Acquired Brown's syndrome

Sir: We were very interested to read the report by Alonso-Valdivieso et al of acquired Brown's syndrome in a patient with systemic lupus erythematosus, and a subsequent letter by McGaillard and Bell drawing attention to the fact that there have been two previously published reports, one of which was their own. There has been another report of this condition with another rheumatic disease, rheumatoid arthritis. 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. The patient was a 27 year old Eurasian woman who had had scleroderma with diffuse skin involvement for 5 years. There was evidence of systemic disease with joint contractures, scleroderma oesophagus, and restrictive lung disease. She had previously been treated intermittently with oral prednisolone and vitamin E. The patient was later seen by the author (R.H.W.) at the Royal Victorian Eye and Ear Hospital.

In April 1989 the patient noticed a vertical double vision of 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 limitation of movements 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 paralysis 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 resolution of this syndrome in 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.

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. The study was randomised, double blind, placebo controlled and compared 2 mg oestriol valerate/day and placebo during four cycles of 90 days. For the last 10 days of each cycle all patients received 200 mg prophenac oxide 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.

We measured carboxyterminal propeptide of type I procollagen (PICP) and carboxyterminal 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 stoichiometric basis with the spot.

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 biopsy. Hassager showed a decrease in PICP during different regimens of HRT in postmenopausal women.

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. The results of 47 bone kinetic studies 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 cannot be measured in urine (calcium, hydroxyproline, pyridinoline). Collection of urine may be inaccurate.

The patients studied and the methods used were described previously. The samples were divided for use in the different determinations and frozen until assay. All measurements were made in duplicate. Osteocalcin was determined with an OSTK-PR radioimmunoassay kit (CIB 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. For ICTP the intra-assay and interassay coefficients are 4% and 6%, respectively. 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 menopause and in active rheumatoid arthritis. PICP was well within the normal range and indicative of the same range in markers of bone turnover. The decrease in serum osteocalcin and PICP after six months and one year with HRT; no changes occurred in ICTP. Previously, a decrease in serum osteocalcin and bone specific collagen and alkaline phosphatase during HRT was shown, 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. The decrease in these markers of bone formation, in combination with an apparent increase in bone mass, led us to expect improvements 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 myeloma and during high dose corticosteroid pulse treatment. Probably, the changes in bone resorption are greater in
these clinical situations than during HRT. This suggests that ICTP might be a less sensitive marker for changes in bone resorption than expected.

In summary, PICP decreases and ICTP do not show significant changes during the year's HRT. PICP seems to be a reliable marker of bone formation. In the present study, however, ICTP does not seem to be a sensitive marker of bone formation.

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**Fibromyalgia in the workplace**

Sir: In his leader 'Fibromyalgia in the workplace: a “management” problem'? Paul Reilly asks what lessons Britain might learn from the Australian experiences. We suggest that Dr Reilly might have missed this publication and he may have not sufficiently considered Australian publications and also the papers describing earlier epidemics in Scandinavia and Japan. He has continued the theme of opinion papers which in Australia led to a distortion of views and discussion in favour of unproved psychological mechanisms and away from scientific research. Presumably because of the important implications for economics and industrial relations, and in the absence of adequate knowledge, the unsubstantiated opinions of authorities were given more prominence in Australia than is usual in medical matters. The emphasis on psychosocial causation was effective in reducing the apparent incidence and in influencing the outcome of investigations' diagnostic criteria, but at a cost of considerable distress to many affected workers. It is to be hoped that henceforth editors will insist on clearer distinctions between knowledge and opinions.

The outstanding shortcoming in this paper is inadequacy of the clinical description; the use of invalidated terminology; an uninformed discussion of pain pathogenesis, which ignores essential concepts of hyperalgasia; the omission of any frank discussion of the work for the elucidation of pathogenesis; and the essentially negative approach to the treatment of affected subjects.

Not unreasonably, Dr Reilly suggests that a descriptive diagnosis be applied—for example, ‘upper limb regional chronic pain syndrome’. Why then the bizarre leap to ‘fibromyalgia’ terminology? We suggest that British rheumatologists maintain their ‘slovenly to roughness’ terminology! Literally, this term suggests pain in the fibrous tissue and muscles. The reality is that the cervicobrachial disorder involves not only pain but also paraesthesia, sensory impairments, sympathetic dysfunction, dystonia and antilagic impairment of motor function, and secondary hyperalgasia, all phenomena which require explanation. Of these, the central concept is secondary hyperalgasia. The latter can be elicited frequently from deep temporal and virtually all musculoskeletal tissues. It is true that the neck and arm disorder acquired in the workplace shares many clinical features with the ‘fibromyalgia syndrome’, but to erect it into this retrograde classification is bizarre.

As stated by Anderson,7 8 terms such as ‘indeterminate pains’ or ‘pains of undetermined origin’, though unsatisfactory to both clinician and epidemiologist, will probably lead to less confusion in the long run than the use of labels which sound scientific but which are not accurately defined.

In assessing a chronic pain syndrome comprehensively, it is necessary to consider somatic tissue damage, dysfunction of nociceptor stimulus, ectopic impulse generation from peripheral nerves or nerve roots, central sensitisation of nociception, and psychosocial factors. No significant somatic abnormality has been identified in these cervicobrachial disorders. Peripheral nerve dysfunction includes well defined entrapment neuropathies, increased mechanosensitivity of peripheral nerves including brachial plexus, and disordered C fibre function as identified in research with capsaicin.3 6 The most striking features on examination are allodynia and hyperalgesia extensively in the soft tissues of the neck and arm, implying central sensitisation of nociception. Together with these observations, research with cerebral event-related responses induced by carbon dioxide laser stimulation and with electrocutaneous stimulation has supported the concept of central sensitisation. It seems likely that altered central processing is maintained dynamically by peripheral nociceptive input along the lines presented by Gracely et al.9 These considerations establish a prima facie case for a relation between persistently painful activities and chronic pain states. Because the evaluation of neuropathic mechanism in these cervicobrachial disorders has not been well established in clinical practice, when doctors find insufficient pathology to account for a disorder, psychosocial inter-

prations are sought. There is no scientifically sound empirical evidence for primary (and causative) psychosocial mechanisms in these disorders, nor are such concepts readily testable. The interplay of the psyche and somatic factors is virtually untouchable. It has been demonstrated, however, in the study by Moulton and Spence.10

Reilly refers to ‘the unproved concept of pain being due to an injury caused by the strain of repetitive movement’. We agree that the term ‘injury’ is not appropriate in this context and that proof in an individual patient is a difficult concept. It is acknowledged that the biological plausibility of the causation of repetitive movement syndromes and the chronic pain state is hampered by incomplete knowledge of pathogenesis. There is however a well established temporal, ergonomic, and epidemiological link between repetitive work and neck-arm pain disorders. The symptomatic worker and his/her advise present a retrodictive causal proposition that the conditions of work resulted in the genesis and persistence of symptoms. The nature and conditions of the repetitive movement, the use of the upper limbs and sustained arm forward postures (unsupported) and repetitive neck movements and sustained neck postures, are risk factors for neck or arm disorders. Each of these activities is not a necessary cause (the pain syndrome is not specific to repetitive work) nor a sufficient cause (not all workers performing this or similar work acquire the disorder). Representative repetitive work and neck-arm disorders have a relative risk of at least 3 to 4 for a neck-arm disorder from numerous categories of repetitive work compared with the risk associated with light domestic or sedentary activities. The real paradigm is the pathophysiology of chronic pain. In the meantime we should observe with enlightenment and ‘quizzical regard’,11 apply our current knowledge of chronic musculoskeletal pain to the benefit of the workers as our patients in their difficult interactions with their employers and with the medicolegal system. Those who act as agents for insurance companies or in the medicolegal system failed to account for the clinical features exhibited by individual patients which are similar across various occupational groups.