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

apparent fall in LAA concentration was simply due to the increasing proportion of granulocytes in the differential white blood cell count, and that a true fall in LAA concentration had not occurred. After the acute "stress" had subsided and the leucocytosis returned to normal, however, the LAA concentration and serum ascorbic acid concentration remained low, presumably because of tissue depletion of ascorbic acid. Both may remain low for up to 56 days.²

We also found that tissue damage is probably necessary to produce the long-term depletion of LAA and serum ascorbic acid concentrations since the acute changes in LAA only can be produced by tetracosactrin infusions in normal subjects.²

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¹ Irvin, T T, Chattopadhyay, D K, and Smythe, A, *Surgery, Gynecology and Obstetrics*, 1978, **147**, 49.

² Vallance, B D, Hume, R, and Weyers, E, *British Heart Journal*, 1978, **40**, 64.

³ Hume, R, et al, *British Heart Journal*, 1972, **34**, 238.

Back pain—what can we offer?

SIR,—It astonishes me to read the suggestion implicit in your leading article (17 March, p 706 that causes of "back-pain" sufficiently severe to warrant reference to a rheumatology clinic may safely be diagnosed without radiography of the relevant portion(s) of the spine, with no loss of accuracy and with a bonus saving to the NHS of "many thousands of pounds each week." This amounts, in my alarmed medicolegal view, to an advocacy of technical professional negligence on a massive scale.

May I, however, offer an observation (based in part on personal experience) on the significance of radiological changes and their relation to symptoms? The latter are commonly caused by pressure on nerves of radiolucent soft structures, such as, for example, a prolapsed nucleus. The development of convincing bony changes, which represent nature's attempt at a healing process, may take many years. Symptoms and radiological signs are usually asynchronous, the latter slowly progressive, the former variably intermittent.

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SIR,—Your leading article "Back pain—what can we offer" (17 March, p 706) rightly questions the routine use of radiographs. The radiologist with limited information about the patient has difficulty making a valid comment about degenerative change, and the general practitioner who does not see the x-rays cannot easily relate a report to the patient's symptoms.

Orthopaedic surgeons are increasingly aware that the size of the lumbar spinal canal can be an important factor in the aetiology of back pain. When canal measurements are available¹ radiographs can demonstrate additional compromising lesions that will compress the canal contents. This may be disc degeneration, posterior vertebral bar formation, shingling of two vertebrae with slight retro-

spondylolisthesis, facet-joint arthritis, spondylolysis, or spondylolisthesis. In themselves these radiological features may be insignificant, but in the presence of a narrow canal they can indicate a structural abnormality responsible for symptoms.

For a patient whose back pain is prolonged or recurrent a diagnosis of "non-specific back pain" is inadequate, and x-rays become an important investigation.

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¹ Porter, R W, Wicks, M, and Ottewill, D, *Journal of Bone and Joint Surgery*, 1978, **60-B**, 481.

Does adipocyte hypercellularity in obesity exist?

SIR,—We are glad that Drs P Björntörp and L Sjöström (20 January, p 197) agree that hyperplastic obesity is a rare condition. If hyperplastic obesity is likely only to be present in individuals with body weights of over 150 kg—that is, a weight range corresponding to that in our three individuals in whom such interest is expressed—then one is dealing with a very unusual and small group of patients. If Dr Björntörp and his colleagues¹ set the upper limit of normality for fat cell number only 1 SD above the mean then obviously one can begin to define a larger proportion of obese patients (and indeed of the normal-weight population) as hyperplastic. We are also glad to note that the Göteborg group now considers a value for total fat cell number as only an index of the true cell number—an index on which we consider one should place little reliance.

The other comments we found somewhat misleading. Our reference standards for obesity, the Metropolitan Life Tables, are those recommended by both United Kingdom and USA expert committees; they are widely used, readily obtained, and accepted by most investigators of obesity. Our three subjects whose body fat measurements worry the Swedish group had additional measurements, as indicated in the paper, with ⁴⁰K and ⁴²K; in two patients body fat had been marginally overestimated and in one underestimated. The number of controls (27) would need to be substantially increased if we wished to establish accurate normal limits for the index of fat cell number, but our values accord with those of other workers and our conclusions stand.

We agree that we did not have adipocyte measurements on omental tissue from grossly obese patients. When this has been done by other workers² the results have matched our predictions in that the internal cells have finally expanded to equal the size of the subcutaneous adipocytes—a development that will lead to a spurious increase in calculated fat cell number when the calculations are based on subcutaneous samples alone.

Odd conclusions can indeed be drawn by mixing our data on fat cell sizes (0.73 µg

triglyceride for subcutaneous and 0.29 µg for omental sites) with an erroneous estimate of 50 kg for body fat rather than the actual 30.5 kg quoted in table II of our paper. At 50 kg of body fat the mean subcutaneous cell size, estimated from Björntörp's own data,³ would be about 0.9 µg triglyceride and that of omental cells, estimated from the work of Salans et al,² would be 0.70 µg. If we retained the 2:1 ratio for subcutaneous and visceral fat then the "true" fat cell number would remain unchanged and therefore similar to that found in other groups of patients with body fat corresponding to 30.5 kg and 16 kg (see table).

We accept the need for improved methods for measuring subcutaneous and deep body fat. Our choice of the best estimates yet available for the proportions of body fat in the subcutaneous tissue indicates the potential magnitude of the errors associated with measuring the total number of fat cells in the body.

We do not agree with the explanation proposed for validating hyperplastic obesity: true hypercellularity of the adipose mass must exist because the limits of normality are defined to exclude the top 3% of the Gaussian range. The question is then whether hypercellularity specifically relates to the problem of obesity, and if so how often and to what effect.

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¹ Björntörp, P, et al, *American Journal of Clinical Nutrition*, 1975, **28**, 445.

² Salans, L B, Cushman, S W, and Wersmann, R E, *Journal of Clinical Investigation*, 1973, **52**, 929.

³ Sjöström, L, and Björntörp, P, *Acta Medica Scandinavica*, 1974, **195**, 201.

Health and safety at work

SIR,—I read with interest Dr B J Boucher's thoughtful article "Guidance on preparing local rules to help implement the Health and Safety at Work, etc, Act, 1974" (3 March, p 599). Dr Boucher stated that "we have found that direct guidance from the DHSS or NHS sources or from professional bodies on what is now required from NHS staff for safety at work has been slow to appear and inadequate in its coverage of the diversity of NHS activities; codes of practice are not yet available for much of our work."

Some parts of hospitals have been subject to the Factories Act and to the Offices, Shops and Railway Premises Act. Areas such as wards, operating theatres, and laboratories became subject to health and safety legislation in 1975, together with many other aspects of activity associated with hospitals. I was informed by the Health and Safety Executive some while ago that an area director has been nominated by the Executive to identify health and safety problems in the hospital service and to

Calculated total body fat cell number with increasing body fat

Total body fat (kg)	Fat cell sizes (µg of triglyceride)		Fat masses on a 2:1 ratio (kg)		Fat cell number (× 10 ¹⁰)		Total number (× 10 ¹⁰)
	SC	Omental	SC	Omental	SC	Omental	
16	0.43	0.16	10.6	5.4	2.5	3.4	5.9
30.5	0.73	0.29	20.4	10	2.8	3.4	6.2
50	0.9	0.70	33.3	16.7	3.7	2.4	6.1

SC = subcutaneous.