LETTERS TO THE EDITOR

The time of blood sampling for osteocalcin determinations

Sir: We have read the interesting article by Pietschmann *et al* about the serum osteocalcin concentrations in patients with rheumatoid arthritis.[1] In their work there was no mention of the time at which blood samples were taken for osteocalcin determination.

Several studies have shown a circadian rhythm of serum osteocalcin in normal adults, with peak values during the night and a nadir during the morning hours.[2 3] Therefore, in our opinion, if osteocalcin is used as a marker in clinical investigations of bone metabolism it is important to mention the time at which blood was collected for its measurement. Otherwise, interpretation of results may be difficult and comparison with values obtained in other studies impossible.

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1 Pietschmann P, Machold K P, Wolosczuk W, Smolen J S. Serum osteocalcin concentrations in patients with rheumatoid arthritis. *Ann Rheum Dis* 1989; **48:** 654–7.
2 Gundberg C M, Markowitz M E, Mizruchi M. Osteocalcin in human serum: a circadian rhythm. *J Clin Endocrinol Metab* 1985; **60:** 736–9.
3 Kaspersen Nielsen H, Charles P, Mosekilde L. The effect of single oral doses of prednisone on the circadian rhythm of serum osteocalcin in normal subjects. *J Clin Endocrinol Metab* 1988; **67:** 1025–30.

Sir: We agree with Drs Nolla and Rozadilla that in applying serum osteocalcin measurements it is important to take account of the diurnal variations of serum osteocalcin concentrations. In a recent study (Pietschmann *et al*, unpublished data) in patients with postmenopausal osteoporosis we found a diurnal rhythmicity of serum osteocalcin concentrations similar to that described by Gundberg *et al* in normal subjects.[1] In contrast, Guillemant and Guillemant did not find circadian fluctuations of serum osteocalcin concentrations in patients with primary or secondary hyperparathyroidism.[2] In our study on serum osteocalcin concentrations in patients with rheumatoid arthritis[3] blood for osteocalcin measurements was collected from all patients and controls between 8 00 and 9 00 am.

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2 Guillemant J, Guillemant S. Plasma osteocalcin in primary and secondary hyperparathyroidism with regard to daily fluctuations. *Horm Metab Res* 1989; **21:** 220–1.
3 Pietschmann P, Machold K P, Wolosczuk W, Smolen J S. Serum osteocalcin concentrations in patients with rheumatoid arthritis. *Ann Rheum Dis* 1989; **48:** 654–7.

Anticardiolipin antibody negative occlusive vascular retinopathy in systemic lupus erythematosus

Sir: A strong association has recently been reported between the presence of anticardiolipin antibody and occlusive ocular vascular disease in patients with systemic lupus erythematosus (SLE).[1 2] We now wish to report a patient with SLE who developed bilateral central retinal artery occlusion and in whom anticardiolipin antibody was not detected despite several other features suggesting the presence of antiphospholipid antibodies.

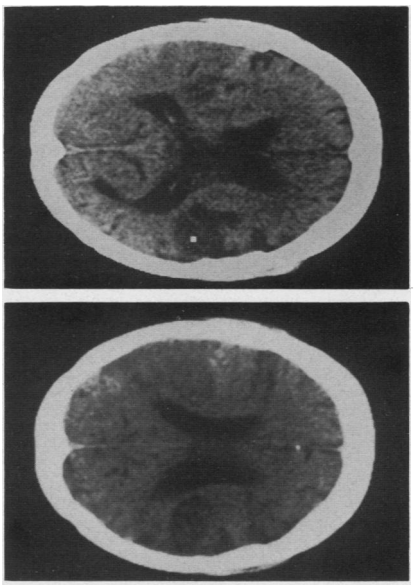
The patient, a 30 year old nursing sister, was diagnosed as having SLE[3] in 1982. She had a history of two spontaneous abortions. In January 1986 she had a 'flare' of SLE, which resolved after one month's treatment with steroids (prednisone 50 mg daily) and chloroquine (200 mg daily). The lupus remained quiescent, both clinically and serologically, for the ensuing 10 months during treatment with prednisone (10 mg alternate days) and chloroquine (200 mg daily).

In November 1986 she developed sudden complete loss of vision in the left eye. Two days later a similar visual deficit developed in the right eye. She was admitted to Kalafong Hospital 20 hours later and ophthalmoscopy disclosed a pale fundus with a bright red fovea bilaterally. The arteries were attenuated and apparently bloodless. Foci of retinal ischaemia ('soft exudates') were evident. An ophthalmologist affirmed the appearances were pathognomonic of central retinal artery occlusion. No other clinical evidence of active lupus or other predisposing factors for central retinal artery occlusion were present. Relevant investigations showed thrombocytopenia of 34×10^9/l, a prolonged activated partial thromboplastin time (APTT) of 50–76 s (control <40 s), and positive antinuclear antibody titre of 1/40. The erythrocyte sedimentation rate, anti-DNA antibody, serum complement, and gammaglobulin concentrations, white cell count, haemoglobin, urine analysis, and echocardiogram were all normal. She declined further hospital treatment.

In February 1987, six days after being admitted to hospital for social reasons, she developed a mild transient ischaemic attack. Again there were no other clinical or laboratory features of active lupus. The APTT was now 37 s, the rapid plasma reagin test was negative, and an enzyme linked immunosorbent assay (ELISA) (The Rayne Institute, St Thomas's Hospital, London) showed absence of anticardiolipin antibody. She again declined further hospital treatment.

Three months later she was readmitted after having developed loss of consciousness abruptly five hours earlier. She was comatose with dilated pupils, which reacted sluggishly to light. She had a right hemiparesis. A computed tomographic brain scan was performed within a few hours after admission. This showed multiple areas of low attenuation in both hemispheres consistent with infarctions. The lateral ventricles were mildly dilated and several cortical sulci appeared unduly prominent (figure). The platelet count was 52×10^9/l and APTT 76 s. Anticardiolipin antibody was once more not detected and the rapid plasma reagin test was again negative. Antibodies to Ro and La were negative but antibodies to RNP and Sm were positive. She was initially anticoagulated with heparin and subsequently with warfarin. High doses of cyclophosphamide, prednisone, and aspirin were also prescribed, but her clinical state remained unchanged and she died six weeks later. Permission for necropsy was not granted.

Recurrent fetal loss, occlusive stroke,



Computed tomographic brain scan showing multiple infarcts and cerebral atrophy.

thrombocytopenia, and a prolonged APTT—all features that existed in our patient—have been associated with the presence of antiphospholipid antibodies.[4] The failure in this case to detect anticardiolipin antibody is therefore noteworthy. In our recent study of SLE in black South Africans clinical features were found to be little different from those described in series from other parts of the world.[5] Four of the 30 patients had a history of cerebrovascular accidents. Of these, three were tested for the presence of anticardiolipin antibody and the levels were found to be normal in each (Dessein PH, Gledhill RF, Asherson RA, unpublished). Moreover, of the 12 other patients tested, only one was found to have a raised anticardiolipin antibody level and this patient had no clinical features of the antiphospholipid syndrome.[4] It is our impression that the incidence of antiphospholipid antibodies may be significantly less in Africans with SLE. Our patient is another example of anticardiolipin antibody negativity in the presence of probable lupus anticoagulant positivity, a finding observed by other investigators.[6 7]

Although occlusion of both central retinal arteries in rapid succession, such as appeared in this patient, seems an exceptional circumstance, the observation by Stafford-Brady *et al*[2] that retinopathy in SLE may be a marker of poor prognosis for survival is shown only too well by our case.

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1 Asherson R A, Merry P, Acheson J F, Hughes G R V. Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the 'primary'

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