the bacteriological findings correlate well with those in that condition. The normal cell count in the CSF is rare in tuberculosis of the central nervous system but may occur.¹⁻³ We think that a positive culture for *M. tuberculosis* might be a more common finding, were one to look for it, and that the possible tuberculous nature of meningitis should not be discarded because of benign presentation only.

ETIENNE M GRANDJEAN
LUC HUMAIR
REMY G H CLOTTU

Service de Médecine,
Hôpital de la Ville,
La Chaux-de-Fonds,
Switzerland

HARALD MODDE

Institut neuchâtelois de Microbiologie,
La Chaux-de-Fonds,
Switzerland

¹ Emond, R T D, and McKendrick, G D W, *Lancet*, 1973, 2, 234.

² Taylor, K B, Smith, H V, and Vollum, R L, *Journal of Neurology, Neurosurgery, and Psychiatry*, 1955, 18, 165.

³ Kocen, R S, and Parsons, M, *Quarterly Journal of Medicine*, 1970, 39, 17.

Premenstrual tension

SIR,—Paraphrasing the opening sentence of the leading article, "Premenstrual tension" (27 January, p 212), I would say that there is nothing pleasant about inaccuracies, especially when they appear in such a well-written, well-documented, up-to-date article.

You cite two studies that "have failed to confirm any rise in prolactin concentrations in patients with premenstrual tension." This statement is incorrect, because Andersch *et al*¹ clearly report: "In patients with PMT prolactin levels were significantly higher premenstrually compared to levels during the follicular phase. In the control group no such increase was observed."

A careful examination of the second article cited² shows a very vague definition, selection, and mental evaluation of their sample group. According to table II in that article, the average severity of mental complaints among the group was 1.01—that is, slight—and they did not mention any control group for the drug-free cycle.

None the less, more than one variable seems to be implicated in the cause of the premenstrual tension syndrome, and, concerning the accumulating data, one may assume that we are dealing with a group of syndromes which may be caused by an imbalance between several factors affecting the central (and possibly CNS peripheral) nervous system.

A better understanding of the aetiology of these syndromes is unlikely before a precise definition is formulated.

URIEL HALBREICH

College of Physicians and Surgeons of
Columbia University,
New York 10032

¹ Andersch, B, *et al*, *Acta Endocrinologica (København)*, 1978, 88, Suppl No 216, p 165.

² Andersen, A N, *et al*, *British Journal of Obstetrics and Gynaecology*, 1977, 84, 370.

Treatment of orthopaedic tuberculosis

SIR,—Absence overseas has prevented my commenting earlier on the letters of Sir John Crofton (6 January, p 52) and Mr M Wilkinson (24 February, p 558) on the treatment of orthopaedic tuberculosis.

I was astounded to read of the practice attributed by Sir John to "some orthopaedic surgeons" of giving no more than one month's chemotherapy to patients with tuberculous sinuses. The absence of any letter questioning the frequency of such maltreatment leads me to fear that Sir John has no need to feel "ashamed" of his letter, but rather that he deserves every support for urging, as I have always urged myself, that any surgeon treating any case of tuberculosis should do so in consultation with an expert in chemotherapy, who will almost always be a chest physician. The simple fact is that tuberculosis of bone and joint, though done nothing but harm by inadequate or inappropriate chemotherapy, will be cured by adequate chemotherapy in almost every case. Mr Wilkinson is quite wrong in asserting that this does not apply to disease of the thoracic or thoracolumbar regions of the spine, even if large paravertebral abscesses are present. Reference to the last two reports^{1 2} of the Medical Research Council's working party on this subject makes this abundantly clear.

Radical anterior surgery of the "Hong Kong" type, performed by experienced experts and reinforced by adequate chemotherapy, hastens cure and lessens deformity, thus conferring great benefit on the patient with spinal tuberculosis. The high expectation of eventual cure, however, is not increased even by this operation and certainly not by any lesser surgical measure such as that suggested by Wilkinson. Our studies in Bulawayo and in Hong Kong indicate without question that even a full debridement of the focus confers no worthwhile benefit on the patient receiving adequate chemotherapy.

D LL GRIFFITHS
Chairman,
MRC Working Party on
Spinal Tuberculosis

Eglwysbach,
North Wales LL28 5TY

¹ Medical Research Council, *Journal of Bone and Joint Surgery*, 1976, 58B, 399.

² Medical Research Council, *Journal of Bone and Joint Surgery*, 1978, 60B, 163.

Steroid treatment in giant cell arteritis

SIR,—In the reported discussion (17 March, p 727) on the first case in the clinicopathological conference held at the Royal College of Physicians questions were asked about steroid treatment, the sedimentation rate, and the age of patients affected by giant cell arteritis.

It might be helpful to recall observations made a quarter of a century ago and reported in the *British Medical Journal* (31 December 1955, p 1593). In case 1 of that report, the patient was aged 55 years at the time of onset of her symptoms and was first seen in medical outpatients in July 1954, when she was 56 years of age. The diagnosis of giant cell arteritis was confirmed by biopsy; her erythrocyte sedimentation rate (ESR) was 80 mm in the first hour. Oral cortisone was started, 200 mg being given daily during the first week. Thereafter the daily dose was 150 mg during the second, 100 mg during the third, 50 mg during the fourth, and 25 mg during the fifth week. After the first week of treatment the ESR fell to normal and remained so. A second biopsy performed five weeks after the first showed no inflammatory cellular infiltration.

In case 2 the initial ESR was 36 mm in the first hour. After 11 days' treatment with

ACTH gel by injection 25 mg three times a day a second biopsy specimen was totally free from cellular infiltration and treatment was stopped.

At that time we thought that these were the first cases reported in which serial biopsies had shown such histological changes. Our clinical and histological evidence suggested that cortisone and ACTH reduced the oedema and the inflammatory cellular reactions. This was probably the cause of the relief of symptoms. There was no evidence that the treatment had any effect on the scarring and intimal thickening that had already taken place; in fact in the first case thrombosis occurred despite treatment. It seems probable that it is thrombus that causes the arterial obstruction and symptoms after cortisone has been given, and it might be argued that there is an indication for using anticoagulants during and after cortisone therapy.

ROBERT J HARRISON

Goring-by-Sea,
West Sussex BN12 4LJ

Drugs and breast-feeding

SIR,—The British physician, at least, should not be ignorant about interference of drugs with breast-feeding, as you imply in your leading article (10 March, p 642). He may obtain for a mere 90p Dr Linda Beeley's marvellous booklet *Safer Prescribing*,¹ where, on page 37, most of the interfering drugs you mentioned and more are listed.

KARL H KIMBEL

Medicines Commission of the
German Medical Profession,
5000 Köln 41

¹ Beeley, L, *Safer Prescribing: a Guide to some Problems in the Safer Use of Drugs*. Oxford, Blackwell Scientific, 1976.

Cimetidine in acute upper gastrointestinal bleeding

SIR,—We write to report a trial of cimetidine in the treatment of upper gastrointestinal bleeding, and a negative result similar to that of Mr R G Pickard and others (10 March, p 661).

Patients admitted to the medical wards of a district general hospital with haematemesis or melaena were randomly allocated to a treatment or non-treatment group: the patients were stratified into two age groups, above and below 55 years. To those allotted to the treatment group cimetidine was given intravenously, 200 mg in 200 ml normal saline, over a period of two and a half hours, repeated six-hourly for 48 hours: this was followed by oral treatment, 200 mg three times a day and 400 mg at night, for five days. Except in a small number of cases, upper gastrointestinal endoscopy was performed within 16 hours of admission. Blood was transfused as necessary. Patients were referred for surgery if (a) there was no apparent improvement after transfusion of six units of blood or (b) deterioration continued during transfusion or (c) after an interval during which there was no sign of bleeding fresh blood was aspirated or there was evidence of hypovolaemic shock or rapidly progressive anaemia. The decision to refer a patient for surgery was made by a member of the team who did not know whether the patient was receiving cimetidine, but who had either performed endoscopy himself or was aware of the endoscopic findings.

Fifty-eight patients were allotted to the group treated with cimetidine and 55 to that without; in each group, eight patients were referred for surgery. In the group treated with cimetidine four

patients died within one week; in those to whom no cimetidine was given five patients died within a week. Of the treated group, 18 required no transfusion; of the untreated, 16. The volume of blood transfused to the treated group averaged 3.1 units, to the untreated 2.9 units.

Although no significant difference has been demonstrated between those patients treated with cimetidine and those without, we have not excluded the possibility that cimetidine may be of some value in the treatment of upper gastrointestinal bleeding; we think it likely that a much greater number of patients would need to be studied to demonstrate any benefit of cimetidine in such patients.

S M Z A SIDDIQI
G TILDESLEY
P T PICKENS
R A McNAY

General Hospital,
Hartlepool TS24 9AH

Cimetidine and duodenal ulcer

SIR,—In his second letter (17 March, p 755) Dr M Drury destroys his already feeble case for the use of cimetidine as a diagnostic agent. I do not see why, in the case of important upper abdominal pain, the "primary physician's diagnostic pathway is necessarily different from that of the hospital doctor." No competent physician refers all patients with upper abdominal pain for endoscopy or radiology; the first step is to make a clinical assessment. That assessment should pick out a small number of patients who are likely to have a duodenal ulcer, gastric ulcer, or gall stones. In these the diagnosis needs proper confirmation; the conditions are chronic and recurrent and it is unfair to the patient to treat him on the basis of provisional diagnosis alone. The response to cimetidine cannot be an adequate way of confirming or refuting these diagnoses. The remaining patients (who do not seem to have one of those three important diagnoses) certainly do not need cimetidine, and any response to that agent would be as meaningless as if they improved after drinking camphorated oil. The suggestion that cimetidine might help to differentiate oesophageal from cardiac pain is too ludicrous even to discuss.

Cimetidine is already being prescribed wastefully and extravagantly all over Britain. Doctors are failing to proceed in a rational, diagnostic manner with regard to dyspepsia. If they mistakenly believe there is some economic advantage in trying this spurious "diagnostic test," let me remind them that the cost of a six-week course of cimetidine is approximately £28. The cost of an NHS barium meal or upper gastrointestinal endoscopy is likely to be considerably less.

J R BENNETT

Gastrointestinal Unit,
Hull Royal Infirmary,
Hull HU3 2JZ

Cimetidine overdosage

SIR,—Since its introduction only a year or two ago cimetidine has been used so much in general practice that your article (17 February, p 453) on the absence of toxicity in its use must have been of great interest to your readers.

Three weeks later, a male patient aged 46, a chronic schizophrenic who was on trifluoperazine, 2 mg twice daily, and hydroxyzine hydrochloride, 25 mg twice daily, took in

a fit of pique a handful (probably about 60) of his mother's cimetidine tablets. When seen half an hour later he was drowsy but could be awakened; his respirations were slow and shallow but his pulse was strong and regular. His removal to the local hospital was arranged, but on removal to the ambulance he became so cyanosed and his breathing gave such cause for alarm that oxygen was administered during the journey to the hospital eight miles away. After gastric lavage his condition rapidly improved. In this case, respiratory depression as described in animal studies, presumably caused by the high dosage of cimetidine, caused for a while considerable anxiety.

J B WILSON

Lockerbie, Dumfriesshire DG11 1PD

Peripheral skin necrosis complicating beta-blockade

SIR,—I should like to add a further case of peripheral skin necrosis developing with beta-blockade to those recently reported by Dr R Gokal and others (17 March, p 722). A 57-year-old man was treated for hypertension with atenolol 100 mg daily and Navidrex K. After 11 weeks of treatment, in February 1979, he complained of cold feet which were very tender to walk on. There was no previous history of peripheral vascular disease and all peripheral pulses were easily palpable. There were numerous areas of skin necrosis up to 1 cm diameter on the toes and heels. Atenolol was discontinued and the tenderness and coldness disappeared over the next seven to 10 days. No new lesions appeared after the withdrawal of atenolol.

The pattern of the ischaemic lesions probably represents involvement of small vessels. In the patient described these lesions developed in the winter, as they did in the three cases previously reported. The mechanism may be potentiation of α -adrenoceptor activity,¹ as suggested by Gokal *et al.* Increases in platelet counts have been described with metoprolol² but such increases have been small and unlikely to produce the necrotic lesions reported.

P J REES

Clinical Science Laboratories,
Guy's Hospital,
London SE1 9RT

¹ White, C de B, and Udawadia, B P, *British Journal of Clinical Pharmacology*, 1975, **2**, 99.

² Kuttli, J, Bergstrom, A L, and Lundborg, P, *New England Journal of Medicine*, 1976, **295**, 1079.

Drug-induced peripheral neuropathies

SIR,—The review by Dr Zohar Argov and Professor Frank L Mastaglia (10 March, p 663) on drug-induced peripheral neuropathies cites a comprehensive list of drugs which may cause this condition. There are, however, some omissions in the list of antineoplastic agents which may not be apparent to those unfamiliar with these drugs. The authors quite rightly indicate that the mechanism of action of vincristine-induced neuropathy is due to its specific effect on neurotubules (microtubules). Vinblastine may also cause a sensorimotor and autonomic neuropathy especially when used in high doses, as in current teratoma regimens.¹

Podophyllum appears in the list when, in fact, the drug used in the study by Falkson *et al.*² was its semi-synthetic derivative etoposide. Podophyllum is not currently

used as an antineoplastic agent but it is of interest that it has a similar mode of action to that of the vinca alkaloids. Etoposide, although a derivative of podophyllum, does not inhibit microtubule polymerisation so a different mechanism of action must be sought for the reported neuropathy.³

Platinum diamminodichloride, which is soon to become commercially available (Neoplatin), is a drug of major interest because of its activity in several solid tumours. It may cause tinnitus and high-pitched frequency hearing loss,⁴ retrobulbar neuritis,⁵ and occasionally seizures^{6,7} (although these may be due to hyponatraemia). Bruckner *et al.*⁷ reported three cases of peripheral neuropathy but did not elaborate on clinical presentation. We have observed a peripheral sensorimotor neuropathy of the lower limbs, with paraesthesiae, loss of vibration sense, and absent ankle jerks in a 62-year-old patient with ovarian carcinoma after five courses of this drug. On withdrawal of chemotherapy the neuropathy resolved over two months. Neuropathy has not been reported with either of the other two drugs (adriamycin and cyclophosphamide) which were administered at the same time.

Heavy metals can cause peripheral neuropathy.⁸ Whether this is the mechanism of action of platinum diamminodichloride remains speculative.

A M ARNOLD
C J WILLIAMS

CRC Medical Oncology Unit,
Southampton General Hospital,
Southampton SO9 4XY

¹ Einhorn, L H, and Donohue, J, *Annals of Internal Medicine*, 1977, **87**, 293.

² Falkson, C, *et al*, *Cancer*, 1975, **35**, 1141.

³ Loike, J D, and Horwitz, S B, *Biochemistry*, 1976, **15**, 5435.

⁴ Kovach, J S, *et al*, *Cancer Chemotherapy Reports*, 1973, **57**, 357.

⁵ Ostrow, S, *et al*, *Cancer Treatment Reports*, 1978, **62**, 1591.

⁶ Wiltshaw, E, and Kroner, T, *Cancer Treatment Reports*, 1976, **60**, 55.

⁷ Bruckner, H W, *et al*, *Proceedings of the American Association for Cancer Research*, 1977, **18**, 339.

⁸ Bannister, R, (editor), *Brain's Clinical Neurology*, p 368. London, Oxford Medical Publications, 1978.

Vitamin C, disease, and surgical trauma

SIR,—Your leading article "Vitamin C, disease, and surgical trauma" (17 February, p 437) refers to changes in leucocyte ascorbic acid (LAA) concentrations after surgery which were reported by Irvin *et al.*¹ in July 1978. They suggested that the fall in LAA concentrations was inversely related to the rise in white blood cell counts and concluded that the postoperative leucocytosis due to the surgical trauma and the release by the bone marrow of leucocytes with a low ascorbic acid content might partly account for the postoperative changes in LAA measurements.

We have carried out similar studies in patients suffering from acute myocardial infarction.^{2,3} It is true that the apparent fall in the LAA concentration is associated with a rise in the white blood cell count, but the rise in the white blood cell count was due to a granulocytosis, presumably from mobilisation of the marginated pool of granulocytes. When, however, the ascorbic acid of granulocytes, lymphocytes, and platelets was measured separately in normal subjects the ascorbic acid content of the granulocyte was found to be about half that of the lymphocyte, and that of the platelet was somewhere between the two. We concluded, therefore, that the initial