doses, pulse methylprednisolone therapy may continue to be a useful rheumatological tool.

D A WALSH
R A DURANCE
Department of Rheumatology
Black Notley Hospital
Black Notley
Braintree
Essex CM7 8NF

- Smith M D, Ahern M J, Roberts-Thomson P J. Pulse methylprednisolone therapy in rheumatoid arthritis: Unproved therapy, unjustified therapy, or effective adjunctive treatment? *Ann Rheum Dis* 1990; 49: 265-7.
- Wong C S, Champion G, Smith M D, et al. Does steroid pulsing influence the efficacy and toxicity of chrysotherapy? A double blind, placebo controlled study. *Ann Rheum Dis* 1990; 49: 370-2.
- Vineyard G C, Fadem S Z, Dmochowski J, Carpenter C B, Wilson R E. Evaluation of corticosteroid therapy for acute renal allograft rejection. *Surg Gynecol Obstet* 1974; 138: 225-9.
- Gardiner P V G, Griffiths I D. Sudden death after treatment with pulsed methylprednisolone. *Br Med J* 1990; 300: 125.
- Bocanegra T S, Castaneda M O, Espinoza L R, Vasey F B, Germain B F. Sudden death after methylprednisolone pulse therapy. *Ann Intern Med* 1981; 95: 122.
- Moses R E, McCormick A, Nickey W. Fatal arrhythmia after methylprednisolone therapy. *Ann Intern Med* 1981; 95: 781-2.
- Garrett R, Paulus H. Complications of intravenous methylprednisolone pulse therapy. *Arthritis Rheum* 1980; 23: 677.
- Liebling M R, Leib E, McLaughlin K, et al. Pulse methylprednisolone in rheumatoid arthritis. A double-blind cross-over trial. *Ann Intern Med* 1981; 94: 21-6.
- Hansen T M, Dickmeiss E, Jans H, Hansen T I, Ingemann-Nielsen M, Lorenzen I B. Combination of methylprednisolone pulse therapy and remission inducing drugs in rheumatoid arthritis. *Ann Rheum Dis* 1987; 46: 290-5.

Response criteria for slow acting antirheumatic drugs

Sir: With great interest we read the recent article by Scott *et al* on response criteria for slow acting antirheumatic drugs.¹ We fully agree with the concept of development of an index of response to slow acting antirheumatic drugs. The authors emphasise the development of a simple index and its relation to clinical practice. The basis for this index was a consensus meeting of 16 rheumatologists. Later the response index was used in the evaluation of penicillamine and sulphasalazine. As the authors explained, however, the index has not been validated.

We have attempted to determine which variables are most useful for measuring disease activity. We evaluated, therefore, the judgment of doctors in clinical practice for high and low disease activity.² The study group comprised 113 patients with recently diagnosed rheumatoid arthritis who were studied prospectively. The follow up ranged from two to 39 months (1816 check ups). We thus obtained a disease activity score (DAS) composed of the Ritchie articular index, the number of swollen joints, erythrocyte sedimentation rate, and general health (visual analogue scale). Subsequently, the DAS was validated by comparison with various single and composite indexes used to measure disease activity, with attention to their correlation with radiographic damage and functional capacity (in preparation). This validation was made with an extended group of patients from the same prospective study (follow up range eight to 58 months, 6011 check ups). The DAS and the

Mallya index were found to be the most valid variables for measurement of disease activity.

In comparison with the response index proposed by Scott *et al*, the DAS has several advantages and one disadvantage. The disadvantage is that the DAS is not as simple to compute as the response index: a calculator is needed. To overcome this problem we have constructed a nomogram, making it easy to determine the DAS in little time without a calculator. The advantages are threefold: first of all the DAS is a reflection of the decision making of doctors in clinical practice. What happens in practice has been expressed in facts and numbers. Hence there is little distance between clinical practice and the outcome variable in evaluation of clinical trials with slow acting antirheumatic drugs. Secondly, the DAS has been shown to be a valid measurement. Last but not least, the DAS is a variable with a continuous scale. Therefore no arbitrary division of the grades of response has to be made. The mean DAS in our large database was 3.25 (range 0.30-8.30). The 'sensitivity to change' was 1.08—that is, the difference which can be measured independent of measurement error and biological variation.

In conclusion, the DAS is a valid measurement for evaluation of clinical trials. Its advantage over Dr Scott's proposed response index and other existing indexes is that it needs no further validation and is ready to use.

DÉSIRÉE M F M VAN DER HEIJDE
PIET L C M VAN RIEL
MARTIN A VAN 'T HOF
LEVINUS B A VAN DE PUTTE
University Hospital Nijmegen
Department of Rheumatology
Postbus 9101
6500 HB Nijmegen
The Netherlands

- Scott D L, Dacre J E, Greenwood A, Treasure L, Huskisson E C. Can we develop simple response criteria for slow acting antirheumatic drugs? *Ann Rheum Dis* 1990; 49: 196-8.
- van der Heijde D M F M, van 't Hof M A, van Riel P L C M, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990; 49: 916-20.

Correlation of iron exchange between the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L₁) and transferrin and possible antianaemic effects of L₁ in rheumatoid arthritis

Sir: Iron and ferritin are probably able to stimulate local free radical damage in joints of patients with rheumatoid arthritis (RA) by forming hydroxyl radicals¹ and in this way contribute to the persistence of synovitis.² In the anaemia of chronic disease in RA iron stores are increased,³ but they are probably less available for erythropoiesis.^{4,5} Owing to

the possible deleterious effects of iron stores on RA activity the treatment of RA with desferrioxamine, a parenteral iron chelator, has been studied,^{6,7} the results being controversial. In addition to the possible beneficial effects of iron chelators on RA activity, it is claimed that iron chelators might improve bone marrow iron availability and hence erythropoiesis. Giordano *et al* found a haemoglobin increase after treatment with desferrioxamine.⁸ We confirmed their findings using a new oral iron chelator—1,2-dimethyl-3-hydroxypyrid-4-one (L₁).⁹ L₁ has been shown to be an effective iron chelator¹⁰ with promising potential in the treatment of haemosiderosis and, possibly, RA. If increased bone marrow iron availability is the mechanism through which a haemoglobin increase occurs after iron chelation it can be assumed that this takes place through a higher iron saturation of transferrin, which indeed was the case in our study.⁹

Hewitt *et al* found that L₁ released 90% of iron-59 (⁵⁹Fe) bound to transferrin.¹¹ This implies that after L₁-iron chelation a high proportion of iron may be bound to L₁ instead of transferrin, suggesting a decreased rather than an increased amount of iron bound to transferrin available for bone marrow. We therefore examined both the ability of L₁ to remove iron from human transferrin and of human transferrin to remove iron from L₁.

The following method was used: 388 µl of L₁ (0.1 mg/ml) was added to 100 µl of ⁵⁹Fe-transferrin (transferrin 9.7 mg/ml). After incubation fractionation was carried out by gel permeation chromatography (Sephadex G 50; pH 7.4 with an elution velocity of 32 ml/h, recovery 76.6%). In the second experiment 20.4 µl (272 µg/l) of ⁵⁹FeCl₃ and 148 µl (2 mg/ml) of FeCl₃ were added to 5 ml (0.1 mg/ml) of L₁. Human apotransferrin (3 mg) was added to 1 ml of the ⁵⁹Fe-L₁ solution, after which fractionation was performed similarly (Sephadex G 50; pH 7.4; velocity of 32 ml/h; recovery 75.8%). The table shows the results obtained. Activity was measured with a Packard-autogamma 500 C.

The results obtained indicate that L₁ is able to remove a substantial amount of iron from transferrin, confirming findings of Hewitt *et al*,¹¹ depending on the time of incubation and the amounts of L₁ and transferrin added. It was also found, however, that apotransferrin can release iron from L₁, depending on the same factors. Thus, possibly, in a patient treated with L₁ the iron saturation of transferrin and L₁ determines the direction of iron exchange between them. In the anaemia of chronic disease in RA iron saturation of transferrin generally is low^{3,12} so it is possible that iron exchange between ferritin and transferrin mediated by L₁ takes place, explaining the haemoglobin increase after iron chelation in these patients.^{8,9} It has also been found that L₁ diffuses easily through the erythroblast membrane¹³ and thus it may incorporate iron into erythroblasts and hence

Iron-59 exchange after incubation of (A) L₁* and ⁵⁹Fe bound to transferrin and (B) apotransferrin and ⁵⁹Fe bound to L₁

	A (L ₁ + ⁵⁹ Fe-TRF*)	B (⁵⁹ Fe-L ₁ +apoTRF)
Recovery (%)	76.6	75.8
Transferrin activity (% of recovery)	64.7	7.4
L ₁ activity (% of recovery)	33.1	88.7
⁵⁹ Fe transfer† (%)	51.2	8.3

*L₁=1,2-dimethyl-3-hydroxypyrid-4-one; TRF=transferrin.

†⁵⁹Fe transfer was calculated in A by dividing L₁ (⁵⁹Fe) activity by transferrin (⁵⁹Fe) activity and in B by dividing transferrin (⁵⁹Fe) activity by L₁ (⁵⁹Fe) activity.

increase haemoglobin synthesis and erythropoiesis. Further clinical and fundamental research is warranted to establish the possible beneficial effects of (oral) iron chelation treatment on RA activity and the anaemia of chronic disease.

G VREUGDENHIL
Department of Internal Medicine
Zuiderziekenhuis
Rotterdam, The Netherlands

A J G SWAAK
Department of Rheumatology
Dr Daniel den Hoed Cancer Center
Rotterdam, The Netherlands

C DE JEU-JASPARS
H G VAN EIJK
Department of Chemical Pathology
Erasmus University
Rotterdam, The Netherlands

Correspondence to: Dr A J G Swaak, Dr Daniel den Hoed Clinic, Department of Rheumatology, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.

- O'Connell M, Halliwell B, Moorhouse C P, Aruoma O I, Baum H, Peters T J. Formation of hydroxyl radicals in the presence of ferritin and hemosiderin. Is hemosiderin formation a biological protective mechanism? *Biochem J* 1986; 234: 727-31.
- Biemond P, Van Eijk H G, Swaak A J G, Koster J F. Iron mobilisation from ferritin by superoxide derived from stimulated polymorphonuclear leukocytes. Possible mechanisms in inflammation diseases. *J Clin Invest* 1984; 73: 1576-9.
- Cartwright G E, Lee G R. The anaemia of chronic disorders. *Br J Haematol* 1971; 21: 147-52.
- Beamish M R, Davies A G, Eakins J D, et al. The measurement of reticuloendothelial iron release using iron dextran. *Br J Haematol* 1971; 21: 617-22.
- Vreugdenhil G, Kroos M J, van Eijk H G, Löwenberg B, Swaak A J G. Impaired iron uptake and transferrin binding by erythroblast in anaemia of rheumatoid arthritis. *Br J Rheumatol* (in press).
- Blake D R, Hall N D, Bacon D A. Effect of a specific iron chelating agent on animal models of inflammation. *Ann Rheum Dis* 1983; 42: 89-93.
- Polson R J, Jawod A M, Bomford A, et al. Treatment of rheumatoid arthritis with desferrioxamine. *Q J Med* 1986; 61: 1153-8.
- Giordano N, Sancasciani S, Borghi C, Fioravanti A, Marcolongo R. Antianemic and potential anti-inflammatory activity of desferrioxamine: possible usefulness in rheumatoid arthritis. *Clin Exp Rheumatol* 1986; 4: 25-9.
- Vreugdenhil G, Kontoghiorghes G J, van Eijk H G, Swaak A J G. Efficacy and safety of the oral iron chelator L₁ in anaemic RA patients. *Lancet* 1989; ii: 1398-9.
- Kontoghiorghes G J, Aldouri M A, Hoffbrand A V, et al. Effective chelation of iron in β -thalassaemia with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one. *Br Med J* 1987; 295: 1509-12.
- Hewitt S D, Hider R C, Sarpong P, Morris C J, Blake D R. Investigation of the anti-inflammatory properties of hydroxypyridones. *Ann Rheum Dis* 1989; 48: 382-8.
- Vreugdenhil G, Wognum A W, van Eijk H G, Swaak A J G. Anaemia in rheumatoid arthritis. The role of iron, vitamin B₁₂, and folic acid deficiency and erythropoietin responsiveness. *Ann Rheum Dis* 1990; 49: 93-8.
- Kontoghiorghes G J, Sheppard L. Simple synthesis of the potent iron chelators 1-alkyl-3-hydroxy-2-methylpyrid-4-ones. *Inorganica Chimica Acta* 1987; 136: 11-12.

Trauma and seronegative spondyloarthropathy

Sir: We have always been intrigued by the topic of trauma and seronegative spondyloarthropathy because of its many implications. Recent reports in the *Annals*¹⁻⁶ have been particularly stimulating and shown how much work is still needed in this area. We decided to

Occurrence of trauma before arthritis onset and B27 positivity distribution among 209 patients with seronegative spondyloarthropathy

	Patients		
	B27+	B27-	Total
With trauma	3	10	13
Without trauma	68	128	196
Total	71	138	209

Fisher's exact test: two tailed $p=0.55$; uncorrected $\chi^2=0.73$; $p=0.39$.

contribute to the subject by considering the following questions: (1) Does a trauma immediately precede the onset of seronegative spondyloarthropathy? (2) Does a trauma immediately precede the onset of a peripheral arthritis in a patient with seronegative spondyloarthropathy? (3) Is there an association between trauma, onset of arthritis, and HLA-B27?

We studied 209 patients affected by different forms of seronegative spondyloarthropathy: 138 with psoriatic arthritis, 49 with arthritis during ulcerative colitis, and 22 with ankylosing spondylitis. The prevalence of HLA-B27 was 34.0% (71 patients: 45 with psoriatic arthritis, six with ulcerative colitis, and 20 with ankylosing spondylitis). In two cases (1.0%) an articular trauma immediately preceded the onset of the seronegative spondyloarthropathy. In both cases the HLA-B27 phenotype was absent.

When we extended the definition of trauma to include every acute disorder that immediately preceded arthritis onset, even extra-articular disorders, 11 more patients were identified (5% of the total). Surgery had been carried out in five cases, spontaneous abortion had occurred in two, and thrombophlebitis, bilious colica, myocardial infarction, and phosphoric ester intoxication in one case each respectively. Three of these 11 patients had the HLA-B27 phenotype.

We then evaluated the possibility that HLA-B27 positivity was associated with the onset of arthritis following trauma. As shown in the table, no significant relation was found.

We then considered from among the total number of patients those with a peripheral arthritis (130 patients: 102 with psoriatic arthritis, 23 with ulcerative colitis, five with ankylosing spondylitis). The prevalence of HLA-B27 was 25.4% (33 patients: 27 with psoriatic arthritis, three with ulcerative colitis, three with ankylosing spondylitis). An articular trauma immediately preceded the onset of peripheral arthritis in three cases, all HLA-B27 negative (2.3%). When the extended definition of trauma (previously mentioned) was used 10 more subjects (7.7%) were included (the above mentioned cases with the exception of one who had had surgery). In three cases HLA-B27 was positive. Again, no significant association was found between the presence of HLA-B27 and peripheral arthritis onset after trauma (Fisher's exact test: two tailed $p=1.00$; uncorrected $\chi^2=0.04$; $p=0.84$).

Therefore on the basis of our results we can conclude that: (1) articular trauma can immediately precede onset of seronegative spondyloarthropathy, though the percentage of cases in which this occurs is small; (2) trauma defined as every acute disorder immediately preceding seronegative spondyloarthropathy onset is detectable in a higher

percentage of cases; (3) HLA-B27 does not seem to predispose to arthritis onset following trauma in patients with seronegative spondyloarthropathy.

RAFFAELE SCARPA
ANTONIO DEL PUENTE
CARLO DI GIROLAMO
GIROLAMO DELLA VALLE
GIOVANNI LARIZZA
ENNIO LUBRANO
PASQUALE ORIENTE
Cattedra di Reumatologia
I^o Facoltà di Medicina
Via S Pansini 5
80131 Naples, Italy

- Wisniewski J J. Trauma and Reiter's syndrome: development of 'reactive arthropathy' in two patients following musculoskeletal injury. *Ann Rheum Dis* 1984; 43: 829-32.
- Masson G, Thomas P, Bontoux D, Alcalay M. Influence of trauma on initiation of Reiter's syndrome and ankylosing spondylitis. *Ann Rheum Dis* 1985; 44: 860-2.
- Olivieri I, Gherardi S, Bini C, Trippi D, Ciompi M L, Pasero G. Trauma and seronegative spondyloarthropathy: rapid joint destruction in peripheral arthritis triggered by physical injury. *Ann Rheum Dis* 1988; 47: 73-6.
- Olivieri I, Gemignani G, Christou C, Pasero G. Trauma and seronegative spondyloarthropathy: report of two more cases of peripheral arthritis precipitated by physical injury. *Ann Rheum Dis* 1989; 48: 520-1.
- Panayi G S. Trauma and seronegative spondyloarthropathy. *Ann Rheum Dis* 1989; 48: 879.
- Olivieri I, Gemignani G, Pasero G. Trauma and seronegative spondyloarthropathy. *Ann Rheum Dis* 1990; 49: 338.

Habitual knuckle cracking and hand function

Sir: In a recent survey Castellanos and Axelrod evaluated 300 consecutive outpatients at Mount Carmel Mercy Hospital to determine whether habitual knuckle cracking is a risk factor for hand dysfunction.¹ They found no relation with osteoarthritis, but noted that 'knuckle crackers were more likely to have hand swelling and lower grip strength' and concluded that 'habitual knuckle cracking results in functional hand impairment'. I believe they have not established cause and effect in these interesting correlations.

Not everyone can crack their knuckles. Some do so with ease, whereas others are quite incapable of performing the feat. No one has determined how the joints of these groups differ. It is quite possible, for instance, that metacarpophalangeal joint laxity may both facilitate knuckle cracking and impair hand function. As this hypothesis implies that hand swelling and diminished grip occur secondary to articular structure rather than abuse, it may be that nervous citizens of Detroit can continue to crack their knuckles without fear of injury.

'Will cracking my knuckles hurt my hands?' remains a common gambit when a rheumatologist is identified as such among new acquaintances striving to make conversation. I still believe that the answer to this question is no, but perhaps it is time that we really found out.

PETER A SIMKIN
School of Medicine
Department of Medicine, RG-28
Division of Rheumatology
University of Washington
Seattle, Washington 98195
USA

- Castellanos J, Axelrod D. Effects of habitual knuckle cracking on hand function. *Ann Rheum Dis* 1990; 49: 308-9.