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

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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.

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Correlation of iron exchange between the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L_1) and transferrin and possible antianaemic effects of L_1 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 radicals[1] 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 (L_1).[9] L_1 has been shown to be an effective iron chelator[10] 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 L_1 released 90% of iron-59 (^{59}Fe) bound to transferrin.[11] This implies that after L_1-iron chelation a high proportion of iron may be bound to L_1 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 L_1 to remove iron from human transferrin and of human transferrin to remove iron from L_1.

The following method was used: 388 µl of L_1 (0·1 mg/ml) was added to 100 µl of ^{59}Fe-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 $^{59}FeCl_3$ and 148 µl (2 mg/ml) of $FeCl_3$ were added to 5 ml (0·1 mg/ml) of L_1. Human apotransferrin (3 mg) was added to 1 ml of the ^{59}Fe–L_1 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 L_1 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 L_1 and transferrin added. It was also found, however, that apotransferrin can release iron from L_1, depending on the same factors. Thus, possibly, in a patient treated with L_1 the iron saturation of transferrin and L_1 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 L_1 takes place, explaining the haemoglobin increase after iron chelation in these patients.[8 9] It has also been found that L_1 diffuses easily through the erythroblast membrane[13] and thus it may incorporate iron into erythroblasts and hence

Iron-59 exchange after incubation of (A) L_1 and ^{59}Fe bound to transferrin and (B) apotransferrin and ^{59}Fe bound to L_1*

	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

*L_1=1,2-dimethyl-3-hydroxypyrid-4-one; TRF=transferrin.
†^{59}Fe transfer was calculated in A by dividing L_1 (^{59}Fe) activity by transferrin (^{59}Fe) activity and in B by dividing transferrin (^{59}Fe) activity by L_1 (^{59}Fe) 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.

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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 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?

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 χ^2=0·73; p=0·39.

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 χ^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.

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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.

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