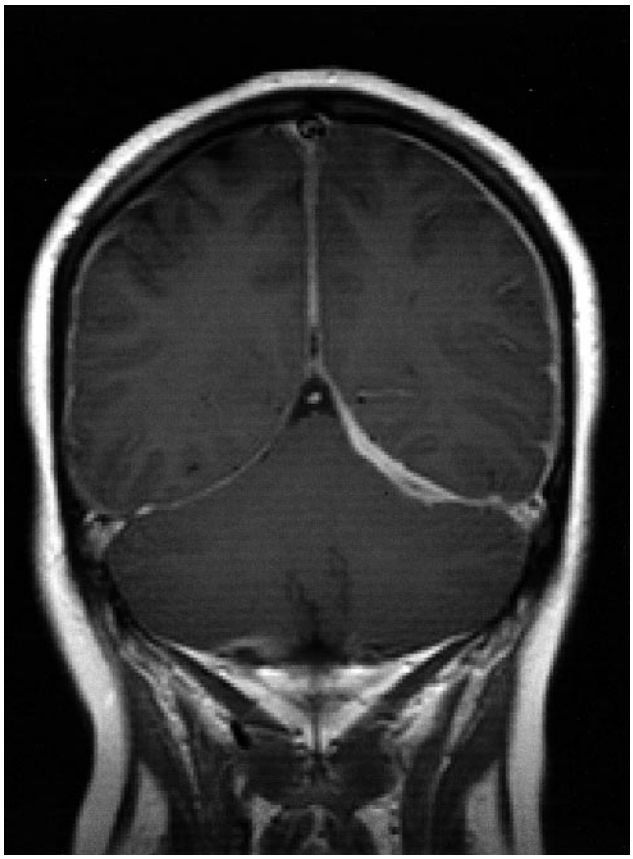

Figure 1. Coronal view, T1 weighted gadolinium enhancement MRI.

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cause of the chronic meningitis had been ruled out with cerebrospinal fluid examination. Biopsy does not increase diagnostic yield[3], and may lead to serious complications. Meningeal biopsy should be reserved for cases of suspected malignancy or when response to treatment is inadequate.

Our patient's disease was initially vasculitic in nature. With time, the disease shifted to the granulomatous end of the spectrum. WG is thought to be a spectral disorder, with vasculitis and granulomatous disease representing opposite ends of the spectrum. Meningeal involvement is thought to be associated with active localized granulomatous disease. In a recent systematic review, headache was usually the presenting feature of Wegener's meningitis[4], as in our case. However, in contrast to previous reported cases[5], our patient showed no evidence of active localized disease clinically, or on imaging of sinuses or mastoids. She also developed papilledema and a XIIth nerve palsy.

Despite clinical and symptomatic improvement, repeat brain MRI showed no radiological improvement. This could represent residual fibrosis. This finding was also reported by Spranger, *et al*[6]. The clinical response shown by our patient has guided the tapering of her prednisolone to avoid undue side effects.

The use of cyclophosphamide in inducing remission in WG has become accepted practice since the 1980s. Remission has become common with standard therapy (> 80%). Despite this, up to 60% of patients relapse within 18 months, depending upon the type of disease and immunosuppression used[7]. Biologic therapies have also been tried. A randomized, placebo-controlled trial of etanercept was found to be no better than placebo in preventing flares[8]. In a metaanalysis of small pilot studies, 81% of patients achieved remission with infliximab[9] — 69% of whom had been resistant to standard treatment. In an open pilot study of rituximab, remission was successfully induced in 11 patients with refractory disease[10].

Meningitis is a rare complication of WG and only 48 cases have been described in the literature. To our knowledge, this is the first reported case of refractory Wegener's meningitis treated with rituximab.

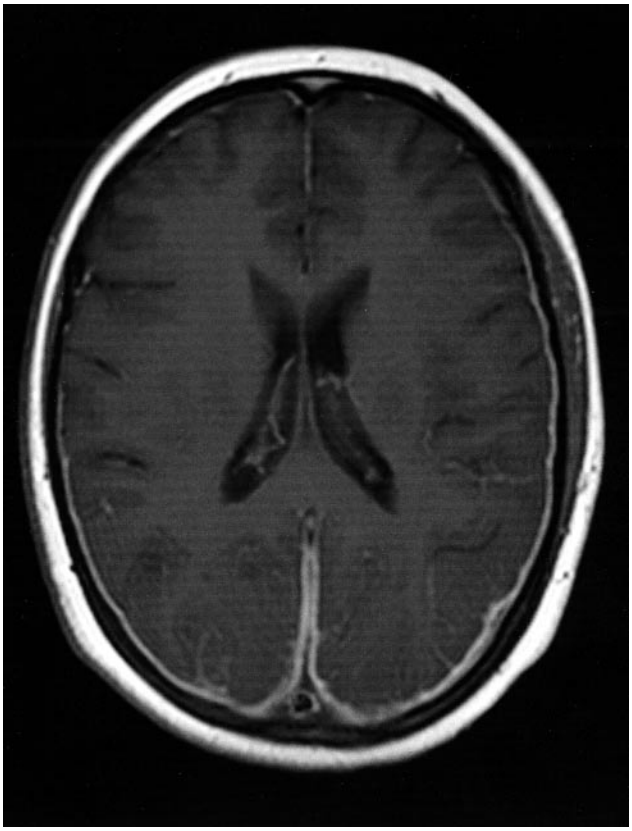

Figure 2. Axial view, T1 weighted gadolinium enhancement MRI.

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Book Reviews

Rheumatoid Arthritis, 2nd edition

Gary S. Firestein, Gabriel S. Panayi, and Frank A. Wollheim, editors. New York: Oxford University Press, 2006, 575 pages, price $275.00 US.

The field of rheumatoid arthritis (RA) has changed significantly since the first edition of this book was published in 2000. This much needed second edition attempts to bring the reader up to date with this rapidly advancing area in rheumatology.

The book includes sections on etiology, mechanisms of inflammation, clinical aspects, drug therapy, non-drug interventions, surgical management, and new frontiers in treatment. Each chapter is by well known experts in the field from around the world. The chapters are well written with abundant references to support the material presented. Many sections are well illustrated, particularly that on imaging in RA. However, in the

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chapter on the hypothalamic-pituitary-adrenal axis, the pixilated images are poorly reproduced.

The section on mechanisms of inflammation highlights recent advances in the understanding of new areas of focus such as the pivotal role of B cells and cytokine networks in RA. The chapter on clinical aspects, which includes imaging, prognosis, and biomarkers, is particularly rich and recommended reading for clinicians. A good discussion of drug therapy is presented in Section 4, while non-drug therapy is covered in Section 5. Aspects of musculoskeletal surgery are well articulated in Section 6. An interesting Section 7, The Frontiers of Therapy, highlights aspects of clinical trials, promising biologic therapies, cartilage breakdown, signal transduction, and the role of mesenchymal stem cells in arthritis.

One caveat would be the option of electronic updates being made available so as to keep the information current between now and the next edition. On the whole, this text is a tour de force. I would highly recommend it to all who have an interest in the rheumatic diseases.

Alfred Cividino, MD, FRCPC, Associate Clinical Professor, Department of Medicine, McMaster University, Hamilton, ON, Canada

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Arthritis in Children and Adolescents

Ilona S. Szer, Yukiko Kimura, Peter N. Malleson, Taunton R. Southwood. New York, NY: Oxford University Press, 2006, 456 pages, price $245.00 US.

This textbook, complete with excellent illustrations and tables, offers a comprehensive approach to arthritis in children and adolescents. Contributors are from Canada, the United States and Europe, and include members of different disciplines including rheumatology, physiotherapy, occupational therapy, and psychology.

The relatively new ILAR classification of juvenile idiopathic arthritis (JIA) is used, replacing the terms juvenile rheumatoid arthritis (JRA; the American College of Rheumatology classification) and juvenile chronic arthritis (JCA; the EULAR classification). The benefit of this approach is that there is consistency of terms between authors, helping to minimize confusion for the reader. However, there are limitations to using this nomenclature in a clinical textbook. This classification, developed a decade ago, was intended primarily for research purposes. It has not been validated for clinical use. The inclusion and exclusion criteria for each subtype will likely be modified as they are applied to clinical practice. Further, the terms JIA, JRA, and JCA are not interchangeable. Therefore when the authors review and interpret the literature, there are likely to be inaccuracies when they directly substitute JIA for JRA or JCA.

The book is divided into 3 parts. Part I provides a thoughtful and organized approach to the child with musculoskeletal complaints. Helpful algorithms are provided for various clinical scenarios, and different causes of musculoskeletal pain are thoroughly explored. Part II details the subtypes of JIA, and discusses histopathology, immunology, genetics, and environmental factors that contribute to the pathogenesis of JIA. Part III discusses management of children with arthritis and stresses the importance of a multidisciplinary approach. Algorithms for treatment are proposed. These algorithms represent one approach to management; others certainly do exist. There is an excellent appendix that describes intraarticular corticosteroid injections, accompanied by illustrations.

The textbook is primarily geared to rheumatology trainees, but can also be used by general practitioners. It is well organized, easy to read, and makes a worthwhile contribution to the pediatric rheumatology literature.

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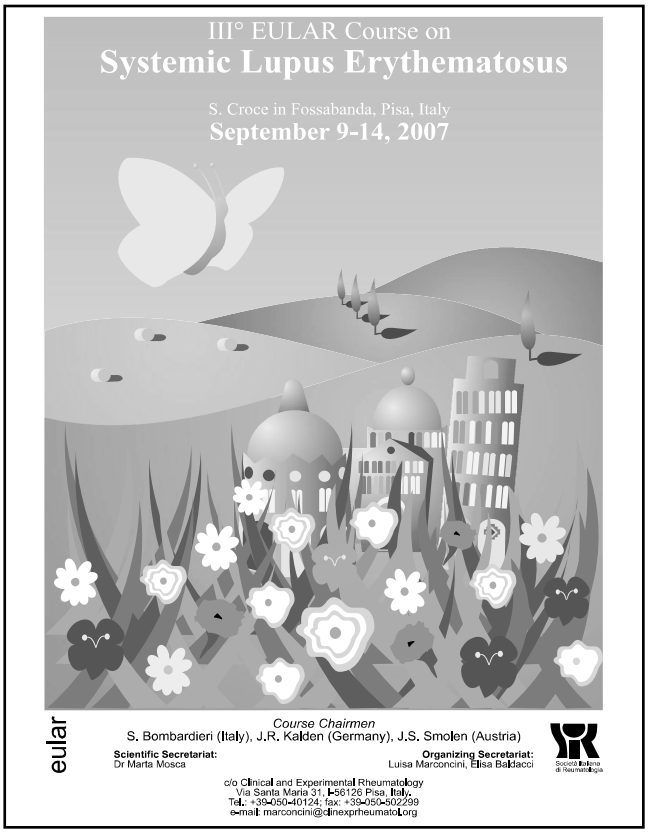

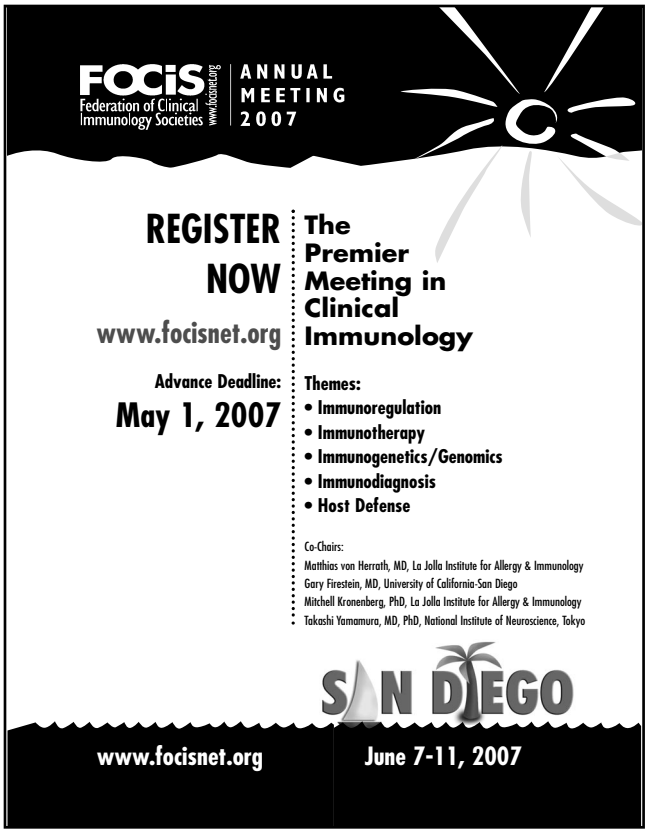

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