with a (selected) placebo group might not be strictly appropriate.

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Intravenous iron in the treatment of rheumatoid arthritis

SIR, There have been several reports on the adverse effects of the administration of intravenous iron to patients with rheumatoid arthritis (RA).¹⁻⁵

In the most recent report Blake *et al.*¹ described the results of total infusion of 1 g dextran iron in 10 patients. Two developed anaphylactic reactions. The remaining eight who completed the course, given over a period of 8-12 hours, all developed an increase in signs of inflammation, mainly in the small joints of the hands and feet, but inflammation also became more intense in joints already involved. Reactions occurred 24-48 hours after completion of the infusion and were measured by calculating the 'thermographic index'.⁶ At this point iron-binding capacity was fully saturated.¹ There was an increase in lipid peroxidase products in the synovial fluid, which are believed to exacerbate inflammation in the synovial membrane. Blake *et al.*¹ suggested that this effect was due to the iron components of the iron-dextran complex.

The experience of other workers using injections of iron complexes in divided doses is very different.

Sinclair and Duthie^{7,8} reported results for 51 patients with classical RA. All were given a total of 1 g intravenous iron in doses of 200 mg daily for five days (Ferrivenin or Iviron). Mild toxic reactions were encountered occasionally but became much less frequent when all-glass syringes were used. The iron preparation was mixed with blood in the syringe before injection. A satisfactory rise in haemoglobin (Hb) was obtained in 38 cases, accompanied by a significant fall in the erythrocyte sedimentation rate (ESR).

In a further paper Richmond *et al.*⁹ assessed the effect of higher doses of saccharated oxide of iron (SOI). Twenty six patients were in the group to be treated and 20 acted as controls. Both groups underwent the same regimen of treatment in hospital—rest in bed, aspirin, splints, and physiotherapy. 200 mg SOI was injected daily for five days a week to a total of 5 g. Side effects occurred in only one patient in the form of flushing and backache after the first three to four injections. The mean Hb level in the treated group showed a rise from 10.5 g% (g/dl) to 12.9 g% (g/dl)

one month after the last injection. No significant change occurred in the control group. The rise in Hb in the treated group was largely accounted for by a rise in the red cell count of 13.5% over the initial level one month after the last injection and was well maintained at three months, providing evidence of an increased capacity of the marrow to produce red cells. Improvement in anaemia, fall in ESR, improved functional capacity, and decrease in disease activity were not correlated with the initial values. There was little change in the mean cell haemoglobin concentration, which remained at the same level in treated and control groups. The rate of clearance of 200 mg of SOI, rapid before treatment, was unaffected after the administration of 5 g SOI. This observation was contrary to the idea that the results observed could be attributed to blockade of the reticuloendothelial system. There was a very significant increase in iron content of synovial tissue before treatment¹⁰ but little increase in the lymph nodes. There was minimal evidence of a decrease in red cell survival.¹¹

These papers present the results of administration of SOI or Ferrivenin in divided doses to a total of 77 cases of RA. It has since been observed that dextran iron is equally effective and largely free from toxic effects. It has been shown by our group (unpublished) that after injection of 200 mg of dextran iron the iron content of the synovial fluid rises rapidly within two to three hours. It must be concluded that the adverse effects reported by Blake *et al.* after continuous infusion of 1 g of dextran iron must be attributed to the release of free iron in the joints in excess of the binding capacity of protein available.

It is regrettable that a very valuable form of treatment in RA should be brought into disrepute by these very limited results in a small group of patients. The list of references lacks the inclusion of many important papers on the use of intravenous iron in RA.

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SIR, Professor Duthie misunderstands the purpose of our study, which was to examine the *mechanism* of the iron promoted synovial flare and *not* to evaluate the efficacy of this form of treatment of rheumatoid anaemia. As our article and Professor Duthie's letter point out many authors have described the synovial flare. We suggest that the reaction is mediated by iron (rather than dextran) promoted lipid peroxidation.

I have no criticism of Professor Duthie's haematological observations and failed to quote them only because our article did not address this issue. However, I would take the opportunity of describing the results of a study that was omitted from professor Duthie's extensive list of references. Bentley and Williams¹ gave iron dextran (800 mg intramuscularly) to 30 anaemic rheumatoid patients. Twenty six of the 30 patients showed a significant rise in haemoglobin at the two-month mark, but values fell back to the pretreatment level at nine months. The rise in haemoglobin was not related to pretreatment iron levels. They concluded and I quote: 'a therapeutic trial of parenteral iron will produce haematological improvement in the majority of anaemic patients and cannot therefore be taken as an indication that the anaemia was primarily due to iron deficiency. In the majority of anaemic rheumatoid patients, however, therapy should be directed at suppression of the activity of their rheumatoid disease, as this is the only current means by which lasting haematological improvement would be achieved'. Though we did not report the haematological indices in our patients, we found much the same . . . a temporary rise only. I would not choose to describe a treatment that causes the disease to flare, has no significant long-term effect on the haemoglobin, but occasionally causes anaphylaxis as 'very valuable'.

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Reference

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Systemic lupus erythematosus

SIR, The report of Soppi, Eskola, and Lehtonen¹ on identical twins discordant over 20 years for clinically

evident SLE adds to our understanding of the importance of both genetic and environmental factor(s) in the expression of this disease. To date it remains unknown whether the genetic factor(s) is requisite and the environmental factor only stimulatory or whether a certain combined quantity (more or less of one and/or the other) of the two sufficient to reach an expressive threshold is critical.

In the twins described it is of interest that the clinically unaffected sibling had a persistently raised erythrocyte sedimentation rate (ESR), for although the presence of antinuclear antibodies and other protein aberrations, including low complement levels, need not be associated with active disease, a raised ESR, though non-specific, usually suggests the presence of active inflammation or tissue damage. Could something subtle have been missed? Twenty years' observation argues against this notion, but it is not necessarily reassuring for the future. I look forward to a follow-up report 10 years from now.

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Detection of anti-dsDNA as a diagnostic tool

SIR, We read with interest the paper by Drs Swaak and Smeenk¹ on the detection of antibodies to double-stranded deoxyribonucleic acid (anti-dsDNA) as a diagnostic tool. Of 441 patients without systemic lupus erythematosus (SLE) but with anti-dsDNA no fewer than 304 (69%) developed SLE within one year as judged by the preliminary classification criteria of the American Rheumatism Association (ARA).² Longer follow up showed a cumulative incidence of SLE of 85%. We have found different results in a group of patients who, in contradistinction to the Dutch study cases, did not have antinuclear antibodies (ANA) on conventional indirect immunofluorescent testing, despite high titres of anti-dsDNA.

By reference to the anti-dsDNA results file in the pathology service laboratory covering the period 1976-83, we have identified 20 patients (12 female, eight male; mean age 51 years) who were followed up for at least a year and who had anti-dsDNA titres in excess of 30 U/ml (anti-DNA kit, Amersham International) on two or more occasions. Tests for ANA with serum diluted 1:16 on a substrate of rat liver slices were negative on every occasion for every patient included in the study. Two patients subsequently developed ANA at 20 and 25 months respectively after the anti-dsDNA were first noted. The other 18 patients remained consistently ANA negative and were tested on three to 12 occasions (mean 5.1).