whether Lyme disease originated in the USA or in Europe remains to be solved.[10]

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A rheumatological dilemma

SIR, Pullar and Capell[1] show how difficult it is to obtain an unbiased view of untreated rheumatoid arthritis (RA) and hence how difficult it is to determine whether second-line drugs in the treatment of RA actually affect the fundamental course of the disease. There is, however, a further problem that they do not address. It is the implications of the small sample sizes that have been used in assessing efficacy, even if only by process measures. If in the statistical testing an α value of 0·05 (95% confidence) and a β value of 0·10 (90% power) are used then the difference in the total proportion of patients achieving success which can be detected is given in the table for the examples drawn from Pullar and Capell.

	Numbers in placebo group at final assessment	*Minimum detectable difference in total proportion with successful outcome*
Multicentre study 1978[2]	85	0·25
Co-operating clinics 1973[3]	21	0·45

This means that even in the 1978 Multicentre study a true difference of as much as 25 percentage points would still be missed 10% of the time.

Neither of the examples cited has sufficient likelihood of detecting a beneficial therapeutic difference of 0·2, i.e. 20% 'extra' patients 'improve' after therapy. To achieve the desired likelihood of detecting a difference of 0·2 a minimum of 105–125 patients in each group at final assessment would be required. This number depends in part on the absolute value of the proportions involved.

It is an uncomfortable fact that to answer the question of whether or not a therapy produces a modest improvement in a disease state, a well-conducted study with a large number of patients is required.

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SIR, We would agree wholeheartedly with the above comments regarding the possibility of a large type II error occurring in some studies of second-line drugs and the large numbers of patients required to overcome this problem. We have in an earlier paper made similar comments about outcome measurements.[1] This question of numbers, however, is an entirely separate issue from the one we raised. Even with large numbers we would still expect a selection process to take place so that patients with initially severe disease would drop out more frequently and rapidly if treated with placebo rather than with active drug. The end result of this would be that even greater numbers might be needed to show a difference between the groups and that, in any case, such comparison

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 treatment[10] 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.*[1] 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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