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LETTERS

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High-resolution ultrasound for the study of target joints in rheumatoid arthritis

To the Editor:

Conventional radiography remains the "gold standard" for the evaluation of joint damage and its progression in rheumatoid arthritis (RA), but changes may not be evident radiographically until late in the disease course (1). Magnetic resonance imaging (MRI) has been used to study patients with early RA, but high cost and lack of standardization limit its use (2). Several studies have now shown that high-resolution ultrasound (US) of the metacarpophalangeal (MCP) joints can be very informative in the evaluation of RA of various durations (3–5). Erosions have been visualized in selected hand joints (second MCP) and foot joints (fifth metatarsophalageal [MTP]) (5). In fact, detection of more erosions per joint and per patient with US as compared with radiography was demonstrated by Wakefield et al in a recent study reported in *Arthritis & Rheumatism* (3).

The present pilot study was undertaken to assess the feasibility of performing US in selected (target) joints of patients with RA, and to determine if this technique offers additional information beyond that obtained with conventional radiography. MRI was chosen as a comparator method because of its high sensitivity. Our Institutional Review Board approved this study.

Ten unselected patients with RA according to the criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (6) and 5 healthy volunteers who, as a group, were of comparable age (mean 45 years), sex (80% women), and ethnicity (80% white) with the patients were studied. The duration of RA was <2 years in 2 patients, 3–5 years in 5, and >5 years in 3. Six of the 10 patients were positive for IgM rheumatoid factor. Five of the 10 were receiving a disease-modifying antirheumatic drug (methotrexate in 4 of the 5); 3 other patients were receiving anti–tumor necrosis factor therapy.

Joints selected for US imaging included the second and fifth MCP joints and the fifth MTP joints. These joints were selected on the basis of their likelihood of early involvement in RA as well as their easy accessibility with the US probe. The first MTP joints, not considered targets for involvement early in the course of RA, were also examined because of their easy accessibility with the US probe.

Conventional radiographs of the hands/wrists and feet were obtained. These included 3 views (anteroposterior, lateral, and oblique) obtained using standard techniques (Kilovolt peak 54, milliampere-second 2.5, fine detail film-screen combination). Coronal T1-weighted MR images of the hands and feet were obtained using a 1.5T body scanner (Signa; GE, Milwaukee, WI), dedicated extremity coils, and the following parameters: repetition time 500 msec, echo time 15 msec, 256×192 matrix, 3 mm thickness with 0.5 mm gap, field of view 20 cm). Finally, US of the joints as noted above was performed by one of us (RL-B), using 10–15 MHz high-resolution linear array transducers with small footprints. Individual scanning parameters were optimized for musculoskeletal detail for the US machines utilized (Sequoia; Accuson, Mountain View, CA and HDI 3000; Advanced Technologies Laboratories, Bothell, WA). In each subject, the 3 studies were performed between a few hours and 10 days apart.

Radiography was considered the gold standard and used to calculate the sensitivity, specificity, and predictive value of US. Radiographic films from patients and controls were coded and blinded and were read independently by 2 experienced rheumatologists (GSA, LWM) for erosions in the same joints imaged by US; the final erosion count recorded per joint and per patient was the average from the 2 readers. US and MR images from patients and controls were mixed and then read for erosions by a fellowship-trained musculoskeletal radiologist (RL-B) with experience in sonography. An erosion by sonography was defined as a cortical defect >2 mm in width with an irregular floor seen in longitudinal and transverse planes. An erosion by MRI was defined as a focus of decreased T1 marrow signal occurring in a juxtaarticular or subchondral distribution.

Table 1 shows the comparison of the findings with the 3 imaging modalities as well as the sensitivity, specificity, and overall accuracy of US and MRI compared with radiography. As in the study by Wakefield et al (3), all erosions found by radiography were also identified by US and MRI. US was superior to conventional radiography in the identification of erosions; moreover, it was superior to MRI in some instances, perhaps due to volume averaging of pixels given the technique used. Erosions detected by US, but not by MRI, were all small (2–3 mm). US, with in-plane axial resolution >1 mm at such superficial depth for the transducers used, would be better able to resolve such small cortical defects.

We have shown that erosions can be identified by US in patients with RA of various durations and that the study can be performed in a busy outpatient clinic. The time to complete the study (and its costs) can be reduced substantially if only joints that are typically affected early in the course of the disease and/or whose surface is easily accessible with the US probe are examined. These joints include the second and fifth MCP joints and the fifth MTP joints. Of interest, no additional information was derived from the assessment of the first MTP joints, since no erosions were detected in these joints. US of target joints in RA patients meets the Outcome Measures in Rheumatology Clinical Trials filter requirements (truth discrimination and feasibility) (7). Demonstrating the presence of erosions early in the course of the disease, before radiographic findings are apparent, may allow the clinician to initiate more aggressive therapy, which in the long term may result in better patient outcomes. This is quite important considering the new therapies now available for RA (8–10).

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Table 1. Total number of erosions and number of patients with erosive disease, detected by radiography, magnetic resonance imaging (MRI), and high-resolution ultrasound (US)*

Method	No. of erosions in joints examined	No. of patients with erosions in joints examined	Sensitivity, %†	Specificity, %†	Overall accuracy, %†
Radiography	8	3	–	–	–
MRI	14	7	100	65	76
US	19	8	100	45	61

* Values are for 10 patients with rheumatoid arthritis; in healthy controls, no erosions were detected with any of the three imaging modalities.
† Compared with radiography.

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Reply

To the Editor:

The conclusions discussed in the interesting letter by Alarcón et al, albeit derived from a small number of patients, confirm the findings of ourselves and others that high-frequency US is an accurate and reliable method of detecting bone erosions in patients with RA (1,2). In Alarcón and colleagues' study, despite 3 views being obtained (compared with a single posteroanterior view in our study), plain radiography remained less sensitive than US.

The authors comment on the advantage of scanning, "selected joints" as a time- and cost-saving exercise. Scanning only a few joints may theoretically be time saving; however, in clinical practice, we find that the most time-consuming step is patient positioning and undressing. A full assessment of all of the MCP joints by an experienced sonographer takes only ~5 minutes. Furthermore, US also provides information on soft tissue involvement (synovitis and tenosynovitis), as well as providing valuable insight into the true extent of disease by demonstrating subclinical involvement. While US has a greater sensitivity for detecting erosions on second and fifth MCP joints and fifth MTP joints where there is better transducer access, MRI studies (3,4) suggest that synovitis affects all joints approximately equally, and therefore, important clinical disease may be missed if scanning is limited to only a few areas.

Alarcón et al also highlight the ability of US to detect small erosions. This may be particularly important in early RA. In our study of 100 RA patients (1), 90% of small erosions in the early-disease group were small, (defined as <2 mm), compared with 63% in the longer-duration group. This explains why conventional radiography is an insensitive technique for detection of erosions in patients with early RA.

Although MRI is a potentially powerful technique, its use is currently limited in many centers, due to availability and cost issues. In our center, US is used extensively in the clinic but has not replaced radiography for the assessment of bone damage. Rather, it is used as a complementary tool with a particular role in evaluating patients who are at high risk for inflammatory arthritis in whom radiographic findings are normal, or for reexamining nonspecific lesions detected on radiography.

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Can very high-dose anti–tumor necrosis factor blockade at onset of rheumatoid arthritis produce long-term remission?

To the Editor:

The combination of methotrexate and infliximab, a chimeric monoclonal anti–tumor necrosis factor α (TNFα) antibody, has been shown to be very effective in reducing the signs and symptoms of rheumatoid arthritis (RA) (1,2). There are theoretical reasons why early use of anti-TNF might interrupt monocyte/macrophage function, producing long-lasting clinical benefits (3). If these theories are correct, then early use of high-dose remission-induction therapy could become standard treatment. Currently, some clinically important questions about this therapeutic approach need to be addressed. First, is nonresponsiveness to anti-TNF attributable to insufficient doses, and, if so, can poor clinical response be overcome by use of an adequately high dose? Second, can use of very high-dose anti-TNF therapy early in the course of disease have a profound influence on outcome, allowing drug-free remission to be achieved? To answer these questions, we conducted a pilot study using high-dose infliximab, with reinduction if no remission occurred. State-of-the-art imaging modalities were used.

The study group comprised 5 patients with newly diagnosed inflammatory arthritis. All patients fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria for RA (4) and had not previously received any disease-modifying antirheumatic drugs (DMARDs). Other inclusion criteria were RA of $<$12 months duration and $\geq$3 poor prognostic criteria (based on sex, C-reactive protein [CRP] level, rheumatoid factor [RF], shared epitope, and Health Assessment Questionnaire score [5]). The protocol was approved by the local ethics committee, and all patients gave informed consent.

Methotrexate therapy (increasing to a maximum dosage of 15 mg/week) began at baseline. Patients received infliximab, 10 mg/kg, at weeks 0, 2, 6, and 10. If remission had not occurred by week 12, they received a repeat, "reinduction" regimen. Standard clinical and laboratory outcome evaluations were performed at all time points. Magnetic resonance imaging (MRI) scans and high-resolution ultrasonography of the dominant hand (2nd to 5th metacarpophalangeal joints) were performed at weeks 0, 12, and 48, as previously described (6). The MRI sequences and scoring method were consistent with recent expert recommendations (7). Bone densitometry scans (spine, both femoral necks, and hands) were also performed at 0 and 48 weeks.

The mean duration of symptoms of the 5 patients was 7.3 months. Four patients were female, 4 had a positive family history of RA, 4 were RF-positive, and all 5 possessed the shared epitope (previously known as HLA–DR4 and DR1). At baseline, 1 patient had erosions on conventional radiographs of the hands and feet. The clinical and imaging outcomes are presented in Table 1. After the initial administration of 4 infusions of high-dose infliximab (3 times higher than the conventional dose), 1 patient was in remission, 3 showed highly significant improvement (2 ACR 70% response and 1 ACR 50% response [8]), and 1 demonstrated no improvement. The 3 patients who underwent reinduction of high-dose infliximab (1 patient did not undergo reinduction because of a previous infusion reaction) did not achieve further remission or improvement. In particular, the patient who showed no improvement following initial therapy also showed no response to reinduction, and that patient's serum CRP level increased after treatment. No patient achieved drug-free remission.

Imaging modalities demonstrated a reduction in global synovitis (see Figure 1) in all 4 patients who responded clinically but not in the nonresponding patient, in whom the degree of synovitis was unaltered by therapy. The reduction in synovitis was accompanied by a dramatic reduction in bone

Table 1. Clinical and imaging outcomes*

Outcome measure	Week 0		Week 12		Week 48, responders
	Responders	Non-responders	Responders	Non-responders	
Early morning stiffness, minutes	105	300	0	300	10
Tender joint count	12	33	3	26	7.5
Swollen joint count	8.8	9	1.3	13	1.3
Patient's global assessment on 100-mm VAS	62	80	6	40	11
C-reactive protein, mg/ml	46	48	6	41	10
Health Assessment Questionnaire, raw score	11.8	19	3	15	2.8
MRI synovitis global score†	7	7	3	6	5
MRI bone edema sites‡	2.5	0	0.5	0	0.5
Ultrasound synovitis global score†	4	2	1.5	3	2.8

* Values for the responders (n = 4) are the means. The nonresponding patient was withdrawn from the study at 6 months, with results similar to those at week 12, except for C-reactive protein (125 mg/ml). VAS = visual analog scale; MRI = magnetic resonance imaging.
† Sum of 4 metacarpophalangeal joints, each scored 0–3.
‡ Sum of sites demonstrating bone edema, counted as proximal and distal for each joint.

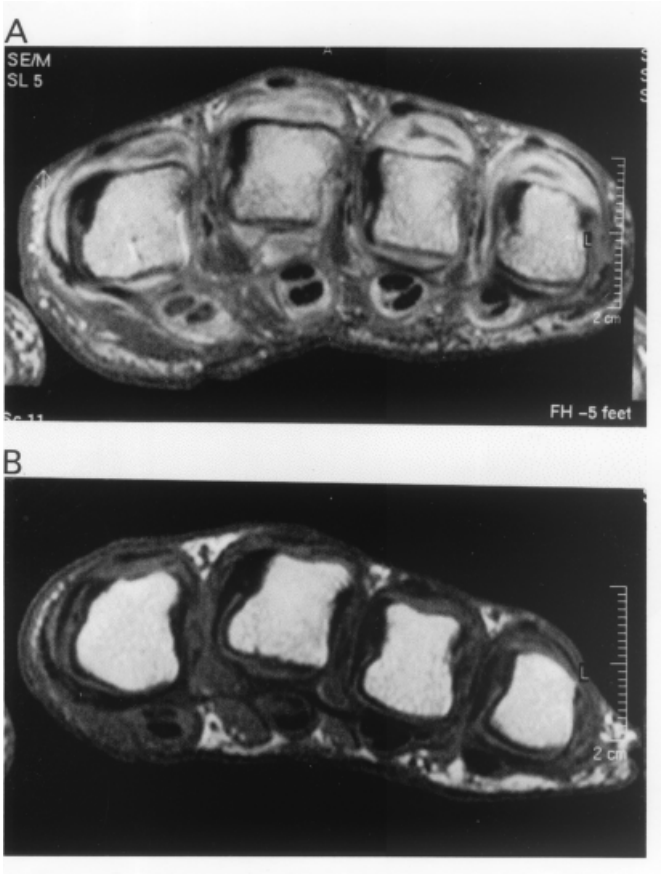

Figure 1. Magnetic resonance imaging of the metacarpophalangeal joints. Axial T1-weighted spin-echo post-gadolinium views of the same patient (responder) at baseline **(A)** and week 14 **(B),** showing dramatic reduction in enhancing synovium (synovitis) and tenosynovitis.

edema as seen on MRI, and no joints with reduced synovitis according to MRI scans developed new erosions. Bone densitometry in the 4 responding patients demonstrated a small loss over 48 weeks compared with the nonresponder (average loss 1.6% versus 3.4%).

This unique experiment examined the effect of very high-dose TNF blockade at the time of presentation followed by reinduction in RA patients who did not achieve remission. We specifically included patients with a poor prognosis, who may be candidates for more aggressive initial therapy. Results of this study answered the questions initially posed. One of 5 patients did not respond to therapy, but the variable clinical response clearly was not attributable to an insufficient dose of infliximab. Repeat induction with high-dose therapy did not produce any greater response in the partial responders, and the nonresponder had no improvement whatsoever. A more likely explanation for the variable response may be the known heterogeneity of synovial TNF expression observed in patients with RA (9).

With respect to the disparity between nonresponse and radiologic damage, imaging showed a close correlation between response and reduction of synovitis in the imaged joints. Among patients who had a good response to therapy, synovitis was reduced, and no further joint damage occurred. The nonresponding patient had no reduction in synovitis and was withdrawn from the study at 6 months, after failed reinduction.

Prevention of damage is clearly relevant to long-term outcome. All previous studies of conventional DMARDs have indicated that bone loss, as measured by bone densitometry, continues despite aggressive therapy. Although this bone loss was slowed in our patients, it was not completely abolished, perhaps because true remission was not achieved in all cases. Finally, although a good response was seen in all but 1 patient (nonresponder), a more profound effect on the disease, allowing drug-free remission, was not seen. All patients had continued disease activity that required treatment with anti-TNF. It is therefore clear that the forces driving RA were not stopped by early administration of high-dose anti-TNF therapy.

We are grateful to Schering-Plough UK for supplying infliximab.

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Reply

To the Editor:

The concept that patients with early RA may exhibit a universal and long-lasting remission following a limited course of high-dose anti-TNF therapy, unlike that observed in published trials of infliximab therapy, is worth exploring. The small study reported by Conaghan et al does not lend support to such a concept and suggests that in a small subset of patients TNFα may not be a pivotal regulator of the inflammatory response.

We have learned a great deal about the pathogenesis of RA, and specifically the role of TNFα in the mechanism of disease, from interventional studies using infliximab (1,2). Occasionally, an RA patient does not express TNFα in synovial tissues, and a correlation between the absence of TNFα and lack of response to infliximab has been previously observed (3). However, we must exercise caution in concluding that responses measured by ACR improvement criteria necessarily reflect the outcome of all aspects of rheumatoid pathology. We should note that in the anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy, assessment of serial radiographs of hands and feet demonstrated that progression of joint space narrowing (cartilage loss) and bone erosions was inhibited by infliximab, but not placebo, in ACR nonresponders (4).

The relationship between synovitis and cartilage, bone, and tendon damage, as evaluated by powerful new imaging techniques such as those used in the study by Conaghan and colleagues, should clarify whether invasive pannus and synovitis are causally interrelated or may be independently regulated. If the latter is the case, a dissociation between the ACR response criteria, which are sensitive to change in synovitis, and measurement of structural damage, may be observed in some patients. Whether use of anti-TNF therapy would be clinically justified in such circumstances is, of course, debatable.

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Morbidity not increased in rheumatoid arthritis patient with profound lymphopenia following CD4 monoclonal antibody therapy: comment on the article by Isaacs et al

To the Editor:

We read with interest the article by Isaacs et al (Isaacs JD, Greer S, Sharma S, Symmons D, Smith M, Johnston J, et al. Morbidity and mortality in rheumatoid arthritis patients with prolonged and profound therapy-induced lymphopenia. Arthritis Rheum 2001;44:1998–2008), in which they report that although profound and long-lasting lymphopenia occurs following treatment of rheumatoid arthritis (RA) with antilymphocyte monoclonal antibody, this therapy is not associated with substantially excessive mortality nor with an unusual range of infection during a medium-term followup period. In addition, the authors stress the dissimilarity between this cohort of lymphopenic post-immunotherapy patients and equivalently lymphopenic patients with human immunodeficiency virus (HIV) infection.

At present, we are providing care for a 71-year-old woman who has had RA for more than 20 years. She had been treated with multiple agents, alone or in combination, including nonsteroidal antiinflammatory drugs, methotrexate, gold, prednisone, and D-penicillamine. She remained symptomatic until 1997, when she was given an intravenous CD4 monoclonal antibody twice weekly for a total of 4 weeks. She had an excellent clinical response, with complete resolution of her symptoms. Remission, however, lasted only ~4 months. The patient has remained symptomatic with symmetric synovitis involving multiple joints, including the metacarpophalangeals, proximal interphalangeals, wrists, elbows, and knees, despite aggressive therapy for the past 30 months with cyclosporine, tumor necrosis factor α (TNFα) inhibitors, and monthly pulses of solumedrol. As expected, following initiation of CD4 monoclonal antibody therapy, her CD4 cell count decreased significantly (Table 1) and remains below normal levels 55 months later.

Our patient has not exhibited any unusual and/or opportunistic infection despite her profound and long-lasting decreased CD4+ cell count and the added therapy with cyclosporine, pulse methylprednisolone, or TNFα inhibitor. This, as discussed by Isaacs and colleagues, contrasts with what occurs in HIV-infected patients. As in HIV patients, however, active synovitis does occur, and this finding is somewhat distressing considering that CD4+ cells are thought to play a key role in the pathogenesis of RA (Espinoza LR, Aguilar JL, Berman A, Gutierrez F, Vasey FB, Germain BF. Rheumatic manifestations associated with human immunodeficiency virus infection. Arthritis Rheum 1989;32:1615–22). This is a relevant issue that deserves further consideration and is most likely illustrative of the complexity of the pathogenesis of RA.

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Table 1. Patient's CD4 cell count from 1997 to 2001

	April 1997	May 1997	August 1997	October 1997	November 1997	August 1998	November 2001
CD4, %	33	48	7	7	8	15	23
Helper/suppressor cell ratio	1.06	1.5	0.14	0.15	0.17	0.32	0.47

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Reply

To the Editor:

We thank Menon and colleagues for their interest in our work and for sharing their own data with us. We do not believe that the presence of synovitis in lymphopenic RA patients denigrates the role of CD4+ T cells in this disease. First, and as we discussed, very few memory T cells are needed to initiate a recall immune response. Whereas this fact may in part explain the resistance to infection observed in our patients, it also makes eradication of their RA less likely. Thus, in order for a depleting therapy to permanently ablate a T cell–driven disease, it presumably would need to kill the vast majority of T cells that have become sensitized to autoantigen. In the absence of such an effect, the disease is likely to recur. Conversely, achieving such an effect would require use of more potent or more prolonged lymphocytotoxic therapy, which may then result in compromised immune defenses. Second, it is now clear that not all autoreactive T cells are pathogenic, but that some are actively regulatory (1). It is unlikely that a depleting therapy, whether targeted at CD52 or CD4 (both of which are expressed on regulatory T cells), would specifically spare them. In this regard, lymphocytotoxic therapy theoretically could worsen autoreactivity if the balance of regulation-to-effector function were altered unfavorably.

Fortunately, cellular ablation is not necessary for control of autoaggressive T cells. In animal models, noncytotoxic therapies targeted at antigens such as CD4 or CD8 appear to empower potent immunoregulatory processes within the recipient and, in that sense, offer more benefit than that of the equivalent cytotoxic therapies (2). Although this phenomenon has yet to be adequately explained at the molecular level, it provides for long-term control of autoreactivity (3). To date, such therapies have not provided impressive disease control in humans. Few have been truly noncytotoxic, however, and as we have previously noted, the doses used in patients, on a weight-for-weight basis, fall far short of those needed to control autoreactivity in animals (4). Furthermore, at present we lack appropriate markers with which to monitor T cell–targeted therapy in humans (5).

In summary, despite the recurrence of synovitis in lymphopenic RA patients, we continue to believe that T cell–targeted therapy may play a role in disease control. In fact, relapsed RA in recipients of CAMPATH-1H appears to be more readily controlled with conventional disease-modifying antirheumatic drugs, even those that were previously ineffective (Isaacs JD, et al: unpublished observations). We recently made similar observations following autologous stem cell transplantation for RA (6), suggesting that lymphocytotoxic therapies may, in fact, be immunomodulatory. Our current efforts, however, are focused on the use of high doses of nondepleting monoclonal antibodies targeted at a variety of cell surface antigens, and on identification of appropriate T cell markers with which to monitor such therapy.

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DNASE I mutation and systemic lupus erythematosus in a Spanish population: comment on the article by Tew et al

To the Editor:

Tew et al (1) did not find any particular mutation in the *DNASE I* gene when studying 18 systemic lupus erythematosus (SLE) patients. Their interest was based on the fact that many studies have indeed found a link between *DNASE I* and the development of SLE. Actually, serum DNase I activity in different organic fluids has been shown to be low both in lupus-prone mice and SLE patients (2,3). Napirei et al (4) further corroborated this fact by generating *DNASE I*–deficient mice that developed clear features of SLE. And

even 2 of 20 SLE patients were recently found to be heterozygous for a nonsense mutation in 1 exon of the *DNASE I* gene (5); besides showing decreased DNase I activity, these patients had high IgG anti-nucleosome antibodies. The mutation was found in exon 2, and a single A→T transversion took place in the signal peptide coding region; it led to the formation of a stop codon, which gave rise to a predicted truncated protein that contained just 4 nucleotides.

To ascertain the true role of this mutation, we evaluated the presence of such a mutation in a Spanish SLE population. We analyzed 108 SLE patients (14 men, 94 women) and 100 healthy control subjects (38 men, 62 women). All the patients fulfilled the revised criteria of the American College of Rheumatology for the classification of SLE (6). Genomic DNA was prepared from peripheral blood mononuclear cells. A 428-bp DNA fragment was amplified by polymerase chain reaction (PCR) and digested with Nsp I since, as seen by Yasutomo et al (5), the base change would generate a new cleavage site for this enzyme. Thus, if the mutation had been found to be present, we would have expected to obtain 2 digested products, 1 of 160 bp and another of 268 bp. We even sequenced the 428-bp PCR product of 5 patients to confirm that it was actually the desired fragment.

To make sure that our digestion reaction was performing well, we also amplified a 428-bp DNA fragment downstream of the region of interest, which happened to contain 2 restriction sites for Nsp I. In this case, 3 fragments of the following sizes were to be generated: 164 bp, 140 bp, and 124 bp. As seen in Figure 1, neither patients nor controls had the mutation. Therefore, this particular nucleotide change does not appear to be associated with SLE in the Spanish population.

Yasutomo et al (5) just studied 20 SLE patients, and although the sample size was smaller than ours, they found the mutation in 10% of the cases. Ethnic differences may obviously account for the disagreement. In accordance with our results are those reported recently by Tew et al (1), in which they did not find the mutation in any of the 18 American SLE patients. It would be interesting to check if other mutations on the *DNASE I* gene exist and whether they are more frequent in Caucasians than in Japanese SLE patients when considering larger cohorts. If the low DNase I serum activity shown by other authors was confirmed in our SLE patients and no other mutations were found, this would open the possibility for the existence of a defective transcriptional or posttranslational mechanism of the enzyme. Tew et al (1) indeed suggested the latter when they found that none of the 13 SLE patients differed in *DNASE I* transcript levels from the 7 healthy controls.

On the other hand, DNAse II activity has been shown to be decreased in neutrophils from peripheral blood in patients with SLE (7). Consequently, other nuclease enzymes could also be blamed for the noncomplete degradation of extracellular DNA in the blood of SLE patients.

We believe that the rate of clearance of extracellular plasma DNA has important implications for the pathologic mechanism of SLE. SLE is mainly characterized by the presence of pathogenic autoantibodies to nucleoprotein antigens, with double-stranded DNA (dsDNA) being the most important. There are substantial data to support the fact that the autoimmune response developed by these patients is antigen driven. Therefore, a noncomplete clearing of cellular debris could trigger the manufacturing of autoantibodies, including anti-dsDNA antibodies, as a result of the lack of DNA degradation.

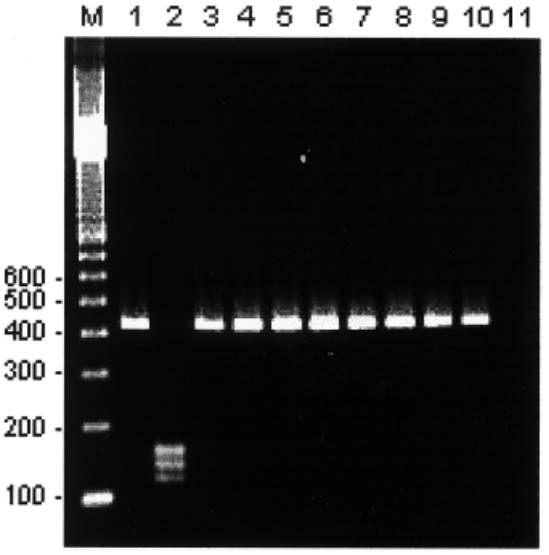

Figure 1. Restriction enzyme digestion analysis of polymerase chain reaction products. Lanes 1–2 = digestion control (before and after Nsp I digestion, respectively); lanes 3–10 = Nsp I digestion of genomic DNA amplified both from systemic lupus erythematosus patients (lanes 3–8) and controls (lanes 9–10); lane 11 = negative control (water); M = 100-bp molecular weight marker DNA; 2.5% agarose gel stained with SYBR Green I.

Nevertheless, this is actually a very complex disease, and believing that only 1 enzyme could be responsible for protection against autoimmunity seems to be too simple. The results of our study do not support the hypothesis of a particular described single mutation being the cause of the abnormality. Further research is needed for us to ascertain whether other genes are involved in the insufficient clearance of DNA in lupus patients.

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Reply

To the Editor:

We thank Dr. Balada and colleagues for their interest in our report (1). Their analysis of Spanish SLE patients for the *DNASE I* exon 2 mutation described by Yasumoto et al (2) is in agreement with the deoxyribonuclease I gene (*DNASE I*) sequencing results in our United States cohort (1). One possibility that may account for the difference that Balada and colleagues have pointed out is ethnic heterogeneity, or a mutation on a different part of the *DNASE I* gene. The latter cannot be formally ruled out in this instance, since Balada et al only tested for 1 mutation in 1 of 9 exons of *DNASE I* in their cohort. Another consideration is age. All of the SLE patients we studied had adult-onset disease. The exon 2 mutation described by Yasumoto et al (2) occurred in 2 young girls, ages 13 and 17 years, raising the possibility that mutations in *DNASE I* may be more prevalent in childhood-onset SLE.

Six known genetic polymorphisms account for the various isoforms of human DNase I (3–5), but there are no significant differences in serum DNase activity among the 3 major isoforms (*DNASE1*1, *2,* and **3*) (6). Thus, while diminished serum DNase activity is a common finding among SLE patients (7), a *DNASE I* mutation that accounts for this phenotype in the majority of SLE patients has yet to be widely reported, suggesting that other contributing factors exist.

As a followup to our earlier report (1), we ascertained serum DNase activity in patients with SLE due to homozygous deficiencies of C4 and C1r. Complete deficiencies of C4 and C1r (and other genes in the early classical pathway of complement) are very rare, but the prevalence of SLE in these patients is extremely high, ~75% and 57%, respectively (8). Because these mutations confer a high relative risk for SLE,

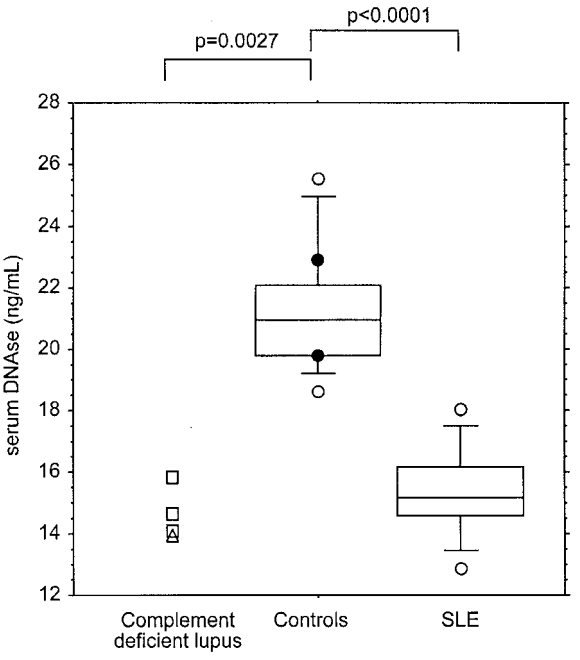

Figure 1. Box plot of serum DNase activity in 4 homozygous, complement-deficient patients. DNase activity was determined in triplicate, as previously described (1,12), except that 2 m*M* $CaCl_2$ was added to the final reaction buffer to increase the sensitivity of the assay because DNase I is an Mg^{+2}/Ca^{+2}-dependent nuclease (13). Serum DNase activity in 4 totally complement-deficient lupus patients, 2 white male siblings (patients 1 and 2) and a white female systemic lupus erythematosus (SLE) patient (patient 3), was completely C4A and C4B deficient, while 1 African American male SLE patient (patient 4) was totally C1r deficient. Patient 1 was diagnosed with SLE at age 7, and clinical manifestations included severe chronic cutaneous lupus (CCL) polyarthritis, leukopenia/thrombocytopenia, and digital vasculitis. Antinuclear antibodies (ANA) and anti-Sm and -RNP were positive, but all other lupus antibodies were negative. Patient 2 also developed CCL, proven by skin biopsy at an early age, but had no other end organ involvement over 30 years of followup (ANA, anti–double-stranded DNA, and other lupus autoantibodies were consistently negative). Homozygous C4A- and C4B-deficient status for patients 1 and 2 was demonstrated as previously described (14,15). Clinical and serologic details on patient 3 were reported earlier (16). Patient 4 developed severe CCL at age 3 months. A renal biopsy showed mesangial glomerulonephritis with focal proliferative changes and IgA and C3 deposition. Serum complement studies showed that the total hemolytic component was not detectable, C1q was 40 μg/ml (60% of normal), C1r was not detectable, and C1s was 22 μg/ml (61% of normal). Levels of C2, C3, C4, C5, C6, C7, C8, C9, C3b inactivator, β-1H globulin, C1 inhibitor, and C1s were all increased but properdin levels were normal. A second renal biopsy at age 18 showed diffuse proliferative glomerulonephritis with deposition of IgG, IgM, IgA, C3, and C1q, but not C4 by immunofluorescence. Fifteen SLE patients without a total complement component deficiency and 15 healthy race- and sex-matched controls were also studied. Except for C4-deficient patient 2 with CCL, all the SLE patients fulfilled the American College of Rheumatology criteria for SLE (17). ○ = individual controls for SLE patients; ● = parents of patients 1 and 2 (both parents were healthy and ANA negative); □ = C4-deficient patients; △ = C1r-deficient patient; horizontal line in each box = median; boxed areas = 25th and 75th percentiles; error bars = 10th and 90th percentiles. Pairwise comparisons between groups were made using the Mann-Whitney U test. The parents of patients 1 and 2 are shown for comparison only and were not included in the comparative analyses.

they are likely to be single-gene diseases. Low serum DNase activity in these patients would be consistent with the idea that factors other than *DNASE I* mutations alone affect serum DNase activity, since the odds of an individual inheriting 2 rare gene mutations would be exceedingly low. Four such patients (3 complete C4 and 1 complete C1r deficient) were studied. The number of patients studied is small, reflecting the very low frequency of homozygous C4 and C1r mutations in the population. The results show that serum DNase activity in patients with SLE due to genetic defects in the classical pathway of complement is not significantly different from that in the usual SLE patients (Figure 1). Both groups had serum DNase activity that was significantly diminished compared with that of healthy controls.

We agree with Dr. Balada and colleagues that defects in the ability to clear extracellular DNA likely contribute to the etiopathogenesis of SLE. While mutations in *DNASE I* could be an occasional, but rare, cause of SLE in humans, the etiology of the low serum DNase activity in SLE is undoubtedly complex. Thus far, the data suggest that in most SLE patients this phenomenon cannot be explained solely by *DNASE I* mutations alone. *DNASE I* transcript levels could be influenced by alternative splicing (9) or messenger RNA stability (10) (although there was no evidence of differences in splicing in our earlier study [1]). There is the potential for epistatic interaction with other genes or, alternatively, enzyme activity could be modulated by posttranslational events such as glycosylation, or by microenvironments particular to specific tissues (6,11). Further investigation will be required to determine if any of these processes downstream from gene transcription are affected in SLE patients, or if defects in other endonucleases are present.

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Call for a trial of Lyprinol, an over-the-counter 5-lipoxygenase inhibitor: comment on the article by Kowal-Bielecka et al

To the Editor:

In their discussion of dermal overexpression of 5-lipoxygenase (5-LOX) in systemic sclerosis (SSc), Kowal-Bielecka et al (1) remind us that disease-modifying therapies for SSc are far from satisfactory. With the demise of benoxaprofen and zileuton, there is not very much to offer in the way of 5-LOX inhibitors. Nonspecific antioxidants (e.g., nordihydroguiaretic acid) have been studied in asthma, without too much success. Each of the alternative strategies for reducing the deleterious effects of leukotrienes, namely curtailing the supply of arachidonate, the 5-LOX substrate, (with corticosteroids) or antagonizing leukotriene receptors (e.g., with montelukast, zafirlukast), presents problems of side effects or specificity.

An alternative 5-LOX inhibitor is Lyprinol, an over-the-counter nutritional supplement that is a lipid extract from the green-lipped mussel (*Perna canaliculus*). These mussels are farmed in pristine waters (Marlborough Sounds) in New Zealand's South Island. Studies to date indicate that Lyprinol is a 5-LOX inhibitor (2,3), has antiarthritic activity without gastric side effects in rats and humans (2,4), and is effective in asthma (5). Particularly valuable is its synergy with low-dose

corticosteroids (e.g., prednisone, dexamethasone) in ameliorating asthma (6) or experimental fibrosis in rats (7). It would seem timely to conduct a trial of Lyprinol in a few patients with SSc, perhaps in combination with a steroid.

The mussel from which Lyprinol is derived has been a traditional staple of the diet of the New Zealand Maori people. Advantages of using the lipid extract, Lyprinol, a ×20 mussel concentrate, are that it is prepared from fresh-frozen, stabilized mussels, it is salt-free, and nonallergenic, and it has no solvent residues (liquified carbon dioxide is being used under supercritical conditions to extract it). There currently are distributors of Lyprinol in the US.

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Reply

To the Editor:

We thank Dr. Whitehouse for his comments on our study. The up-regulation of 5-LOX in skin biopsy specimens from SSc patients compared with those from healthy controls, along with reports about positive effects of LOX inhibitors in fibrotic animal models, led us to the conclusion that inhibition of the 5-LOX pathway might be a treatment option in SSc. This hypothesis is further supported by recent data from our laboratories showing that leukotriene B_4, a product of the 5-LOX pathway, is also up-regulated in bronchoalveolar lavage fluids from patients with SSc. Thus, treatment with inhibitors of the 5-LOX pathway not only might have favorable effects on the progression of skin fibrosis but also might influence the pathogenesis of scleroderma lung disease.

In general, the biologic action of leukotrienes can be blocked by selective inhibitors of 5-LOX (e.g., zileuton), leukotriene receptor antagonists (e.g., montelukast and zafirlukast), inhibitors of the 5-LOX activating protein (e.g., MK-591), and newly developed dual inhibitors, which are able to block both cyclooxygenase and LOX pathways. Lyprinol is not a specific 5-LOX inhibitor but has been suggested to exert its antiinflammatory action in part via inhibition of the 5-LOX pathways.

Several points should be considered before trials with 5-LOX inhibitors are started in patients with SSc. As outlined in our report, there was considerable basal synthesis of 5-LOX in the skin of healthy controls, indicating that this pathway might be involved in physiologic processes. In addition, the SSc group was heterogeneous in that many patients showed a strong up-regulation of 5-LOX, while some others showed expression of 5-LOX in the range of that of the healthy controls. Because only the former group is likely to benefit from inhibition of 5-LOX, these patients should be selected for early trials. Certainly, the American College of Rheumatology guidelines for clinical trials in SSc should be considered (White B, Bauer EA, Goldsmith LA, Hochberg MC, Katz LM, Korn JH, et al. Guidelines for clinical trials in systemic sclerosis [scleroderma]. I. Disease-modifying interventions. Arthritis Rheum 1995;38:351–60).

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Congenital fascial dystrophy, a new scleroderma-like genetic disease with limitation of joint mobility: comment on the clinical image presented by Di Rocco

To the Editor:

Congenital fascial dystrophy, described by Di Rocco as stiff skin syndrome (1), is a scleroderma-like syndrome that is virtually unknown to rheumatologists, even though patients with this condition are usually receiving treatment at rheumatology institutions. This autosomal recessive disease is often identified as scleroderma or sclerodermatomyositis because of indurations of the soft tissues, contractures, and limitation of joint mobility. Because of such misidentification, patients may be subjected to aggressive and harmful therapy.

In 1971, Esterly and McKusick (2) described stiff skin syndrome, a condition recognized as a localized connective tissue disorder or limited mucopolysaccharidosis without mucopolysaccharidurıa. Subsequently, highly heterogeneous disease processes and various scleroderma-like dysmorphic syndromes were reported under this name (3–6). In single cases, Alcian blue deposits were observed between collagen fibers (2,7–9), which favored some relationship with mucopolysaccharidosis.

Our group has reported cases in which patients display stony-hard generalized indurations of the soft tissues, with no visceral involvement and no immunologic or vascular abnormalities (10,11). Frequently, these changes are already noticeable on the buttocks and thighs during the first year of life, with progressive involvement of the trunk and limbs. Because of contractures of the limbs, patients have characteristic tiptoe

posture and difficulty walking (Figure 1). Sharp demarcation of the sclerotic tissues at the inguinal channel is also characteristic; thus, the vessels and nerves pass freely into the limbs, causing no vascular or nervous system derangement. The general condition of patients is quite satisfactory. The only life-threatening aspect is tightening of the thoracic fascia, which may result in underdevelopment of the thorax and pulmonary insufficiency in older patients.

All patients that we described as having congenital fascial dystrophy (10,11) had markedly thickened fascia, with no inflammatory infiltrates (Figure 2A). However, electron microscopic evaluation of the fascia disclosed giant (up to 300 nm) amianthoid-like fibrils, some of which were not adequately linked to form definite collagen fibrils (10,11) (Figure 2B). Our most recent immunohistochemical and electron microscopic studies of fascia and cultured fibroblasts from patients with congenital fascial dystrophy showed the absence of collagen III, the presence of a large amount of myofibroblasts, and overproduction of spectrin and the filamentous form of collagen VI (12). This would suggest that the abnormal composition of the fascia depends on modulation of fibroblasts into myofibroblasts capable of producing spectrin and long-spacing collagen.

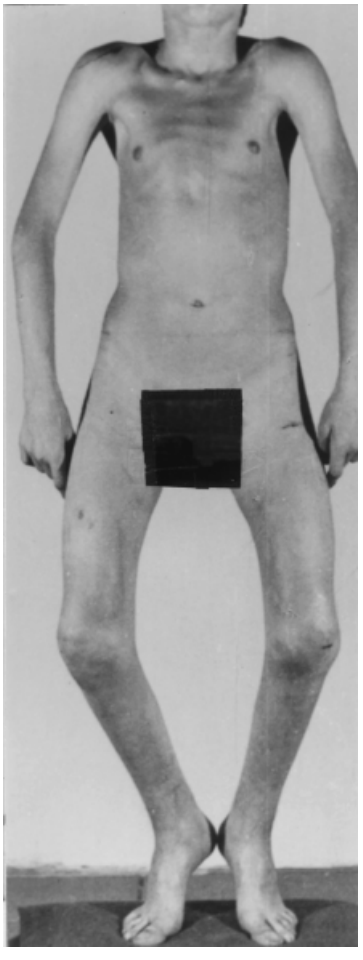

Figure 1. Congenital fascial dystrophy. The patient has stony-hard, profound indurations involving the skin and deeper tissues of the whole body, which are especially pronounced on the thighs and buttocks. The tiptoe posture, caused by contractures of the lower limbs and limitation of mobility of the knees and hips, is characteristic. The thorax is thinned, in contrast to the well-developed shoulder muscles.

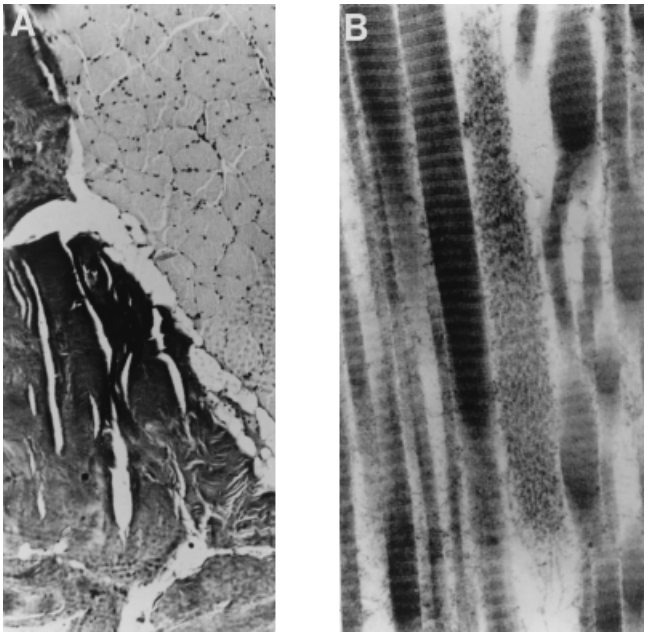

Figure 2. Fascia from a patient with congenital fascial dystrophy. **A,** Verhoeff-van Gieson–stained section, showing marked thickening of the fascia (4 times normal). No inflammatory infiltrates were observed, and the muscle was not involved (magnification × 60). **B,** Electron microscopic image, showing amianthoid-like collagen fibrils with major and minor periodicity. A bundle of aggregated microfibrils runs parallel to the collagen fibrils. Some giant fibrils showed divisions into 2 or 3 branches (magnification × 50,000).

Of special practical interest is the occurrence of abortive forms of congenital fascial dystrophy that mimic deep morphea or deep linear scleroderma (13,14). Such cases are most frequently thought to be scleroderma and are treated as such, with no effect. In our experience, patients with congenital fascial dystrophy can improve considerably if rehabilitation is started early after onset and is continued throughout life. An intensive rehabilitation program may prevent severe pulmonary side effects. We have patients who, in spite of persistent stony-hard indurations, are sportsmen, and 3 of our female patients have given birth to normal babies. We believe that congenital fascial dystrophy, although related to a highly heterogeneous group of diseases referred to as stiff skin syndrome, is a distinct entity in terms of pathology, composition of fascia, course, and outcome.

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Cognitive function in fibromyalgia: comment on the article by Park et al

To the Editor:

Physicians recognize memory complaints to be frequent in patients with fibromyalgia. It is not clear, however, how the recent study by Park et al (1) did more than allow those patients who chose to reveal their concerns to do so in a quantifiable manner. Thus, if a patient tells you he or she cannot repeatedly lift a 10-pound weight because of pain, then on testing it would be no surprise to find this result. There are techniques to assess consistency of effort, and where these are included, the results of previous studies (2,3) suggest that the failure of memory is more likely a failure of effort. Results of our own very recent study (4) suggested that this effort failure correlated well with patients' perceptions and certification for disability. Given this background, surely this aspect of proof of effort should be included in any similar study; otherwise, one will merely find that patients validate their predictions of their memory by their responses.

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Edmonton, Alberta, Canada

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Reply

To the Editor:

Drs. Russell and Gervais suggest that our findings of significant cognitive deficits in patients with fibromyalgia (FM) can be attributed to a failure of effort on the part of FM patients. There are two lines of evidence to suggest that this is not the basis for our findings. First, perhaps the most sensitive measure of cognitive function is speed of processing (Park DC, Lautenschlager G, Hedden T, Davidson N, Smith AD, Smith P. Visuo-spatial and verbal memory across the lifespan. Psychol Aging. In press), and this is a measure on which FM patients performed better than older adults and as fast as young adults. The finding of intact speed of processing, but impaired working memory and long-term memory, does not accord with a motivational explanation, since one would expect to see a general decrement across tasks rather than selective decrements specific to certain tasks. Second, to address effort and fatigue issues, our study was designed to have 3 blocked segments of tasks, each block of which included measures of speed, working memory, long-term memory, recognition memory, verbal fluency, and vocabulary. We found no evidence whatsoever indicating that FM patients showed decreased performance across the 3 testing blocks, although they did consistently show deficits in working memory and long-term memory within each block. Thus, we measured consistency of effort and found it to be unchanging for FM patients as well as for young and old adults across a 2-hour period.

These two combined findings suggest a high/sustained level of motivation in FM patients in this study and no response bias toward poor performance, since performance was excellent on some cognitive tasks but not on others. The data are more suggestive of frontal and/or hippocampal dysfunction than they are of motivational deficits. We are actively pursuing studies to investigate neural mechanisms underlying the observed deficits.

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