from breast carcinoma. The onset of this type of polyarthritis is during old age and usually the polyarthritis is asymmetric (2). There have been 3 case reports of RS3PE syndrome associated with carcinoma, specifically involving endometrial adenocarcinoma (6), pancreas carcinoma (7), and gastric carcinoma (8). It is possible that alterations in immunity induced by malignancy could be the trigger of RS3PE syndrome.

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Treatment of thrombophlebitis of Behcet's disease with low dose cyclosporin A

Sir,

Recurrent thrombophlebitis (TP) of the lower limbs are the most common vascular manifestations of Behçet's disease (BD) (1, 2). Pulmonary embolization is rare (1, 3). Postphlebitic syndrome and leg ulcers are the most frequent complications of TP (4). The treatment of TP of BD is still controversial. Controlled studies demonstrating the efficacy of anticoagulants alone and/or of a single immunosuppressant drug are lacking. In recent years the important therapeutic role of cyclosporin A (CSA), through its selective action on helper T-cells, in BD has been demonstrated (5).

Considering the rarity of thromboembolic complications (1, 3), the absence of specific abnormalities of coagulation or fibrinolytic activity (6), the potentially dangerous role of anticoagulants in the treatment of TP in BD (7, 8), the evidence that venous immune-mediated vasculitis represents the prominent histological lesion and the central role played by T-cells in the pathogenesis of the disease (9), we decided to evaluate the efficacy of CSA, without adding anticoagulants, in the treatment of deep TP of the legs in a consecutive series of patients with BD.

Between January 1990 and December 1995, after approval by the appropriate local ethical committees and the patients' informed consent were obtained, we treated 9 episodes of deep TP of the lower limbs occurring in 7 consecutive patients meeting the ISG criteria for BD (10). All episodes of TP were diagnosed within 15 days from the onset. The demographic and clinical characteristics, including the site of venous occlusions, of the 7 patients are summarized in Table I. None of the patients had contra-indications for CSA therapy (high blood pressure, abnormal liver and renal function, or altered blood cell counts).

Patients 3 and 7 had a second episode of TP 2 years and 2 months after CSA withdrawal and were treated with CSA again. Three patients had TP at diagnosis and 4 during the course of the disease (mean interval from the diagnosis: 22 months; range: 2-36). The latter 4 were in treatment with colchicine, methylprednisolone (2 patients) and azathioprine.

The diagnosis of deep TP was made by clinical evaluation (local pain over the affected veins, dilatation and varicosity of the superficial veins with evidence of collateral circles, swelling and edema of the leg), doppler/ultrasonography and ^{99m}Tc red blood cell phleboscintigraphy (3 patients).

Previous therapy was interrupted and CSA was given at an initial dose of 5 mg/Kg/day, At clinical remission of TP the drug was reduced monthly by 1 mg/Kg/day to a maintenance dose of 2 mg/Kg/day for a further 6 months. If required, acetaminophen was given to control the symptoms during the first weeks.

Patients were examined at one-month intervals. Each visit included a physical examination, blood pressure measurement, blood samples to monitor the response to CSA therapy and doppler/ultrasonography. After 1 and 6 months phleboscintigraphy was repeated in 3 patients. After CSA withdrawal the patients were evaluated every 3 months. TP coexisted with erythema nodosum in 6/9 (66%) episodes, aphtous stomatitis in 5/9 (55%), uveitis in 4/9 (44%), arthritis in 3/9 (33%), mucocutaneous lesions in 1/9 (11%).

Table I. Demographic, clinical characteristics of the 7 patients with BD and deep TP of the lower limbs.

Clinical features	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6	Pt. 7
Sex/age (years)	M/49	M/26	F/21	F/30	M/25	M/25	M/45
HLA B5/51	-	+	+	+	+	-	-
Pathergy test	-	+	+	-	+	-	-
Aphtous stomatitis	+	+	+	+	+	+	+
Uveitis	-	+	+	+	+	+	-
Genital ulcers	+	-	+	-	-	-	+
Erythema nodosum	+	+	+	+	+	+	+
Cutaneous lesions	+	-	-	+	+	+	+
Arthritis	+	+	+	-	+	-	+
Colitis	-	-	-	-	-	-	-
CNS involvement	+	-	-	-	-	-	-
Arterial lesions	-	-	+	-	-	-	-
Thrombophlebitis	+	+	+	+	+	+	+
Leg involved	L	L	L/1st, R/2nd	L	R	R	R/1st, L/2nd
Vein occlusion	P	I-F	I-F-P/1st, F-P/2nd	I-F	I-F	P	P/1st, P/2nd

L = left, R = right, 1st = first episode, 2nd = second episode, I = iliac, F = femoral, P = popliteal

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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