MATTERS
ARISING

Acquired Brown's
syndrome

Sir: We were very interested to read the report by Alonso-Valdivielso *et al* of acquired Brown's syndrome in a patient with systemic lupus erythematosus,¹ and a subsequent letter by McGalliard and Bell drawing attention to the fact that there have been two previously published reports, one of which was their own.² There has been another report of this condition with another rheumatic disease, rheumatoid arthritis.³ As such cases tend to be reported in ophthalmological journals it is possible that this association may be more common than is realised.

We would like to draw your attention to a case of 'Brown's syndrome' that we have previously reported in association with another connective tissue disease, scleroderma.⁴ The patient was a 27 year old Eurasian woman who had had scleroderma with diffuse skin involvement for 10 years. There was marked systemic disease with joint contractures, scleroderma oesophagus, and restrictive lung disease. She had previously been treated intermittently with oral prednisolone and D-penicillamine without any marked benefit and was currently taking cimetidine and receiving periodic oesophageal dilatation for her gastro-oesophageal reflux and consequent oesophageal stricture.

In April 1989 she noticed increasingly frequent vertical doubling of visual images on attempted upward gaze. This problem was frequently relieved in association with a palpable 'click' in the upper medial corner of her left orbit. The disability later became persistent. Examination in April 1990 disclosed features of severe scleroderma with diffuse skin involvement. There was restriction of elevation of the left eye in adduction and local tenderness in the region of the left trochlea. Hess charts were consistent with Brown's syndrome: as described by him in relation to acquired isolated inferior oblique paralysis⁵ or, as probable in our case, restriction of the superior oblique tendon in the trochlea.

Several months later the patient woke at night with pain behind her left eye and found that her diplopia had disappeared and has not recurred. Subsequent examination showed normal ocular muscle balance but a mobile nodule could be palpated in the anteromedial part of the superior oblique tendon.

The relation of this syndrome to scleroderma is not clear, but relief of the symptoms associated with a click suggests the presence of a nodule in the superior oblique tendon at the point of its passage through the trochlea. Connective tissue nodules are recognised in various rheumatic conditions. The spontaneous remission is interesting. Possibly, there was an element of traumatic inflammation associated with the passage of the nodule through the trochlea and this might have subsided with rest.

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1 Alonso-Valdivielso J L, Lario B A, López J A, Tous M J S, Gómez A B. Acquired Brown's syndrome in a patient with systemic lupus erythematosus. *Ann Rheum Dis* 1993; 52: 63-4.
2 McGalliard J, Bell A. Acquired Brown's syndrome in a patient with SLE. *Ann Rheum Dis* 1993; 52: 385-6.
3 Killian P J, McClain B, Lawless O J. Brown's syndrome. An unusual manifestation of rheumatoid arthritis. *Arthritis Rheum* 1977; 20: 1084.
4 West R H, Griffiths J C, Barnett A J. Transient superior oblique syndrome in scleroderma. A case study. *Australian Orthoptic Journal* 1991; 27: 59-62.
5 Brown H W. Isolated inferior oblique paralysis. *Trans Am Ophthalmol Soc* 1957; 57: 415.

Effect of hormone
replacement therapy on
markers of bone
metabolism in RA

Sir: Recently, we reported in this journal the positive effect of one year's hormone replacement therapy (HRT) on bone mass in postmenopausal patients with rheumatoid arthritis.¹ The study was randomised, double blind, placebo controlled and compared 2 mg oestradiol valerate/day and placebo during four cycles of 90 days. For the last 10 days of each cycle all patients received 200 mg progesterone daily to induce a withdrawal bleeding. Forty patients were studied: 20 in the placebo group and 20 in the treatment group. The groups were compatible for age, disease duration, and American Rheumatism Association functional class. No statistically significant differences were found in articular indices (Ritchie and Thompson), erythrocyte sedimentation rate, pain score (determined by a visual analogue scale), and health questionnaire before, during, and at the end of the study. We noted a decrease in serum osteocalcin in the treatment group, while no changes occurred in the serum alkaline phosphatase level and fasting urinary calcium and hydroxyproline excretion.¹

We measured carboxyterminal propeptide of type I procollagen (PICP) and carboxy-terminal cross linked telopeptide of type I collagen (ICTP) in the stored serum from patients of this study. Both PICP and ICTP are markers of collagen type I turnover; type I collagen accounts for 90% of the organic matrix of bone.

Type I collagen is synthesised as a larger protein, type I procollagen. During incorporation of type I collagen in bone PICP is released in blood, in a 1:1 ratio of newly formed collagen. Therefore, serum PICP reflects the synthesis of type I collagen. Theoretically, it is an advantage that the deposition of type I collagen can be measured on a 1:1 stoichiometrical basis with serum

PICP. (In contrast, it is unknown which fraction of newly synthesised osteocalcin is incorporated into bone matrix, and which fraction is released into the circulation.) Serum PICP correlates with bone formation, measured by bone histomorphometry.² Hassager showed a decrease in PICP during different regimens of HRT in postmenopausal women.³

ICTP is liberated during the degradation of type I collagen. This peptide is found in an immunochemically intact form in the blood. ICTP is decreased during high dose corticosteroid pulse treatment in patients with rheumatoid arthritis.⁴ The results of 47 calcium kinetic studies⁵ suggest that ICTP is a marker of bone resorption. An important advantage of ICTP is that it can be measured in blood. Other markers of bone resorption are influenced by daily diet (hydroxyproline) and have to be measured in urine (calcium, hydroxyproline, pyridinolines). Collection of urine may be inaccurate.

The patients studied and the methods used were described previously.¹ The samples were divided for use in the different determinations and frozen at -20°C until assay. All measurements were made in duplicate. Osteocalcin was determined with an OSTK-PR radioimmunoassay kit (CIS Bio International Gif-sur Yvette, Cedex, France). Measurement of PICP and ICTP was made with a radioimmunoassay kit from Orion Diagnostica, Finland. Both kits were kindly supplied by Orion Diagnostica, Finland. For PICP the intra-assay and interassay coefficients of variation are 3 and 5%, respectively.⁶ For ICTP the intra-assay and interassay coefficients are 4 and 6%, respectively.⁷ The table gives the results for osteocalcin, PICP, and ICTP.

At the start osteocalcin and ICTP were at the upper limit of the normal range. This is in accordance with the increased bone turnover after the menopause⁸ and in active rheumatoid arthritis. PICP was well within the normal range, and in the same range as in the study of Kröger *et al*.² We noted a decrease in osteocalcin and PICP after six months and one year with HRT; no changes occurred in ICTP. Previously, a decrease in serum osteocalcin and urinary excretion of calcium and hydroxyproline during HRT was shown,⁹ indicating that HRT inhibits both bone formation and bone resorption.

In the present study both markers of bone formation, osteocalcin and PICP, decreased during HRT. The decrease in PICP confirms the results of Hassager *et al*.³ The decrease in these markers of bone formation, in combination with an apparent increase in bone mass,¹ led us to expect a decrease in markers of bone resorption. However, ICTP did not change during one year of HRT. It is relevant to note that during the treatment period there was no change in disease activity. A decrease in ICTP has been found in patients treated for multiple myeloma¹⁰ and during high dose corticosteroid pulse treatment.⁴ Probably, the changes in bone resorption are greater in

Effect of one year's hormone replacement therapy on markers of collagen type I turnover in postmenopausal patients with rheumatoid arthritis. Values are given as mean (SD)

Time	Oestrogen			Placebo		
	PICP†	Osteocalcin†	ICTP†	PICP	Osteocalcin	ICTP
Start	114.3 (30)	8.1 (2.9)	4.7 (2.0)	111.3 (24)	8.3 (2.4)	5.4 (1.9)
6 Months	95.5 (21)**	6.8 (1.7)*	4.6 (2.2)	109.4 (35)	8.9 (2.0)	5.1 (2.6)
1 Year	96.5 (27)*	5.8 (1.1)**	5.3 (2.8)	114.2 (24)	8.3 (2.5)	4.6 (1.8)

*p < 0.05 from starting value; **p < 0.01 from starting value.
†Normal values: osteocalcin 0.5-9 µg/l; PICP 50-220 µg/l; ICTP 1.7-5.0 µg/l.