As confirmed by doppler/ultrasonography and phleboscintigraphy, at the one-month visit a complete resolution of venous occlusion was evident in 7 (77%) episodes and all episodes of TP were completely resolved at the two-month visit. During the period of CSA treatment no relapse of TP occurred. In no patients did doppler/ultrasonography demonstrate residual venous insufficiency over the follow up (mean follow-up: 48 months; range: 12-70).

CSA was well tolerated without a significant rise in blood pressure or renal or hematologic toxicity. During CSA therapy 2 patients had recurrences of aphtous stomatitis, whereas other clinical features associated with TP were completely resolved at the 6-month visit.

Our open study seems to indicate that low dose CSA could play an important therapeutic role in the treatment of acute episodes of deep TP of the legs complicating BD and in the prevention of post-phlebitic syndrome. However, a randomized blinded trial is necessary to confirm these results.

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Hormones, sex ratios and juvenile rheumatoid arthritis

Sirs,

Khalkhali-Ellis *et al.* (1) report that patients with juvenile rheumatoid arthritis (JRA) have low levels of testosterone and dehydroepiandrosterone sulphate.

I have proposed that the endocrine status of patients with some classes of rheumatic disease may be associated with the unusual reported sex ratios (proportions male) of probands and their relatives (2). I cited evidence that patients with HLA B 27-related diseases (who are predominantly male) reportedly have an excess of brothers, and that patients with rheumatoid arthritis (who are predominantly female) reportedly have an excess of sisters. This paper prompted the publication of evidence confirming both propositions (3-5), so it seems reasonable to suspect that both may be correct.

There is now very substantial evidence that the hormone levels of both parents around the time of conception partially control the sexes of mammalian (including human) offspring, high levels of parental androgens being associated with sons and low levels with daughters (6). Other evidence suggests that HLA B 27 codes for high testosterone levels in men (7) and B 15 for low levels in women (8). Thus the hormone levels in some HLA-related diseases seem to be genetically determined precursors of the diseases rather than their consequences.

The question arises: Could such a conclusion apply to JRA? Aaron *et al.* (9) published data which strongly suggest that the sex ratios of sibs of probands with pauci- and poly-articular JRA are highly significantly different (chi-squared = 7.2, $p < .01$), the former having an excess of sisters, and the latter an excess of brothers.

In general, two quite different hypotheses are available if the above data are accepted:

1. If probands **and** their sibs are disproportionately often of the same sex, then parental (including maternal) hormone levels are presumably skewed in the appropriate direction. So the unusual intra-uterine hormone levels may be (partially) the cause of the disease.
2. Given that the parents have an unusual hormone profile (to account for the unusual sex ratio of probands **and** their sibs) the proband may have inherited this and thus the **proband's** post-natal hormone profile may (partially) cause the disease.

It is, in principle, possible to discriminate between these two hypotheses. But a good deal of work would be required to do so. Before that, I suggest that attempts should be made to confirm the result of Aaron *et al.* (9) described above. Do pauci- and poly-articular JRA probands really have sibs with a significantly different sex ratio? If this should be confirmed, that would suggest that poly- and pauci-articular JRA are very different with regard to their endocrinological antecedents.

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Reply

Sirs,

In regard to Dr. James' comments on our paper, we reported that patients with JRA have low levels of testosterone and dehydroepiandrosterone sulphate. Dr. James suggested that Aaron *et al*. published data strongly suggesting that the sex ratios of siblings of pro-bands with pauci- and polyarticular JRA are highly significantly different, with the paucis having an excess of sisters and the polys an excess of brothers. In our study, looking at the ratio of sisters and brothers in the patients that we evaluated, this theory could be debated. We evaluated ten polyarticular patients, of which one had four sisters, one had two sisters, two had one sister only, one had one sister and one brother, one was an only child, and four had one brother only. In the pauciarticular group we evaluated nine patients, of which five had one sister only, three were only children, and one had one brother. This did confirm that the pauciarticulars had an excess of sisters and the polyarticulars had more brothers; however, the dominant sibling type was female for both the polyarticular and pauciarticular groups. This would also suggest that polyarticular and pauciarticular JRA are not different with respect to their endocrinological antecedents. We thank Dr. James for his interesting comments and for the opportunity to address his intriguing theories.

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Treatment of recurrent oro-genital ulceration with low doses of thalidomide

Sir,

Thalidomide in a dosage of 100 mg/day is an effective treatment for severe aphthous stomatitis but it is not without some risk (1). Some recent studies confirm that thalidomide in a dosage of 200 mg/day is an effective treatment for aphthous ulceration in patients with HIV infection (2), and that 100 mg/d is as effective as 300 mg/d for oral and genital ulcers (OGU) in Behçet's syndrome (3). Previous studies (4) have suggested that thalidomide was as effective at the dosage of 50 mg/d for aphthous ulceration and that the duration of treatment might be a major factor in the significant risk of polyneuropathy. In order to assess the dosage of thalidomide with the best efficacy/toxicity ratio, we performed a prospective study from 1993 to 1996.

The study was monocentric with an open design. The aim of the study was to define the lowest dosage of thalidomide required for complete clearing of all OGU after an initial dosage of 50 mg/day for one month. The inclusion period was from 1993 to 1996. The patients who participated gave their written informed consent. Precautions were taken to prevent pregnancy; all women of childbearing age were given pregnancy tests every month and used a reliable method of contraception.

The diagnosis of OGU, made by three of the physicians who participated in the study, was based on the clinical appearance of the lesions. Seventeen patients with OGU (mean age 43 yrs.; sex ratio M/F: 12/5) were included. The diagnosis was: recurrent oral ulcerations (8 pts.); oro-genital ulcerations (3 pts.); Behçet's syndrome (4 pts.); and recurrent OGU associated with leukemia (2 pts.). All patients had failed to respond to any other treatment (prednisone, colchicine, dapsone) and had serious (food intake impeded) or severe (only liquid intake) functional impairment.

The initial dosage of thalidomide was 50 mg/d (1 tablet) for all patients for one month ; if the patient's status improved, the dosage was reduced to one tablet every other day for one month, then one tablet twice a week for the following months. Electrophysiologic tests were performed at the start of the study and every 6 months thereafter, using the methodology recommended by Gardner (5). A clinical neurological evaluation was carried out monthly.

Out of the 17 patients, 10 entered remission within the first month and 7 improved. Six of these entered remission after 2 months, and the last one after 4 months. Remission was prolonged on a 200 mg dosage administered over one week in 12/17 patients: out of 10 patients who tried a 150 mg dosage administered over one week only 4 relapsed, and out of the 6 patients who tried a 100 mg dosage administered over one week only one relapsed. The mean time of treatment was 22 months (5- 54). The side effects were drowsiness (6 pts.), weight increase (2 pts.), mood disturbances (2 pts.), dry mouth (2 pts.) and hypotension (2 pts.). Electrophysiologic tests showed a decrease of sensory nerve action potential in 6 patients after a mean treatment time of 9 months. Treatment was withdrawn from only 3 patients because of paresthesia (2 pts.) and areflexia (1 pt). There was no difference in efficacy and toxicity of the treatment for Behçet's disease, leukemia or idiopathic OGU. All patients who tried to stop the drug (5 pts.) relapsed in a mean time of 7 weeks.

Our study shows that thalidomide is effective in the treatment of OGU at the low dose of 50 mg/d and that 1 tablet every 2 or 3 days was effective in maintaining remission in more than 60% of the patients. Mild electophysiologic abnormalities were frequent (6/17), but we never observed severe polyneuropathy. We conclude that in the treatment of OGU with thalidomide, a low dosage of 50 mg/d is effective in most cases, provided that the patient is carefully followed up to assure the early detection of peripheral neuropathy.

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