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.

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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.

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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 wakened; 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.

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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.

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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.

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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