8. Heytman M, Ahern MJ, Smith MD, Roberts-Thomson PJ. The long-term effect of pulsed corticosteroids and the efficacy and toxicity of chrysotherapy in rheumatoid arthritis. J Rheumatol 1994;21:435–41.
9. Beato M. Gene regulation by steroid hormones. Cell 1989;56: 335–44.
10. Youssef PP, Triantafillou S, Parker A, Coleman M, Roberts-Thomson PJ, Ahern MJ, et al. Effects of pulse methylprednisolone on cell adhesion molecules in the synovial membrane in rheumatoid arthritis: reduced E-selectin and intercellular adhesion molecule 1 expression. Arthritis Rheum 1996;39:1970–9.
11. Youssef PP, Haynes DR, Triantafillou S, Parker A, Gamble J, Roberts-Thomson PJ, et al. Effects of pulse methylprednisolone on inflammatory mediators in peripheral blood, synovial fluid, and the synovial membrane in rheumatoid arthritis. Arthritis Rheum 1997;40:1400–8.
12. Youssef PP, Cormack J, Evill CA, Peter DJ, Roberts-Thomson PJ, Ahern MJ, et al. Neutrophil trafficking into inflamed joints in patients with rheumatoid arthritis, and the effects of methylprednisolone. Arthritis Rheum 1996;39:216–25.

Reply

To the Editor:

We agree with Dr. Roberts-Thompson et al that there are parallels between the effects of corticosteroids in RA and the clinical and molecular effects of monoclonal anti-TNFα therapy that we have been charting since 1992. Our studies suggest that the mechanism of action of anti-TNFα antibody in RA involves multiple pathways, including downstream effects on the production of other cytokines, vascular adhesion molecules, matrix metalloproteinases, and angiogenic factors (for review, see refs. 1–4).

We have speculated that one reason the effect of anti-TNFα therapy may outlive its biologic activity is a function of the time it takes to reestablish cellular influx, interactions, and critical mass of tissue for sustaining the inflammatory reaction. Presumably, the signals that drive TNFα production are not abolished by the therapy and result in the relapse of disease manifestations.

While we do not yet understand the reason only ~80% of patients in our clinical trials respond to anti-TNF therapy, we do not agree with the assertion of Roberts-Thomson and colleagues that tachyphylaxis is universal with this form of therapy. In an open study on repeated use of anti-TNF antibody, we had found a trend in some (but not all) patients toward a reduction in the duration of response (5). However, in a recently completed randomized clinical trial (6), we were able to define optimal conditions that permitted repeated and efficacious use of the anti-TNF antibody infused over a period of 14 weeks. In the groups with optimal response, >70% of patients showed very good response during the active treatment period and <50% of treated patients had relapsed at the termination of the study, 12 weeks after the last infusion of the antibody.

The long-term treatment of RA with TNFα blocking agents has only just begun, and its efficacy and safety profile will become established in the foreseeable future. Comparisons with corticosteroid therapy will become more meaningful with increased knowledge, but the hypothesis that the effect of corticosteroids in RA is due mainly, or solely, to the suppression of TNFα production is an interesting one and deserves further examination. We are convinced that such molecular and cellular investigations will prove valuable in the development of new and better therapies for RA.

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1. Maini RN, Elliott MJ, Brennan FM, Williams RO, Chu CQ, Paleolog E, et al. Monoclonal anti-TNFα antibody as a probe of pathogenesis and therapy of rheumatoid disease. Immunol Rev 1995;144:195–223.
2. Maini RN. The role of cytokines in rheumatoid arthritis: the Croonian Lecture 1995. J R Coll Physicians Lond 1996;30:344–51.
3. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol 1996;14:397–440.
4. Feldmann M, Elliott MJ, Woody JN, Maini RN. Anti-tumour necrosis factor-α therapy of rheumatoid arthritis. Adv Immunol 1997;64:283–350.
5. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Bijl H, et al. Repeated therapy with monoclonal antibody to tumour necrosis factor α (cA2) in patients with rheumatoid arthritis. Lancet 1994;344:1125–8.
6. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. The therapeutic efficacy and immunogenicity of multiple intravenous infusions of anti-TNFα monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis. Submitted for publication.

A potential mechanism of cyclosporine-associated bone pain: comment on the radiologic vignette by Stone et al

To the Editor:

The radiologic vignette by Stone et al on bone pain in a transplant recipient (1) raises the issue of the bone pain syndrome associated with cyclosporine (CsA). This syndrome was first described in 1994 (2,3) and has been shown to be responsive to calcium channel blockers (2,4). We would like to propose a mechanism for the bone pain syndrome and its responsiveness to calcium channel blockers.

CsA exerts its immunosuppressive effect by forming a complex with an intracellular protein called cyclophilin, one of a class of proteins known as immunophilins. This complex then binds calcineurin, inactivating it. Calcineurin is a Ca^{2+}-regulated protein phosphatase required for the activation of T cells in response to antigen stimulation (for review, see ref. 5). Calcineurin participates in a signal transduction pathway in T cells, leading to activation of a specific set of genes (6). Transcription of these genes results in T cell proliferation and initiation of an immune response. Elimination of calcineurin activity (by treatment with CsA) blocks the cellular immune response, resulting in suppression of cell-mediated transplant rejection.

Inhibition of calcineurin is likely to generate not only immunosuppression, but also some of the toxicities associated with CsA use. The pathophysiology of the nephrotoxicity commonly seen with CsA might be relevant to the bone pain syndrome described by Gauthier and Barbosa (2) and Naredo Sanchez et al (3). Kidney tubule epithelial cells die when

cultured with CsA, but can be partially protected from the toxic effects of the drug by either removing Ca^{2+} from the growth medium or co-treating the cultured cells with calcium channel blockers (7).

A unifying hypothesis is that activation of Na^+/K^+-ATPase by the Ca^{2+}-regulated phosphatase calcineurin is an important mechanism for regulating intracellular concentrations of Ca^{2+}. Inhibition of calcineurin by CsA would lead to an overall decrease of Na^+/K^+ pump activity, and thus increase the intracellular concentration of Ca^{2+}, leading to the pathologic activation of calpain, a Ca^{2+}-dependent proteolytic enzyme, which in turn would lead to cell death. Any cell type in joints or bones that had a Na^+/K^+-ATPase regulated by calcineurin would be affected by CsA. Furthermore, given this potential link between calcium-mediated bone pain and nephrotoxicity, it would be interesting to know whether transplant patients treated with calcium channel blockers have a decreased incidence of nephrotoxicity.

It is fortunate for individuals requiring treatment with CsA that the mechanism-based toxicities involve different roles for calcineurin in non–T cells (Na^+/K^+-ATPase-dependent Ca^{2+} regulation) and T cells (calcium-dependent transcription factor regulation). This allows treatment of a toxicity (bone pain) without mitigation of the clinically desirable effect (inhibition of T cell activation). Calcineurin has also been implicated as a factor regulating nitric oxide synthase (8) and dynamin I GTPase in nerve cells (9), and so it might also play a role in the neurotoxicity associated with CsA treatment.

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1. Stone JH, Peterfy CG, Sack KE. Bone pain in a transplant patient. Arthritis Rheum 1997;40:1361–3.
2. Gauthier VI, Barbosa LM. Bone pain in transplant recipients responsive to calcium channel blockers. Ann Intern Med 1994; 121:863–5.
3. Naredo Sanchez E, Balsa Criado A, Sanz Guajardo A, Pantoja Zarza L, Martin Mola E, Gijon Banos J. Leg bone pain syndrome due to cyclosporine in a renal transplant patient. Clin Exp Rheumatol 1994;12:653–6.
4. Barbosa LM, Gauthier VJ, Davis CL. Bone pain that responds to calcium channel blockers: a retrospective and prospective study of transplant recipients. Transplantation 1995;59:541–4.
5. Kincaid RL, O'Keefe SJ. Calcineurin and immunosuppression: a calmodulin-dependent protein phosphatase acts as the "gatekeeper" to interleukin-2 gene transcription. Adv Protein Phosphatase 1993;7:543–83.
6. Crabtree GR. Contingent genetic regulatory events in T lymphocyte activation. Science 1989;243:355–61.
7. Wilson PD, Hartz PA. Mechanisms of cyclosporin A toxicity in defined culture of renal tubule epithelia: a role for cysteine proteases. Cell Biol Int Rep 1991;15:1243–58.
8. Dawson TM, Steiner JP, Dawson VL, Dinerman JL, Uhl GR, Snyder SH. Immunosuppressant FK506 enhances phosphorylation of nitric oxide synthase and protects against glutamate neurotoxicity. Proc Natl Acad Sci U S A 1993;90:9808–12.
9. Liu J-P, Sim ATR, Robinson PJ. Calcineurin inhibition of dynamin I GTPase activity coupled to nerve terminal depolarization. Science 1994;265:970–3.

Limitations on the usefulness of procalcitonin as a marker of infection in patients with systemic autoimmune disease: comment on the article by Eberhard et al

To the Editor:

In a recent article in *Arthritis & Rheumatism*, Eberhard et al (1) reported that procalcitonin (PCT), the 116–amino acid precursor of calcitonin, is a useful marker for differentiating between systemic autoimmune disease activity and bacterial infection. Although we mainly concur with this finding, we would like to point out that patients with very highly active underlying disease, but without infection, sometimes also have markedly elevated serum PCT levels. In our studies on a group of 26 patients with active generalized Wegener's granulomatosis, we found 3 patients with PCT serum levels ranging from 0.7 ng/ml to 3.5 ng/ml (Figure 1), considerably above the normal value (upper limit 0.5 ng/ml, PCT-LumiTest; Brahms-Diagnostica, Berlin, Germany). None of the patients had any signs of infection at the time of serum collection. Initiation of immunosuppressive therapy brought clinical improvement and reduced PCT levels in these patients (2). Further limiting the value of PCT as a marker of infection is the lack of increased serum levels of PCT in patients with viral infections (3), which are at least as important as opportunistic bacterial complications in immunocompromised patients (e.g., cytomegalovirus).

In conclusion, we believe that PCT might be useful as a marker for inflammation of bacterial origin, but that it can be

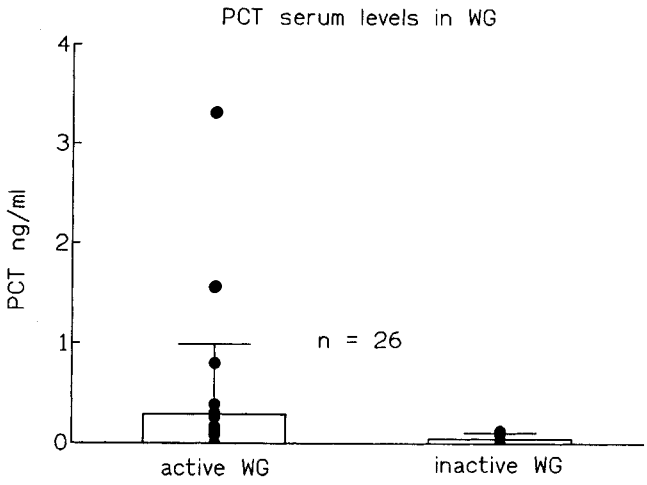

Figure 1. Serum procalcitonin (PCT) levels in 26 patients with Wegener's granulomatosis (WG). One sample from each patient was obtained during active disease and 1 during inactive disease. Boxes show the mean values; bars above boxes show the SD. The difference between the mean value for active disease and the mean value for inactive disease was statistically significant ($P = 0.02$, Wilcoxon matched pairs test).