malisation of acute phase reactants.
Nevertheless, tachycardia and irritability occurred spontaneously 6 months later, while the patient was still taking this treatment. She had no diarrhoea or trembling. Weight and joints remained stable. Biological examination (Bayer Immuno-one; immuno-enzymatic procedure) detected hyperthyroidism: the ultrasensitive thyroid-stimulating hormone concentration was 0.05 mIU/l (normal: 0.6-6) and the free T4 concentration was 23 pmol/l (normal: 11-24). Clinical examination and scintigraphy showed the thyroid gland to be normal. We investigated possible autoimmunity: rheumatoid factor was as previously detected (ELISA: 20 IU - Normal < 10), but no significant quantities of anti-nuclear (50 IU) or anti-thyroglobulin or anti-peroxidase antibodies were detected.
Propranolol (40 mg/day) was introduced as a symptomatic treatment with success, and etanercept was continued. All clinical symptoms disappeared within a few weeks and one month later, thyroid function was normal (usTSH: 0.6 and fT4: 16.8).
We believe that this patient had transient mild hyperthyroidism with clinical and biological manifestations, possibly facilitated by tumour necrosis factor alpha antagonist.
An association between autoimmune thyroiditis and RA has long been suspected, but remains a subject of debate (2). Tumour necrosis factor alpha (TNF-) antagonists are an important new addition in RA treatment. Etanercept is a recombinant fusion protein consisting of the soluble TNF receptor (p75) linked to the Fc portion of human IgG1, produced in a hamster cell line. Safety analysis has demonstrated that this treatment is well tolerated. However, the production of non-neutralising antibodies directed against the etanercept molecule has been observed in ≈16% of patients taking the drug. In addition, antibodies against double-stranded DNA have been detected in 15% of treated patients and anti-nuclear antibodies in 11% (3). Furthermore, patients receiving etanercept may develop anti-animal antibodies that interfere with laboratory monoclonal antibody assays. Thyroid-stimulating hormone and T4 abnormalities, in particular, may have been underestimated for this reason (3). Similarly, autoimmunity may result from cross-reactive immunogenicity with these antibodies. The thyroid seems to be very sensitive to autoimmunity. Thus, thyroid dysfunction and thyroiditis have already been reported with various immunological treatments for multiple sclerosis, such as interferon beta-1a and pulses of humanised anti-CD52 monoclonal antibody (4), and also with the use of recombinant human TNF receptor: IgG chimera (rhu TNFR:Fc; Immunex) in combination with interleukin 2 for metastatic cancer (5).
This is the first report of a case of transient hyperthyroidism in a patient with rheumatoid arthritis treated by etanercept. Thyroid function should be taken into account in patients receiving this treatment.

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Minor but important symptoms and signs in primary hypertrophic osteoarthropathy

Sirs,
Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by clubbing fingers and proliferative periostitis of the long bones. HOA may be classified as either primary (PHOA) or secondary, and is most often associated with neoplastic or infectious diseases. There are three incomplete forms of HOA: clubbing fingers, periostitis without clubbing fingers, and pachydermoperistosis with so-called "minor manifestations". Minor manifestations include synovial effusion, seborrhea, folliculitis, hyperhydrosis, hypertrophic gastropathy and acroosteolysis. Some of the minor signs and symptoms of PHOA are not included in present diagnostic criteria, but may be helpful in establishing the diagnosis of HOA. We present the results of our study regarding the prevalence of these symptoms and signs in patients with primary HOA.
At the Department of Rheumatology of the University Hospital "Sestre milosrdnice" in Zagreb-Croatia, during the period 1970-1996 we diagnosed primary HOA in 76 patients, 71 men (93.5%) and 5 women (6.5%). We followed up the majority of these patients for several years,and some of them for more than 2 decades (11± 8.4 yrs). The patient history and results of clinical examinations were recorded in a simple chart designed in our department. The average age of the patients was 38.7 years (range 18-64 years). The disease started in childhood (up to age 14) in 62 patients and in adolescence in 14 patients.
The frequency of minor symptoms and signs are presented in Table I. Palmar and periungual erythema is accompanied by velvet-like and thickened skin, whilst excessive sweating is accompanied by a strong and penetrating odour. Changes regarding the angle between the nail and nail-bed region, and accordingly changes in shape are dependent on the phase of clubbing. Apart from changes in shape (convexity in all directions), the nails have longitudinal grooves and white dots. Stiffness in the hands and feet (lasting no longer than 30 minutes) were mainly present in the evening. Periarticular edema was present mostly in the ankle joints, and occasionally in the wrists and knees. Pathohistological

Table I. Minor symptoms and signs present in patients with primary hypertrophic osteoarthropathy (n = 76).

Symptoms and signs	No.	%
Fatigue	18	23.7
Palmar & periungual erythema	37	48.1
Enlarged fingers	52	68.4
Sense of warmth and burning in hands and feet	76	100.0
Deeper nasolabial fold	76	100.0
Loss of mimics	64	84.2
Leonine face	15	19.7
Cutis verticis gyrata	28	36.8
Arthralgia	30	39.5
Periarticular edema	40	52.6
Erythematous skin over joints	7	9.2
Gynaecomastia	3	3.9
Delayed sex development	51	67.1

findings performed on 9 patients revealed edematous synovium with mild infiltrations of lymphocytes, and no hyperplasia.

Various signs and symptoms can be found in HOA. The presence of digital clubbing and periostitis of the long bones is the minimum for the diagnosis of HOA. A detailed history and physical examination enable one to find other signs and symptoms of the disease. Some of the so-called minor symptoms are not always present, and are mostly associated with progression of the disease. These are erythema, hyperhydrosis, velvet-like skin, edema of periungual tissue, skin changes over the affected joints, and an unpleasant odour of perspiration. Periosteal reaction is the most dependent factor for less stable symptoms and signs of HOA. On the other hand, hypotonia and general fatigue, lionel face and cutis verticis gyrata, if present, are constant symptoms. Other constant signs are tight skin and a sensation of warmth and burning in the hands and deeper nasolabial fold.

In conclusion minor symptoms and signs of primary HOA can be divided into variable and stable ones. Their duration and level of expression depend on the progression of the disease. More stable signs and symptoms are more reliable in the diagnosis of HOA, but both can be helpful in establishing the diagnosis.

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Prostaglandin E_1 restores the levels of vWF and ACE in chronic critical limb ischemia in systemic sclerosis

Sirs,

Systemic sclerosis (SSc) is a multisystem disease that induces tissue fibrosis and involves mainly the microvascular system leading to endothelial damage and profound modification of the control of the vascular tone (Raynaud's phenomenon) (RP). The modification of the vessel wall provokes a progressive reduction of vessel patency that leads to chronic critical limb ischemia. The injury to the endothelium is reflected in changes in the circulating levels of endothelial cell markers such as von Willebrand factor antigen (vWF) and angiotensin converting enzyme (ACE).

Prostanoids have been successfully employed in the management of RP and in particular in the control of ulcers of the fingertips and lower limbs. In particular, prostaglandin E_1 (PGE_1) has been employed in the treatment of chronic critical limb ischemia in several diseases (1) and in RP in SSc (2). A potent vasodilator effect, as well as the inhibition of platelet adhesion and aggregation, may explain the significant increase in peripheral blood flow after intravenous infusion of PGE_1. However, despite the rapid and almost complete removal of PGE_1 after lung passage, the molecule still has beneficial long-term effects. The drug has also been demonstrated to reduce circulating immunocomplex levels in connective tissue diseases (3) and to inhibit superoxide generation (4). The aim of our work was to evaluate the influence of PGE_1 on the plasmatic levels of the markers of endothelial cell injury in SSc. We report the efficacy of PGE_1 in obtaining the significant restoration of vWF and ACE in SSc patients suffering from RP and fingertip ulcers.

Forty-five SSc patients (mean age 42.4 years, mean disease duration 9.5 years) with disabling attacks of RP complicated by digital ulcers, were selected for the study. After a week of wash out, PGE_1 (Prostavasin®, Scwarz Pharma) was infused intravenously every day (60 g) for 5 days: after consent was obtained, blood was drawn on the first day before starting the treatment and on the day after the end of the treatment. vWf and ACE levels were measured with an ELISA and a fluorimetric method, respectively. The patients reported the number of attacks of RP before and immediately after the treatment. The unpaired Student's t-test was used for statistical evaluation.

In SSc, vWF was significantly increased and ACE significantly lowered with respect to the controls. Five days after the infusion of PGE_1 both ACE and vWF returned to normal levels (Table I). The number of RP attacks was significantly reduced, from 5.2 attacks per day before the infusion to 1.1 attacks per day after the treatment.

These data confirm the decrease of ACE and increase of vWF in SSc and show that PGE_1 infusion may not only reduce the number of attacks of RP but may also significantly affect the levels of some markers of endothelial injury. Recently, PGE_1 has been demonstrated to reduce, after a 4-week treatment, the levels of plasma endothelin in patients with intermittent claudication (5). PGE_1 acts in particular on vascular tone, but may also exert a protective effect on endothelial cells. The mechanism that mediates the protective action of PGE_1 on the endothelium with the potential reversal of endothelial injury is a matter of debate and may involve different pathways. PGE_1 plasma levels may protect the endothelium against reperfusion injury (6),or against the damaging potential of reactive oxygen species (7) and protease neutrophil cytotoxicity (8). Indeed, PGE_1 may inhibit leukocyte adherence and transendothelial migration (7-9); it may modulate humoral immune responses such as B cell activation or antibody production as well (15). Indeed, PGE_1 has been shown to be effective in preventing vessel restenosis after vascular surgery and angioplasty (10).

The evidence that PGE_1 restores the levels of markers of endothelial injury may support its frequent use in the management of early SSc before the damage to the endothelium is irreversible.

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Table I.

	Before PGE_1	After PGE_1	p
VWF	260 ± 35 %	170 ± 44 %	P < 0.01
ACE	2.9 ± 0.6 pM/ml/min	6.6 ± 1.1 pM/ml/min	P < 0.001