The second point is the matter of visceral fat cells. We are happy that we were reminded of the excellent, careful work by Salans *et al.*¹ These authors have as a matter of fact already studied this question very carefully. They studied the fat cell sizes at three subcutaneous and three visceral depots in fairly extensive material from obese and non-obese subjects. They then analysed their data from a number of different aspects, including calculations of fat cell number with and without visceral fat cells taken into account, and with different assumed percentages of visceral fat. Their conclusion was that "... mean adipose cell number for the obese group is always significantly greater than that for the non-obese, irrespective of the cell size used and of the assumed distribution of total body fat."

Not only the conclusions but also the results obtained are to a rather large extent different from those of Jung *et al.*, and it is a pity that the reason for this has not been analysed in their report. The study by Salans *et al.* shows conclusively that hypercellularity does exist. If we use the data of Jung *et al.*, it does not exist if there are large differences in adipocyte distribution between subcutaneous and visceral fat in obese and non-obese subjects; and this is a very unlikely situation.

Both these arguments demonstrate that the difference in opinion between our groups is actually quantitative. We believe that both groups agree on the basic point—that is, that adipose hypercellularity does exist, only its significance being evaluated differently. We do, of course, not use mean plus one SD of controls as cutting point for definition of hyperplastic obesity other than for analytical purposes.² In this report the low limit had to be set (arbitrarily, as stated in our paper) in order to get a large enough group of hypercellular patients. This again emphasises the quantitative aspects here: these are rare patients. We do, however, apparently see more such patients than Dr Jung and his colleagues, probably because we have a referring "filter," the very frequent everyday problem of slight obesity usually being taken care of outside our hospital. These severely obese subjects are, however, a considerable clinical problem although they are relatively few.

To sum up and close the discussion from our side, Dr Jung and his colleagues have brought up some important technical problems remaining in the field of adipocyte counting. We believe that we both think that adipose hypercellularity exists, although the division line is rather elusive and arbitrary, just like the definition of obesity itself. We see more of the seriousness of the hypercellularity problem than the English group does because we apparently get different patient material.

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¹ Salans, L., Cushman, S W., and Weismann, R E, *Journal of Clinical Investigation*, 1973, **52**, 929.

² Björntorp, P, *et al.*, *American Journal of Clinical Nutrition*, 1975, **28**, 445.

Long-term parenteral nutrition

SIR,—As directors of the Home Parenteral Nutrition Programme at the University of Washington, Seattle, we would like to make several comments regarding the article on home parenteral nutrition by Drs Karin Ladefoged and Stig Jarnum (22 July 1978, p 262). These comments are based on our own extensive experience over the last nine years.¹

The authors do not make any differentiation between the complication rate for the standard subclavian vein catheter and the Broviac catheter. We have exclusively used the

Broviac catheter and have a much lower complication rate in our patients than the authors have reported. Specifically, in 137 catheters used in 94 patients with a total infusion time of 1644 patient months, we have noticed only 23 episodes of associated septicaemia and five episodes of venous thrombosis.² It is noteworthy that none of our patients are on long-term anticoagulation.

The authors commented that unlike other programmes they have found it difficult to maintain a standard parenteral nutrition infusion programme. This may be due to the unusually high percentage of patients that they have with jejunostomies. However, in our patients with short-bowel syndrome and either jejunostomies or ileostomies we keep the patients on a standard total parenteral nutrition programme and supplement them with normal saline as needed to replace excessive gastrointestinal loss. We have been able to instruct our home patients to use a two-channel infusion system—one channel for nutrients is connected by a "Y" to the other channel, which handles the normal saline.

Although some of our patients have been on home parenteral nutrition for over five years, we have seen vertebral compression fractures only in patients who have been on steroids. We have never seen significant osteomalacia with spontaneous bone fractures. However, we give patients 400 units of vitamin D daily, while the authors in this study gave them only 1200 units weekly. Perhaps their patients are therefore deficient in vitamin D.

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¹ Rault, R M J, and Scribner, B H, *Progress in Gastroenterology*, 1977, **3**, 545.

² Miller, D G, *et al.*, *Surgery, Gynecology and Obstetrics*, in press.

Nutrition and cancer

SIR,—Your leading article on malnutrition and cancer (7 April, p 912) reminds us that the cachexia of cancer is wrongly compared with the state of starvation. Starvation is a hypometabolic state in which there is a reduction in the turnover of carbohydrate, fat, and protein stores.¹ Ketone bodies appear to play a major regulatory role.² On the other hand, cancer cachexia is a hypermetabolic state³ with increases in glycolysis, gluconeogenesis, lipolysis, and protein catabolism.^{4,5} Moreover, ketosis is an uncommon phenomenon in cancer patients (personal observations).

Using intravenous lipid solutions, we induced ketosis for eight days in a patient who had advanced hepatic cancer and peritoneal metastases. During that time she received only 56% of her usual calorie intake. However, she did not experience any change in her body weight, abdominal girth, or general well-being. Furthermore, she felt sated for the first time in months. Her serum albumin concentration gradually increased and her urinary and serum urea concentrations decreased, suggesting a reduction in endogenous protein catabolism. Neither hypoglycaemia nor lactic acidosis was observed.

Ketone bodies have been shown to reduce the growth, in culture, of transformed

lymphoblasts from Burkitt's lymphoma and this effect is reversible, non-toxic, and proportional to the concentration of the ketone body up to 20mM.⁶ Normal cells are also known to have reduced cell growth rates in starvation.^{7,8} In leukaemia patients it has been shown that elevations in the proportion of immature cells in the bloodstream can be correlated with elevations in the basal metabolic rate.⁹

Surely these experimental findings raise the question: are forced feeding regimens for the treatment of advanced cancer metabolically sound? We have commenced a clinical trial to evaluate the role of hypometabolic (that is, ketotic) states in cancer therapy.

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¹ Cahill, G F, *Clinical Endocrinology and Metabolism*, 1976, **5**, 397.

² Newsholme, E A, *Clinical Endocrinology and Metabolism*, 1976, **5**, 543.

³ Tannenbaum, A, and Silverstone, H, *Advances in Cancer Research*, 1953, **1**, 452.

⁴ Waterhouse, C, *Annals of the New York Academy of Sciences*, 1974, **230**, 86.

⁵ Gold, J, *Annals of the New York Academy of Sciences*, 1974, **230**, 103.

⁶ Magee, B, *et al.*, in *Proceedings of Australian Symposium on Nutrition and Cancer*, 1978, p 25.

⁷ Aldewachi, *et al.*, *Journal of Anatomy*, 1975, **119**, 105.

⁸ Stragand, J J, and Hagemann, R F, *American Journal of Clinical Nutrition*, 1977, **30**, 918.

⁹ Gunderson, A H, *Boston Medical and Surgical Journal*, 1921, **185**, 785.

Cancer after cardiac transplantation

SIR,—Your leading article "Cancer after cardiac transplantation" (24 February, p 509) remarks: "The striking increase in the incidence of lymphoid neoplasms in patients who have transplants is intriguing but unexplained." It may therefore, be pertinent to draw attention to some animal models in which high incidences of malignant lymphoma were the long-term clinical result of a variety of experimental situations.

Armstrong *et al.*¹ trace the development of lymphomas associated with chronic allogeneic disease in mice as a "continuous transition from an immunological disorder, allogeneic disease, to a malignant growth... initiated by the transplantation of foreign lymphoid cells." Chronic antigenic stimulation of host tissues by allogeneic histocompatibility antigens resulted in neoplasia in this instance.

Another murine system excludes major histocompatibility by using syngeneic recipients.² In this system malignant lymphoma has also been the sequel to syngeneic transplantations without immunosuppression. A high incidence of lymphoma (60-70%) was the neoplastic outcome in syngeneic recipients of mammary gland and lymph node tissue,³ irrespective of the different treatments of the grafts before transplantation. Von Boehmer *et al.*⁴ reported that a syngeneic mixed lymphocyte reaction in mice between thymus cells and peripheral lymphocytes indicates the presence of antigenic differences between syngeneic lymphocytes even without a difference at a major histocompatibility locus. These authors postulate the presence of an antigen on peripheral lymphocytes not coded for by the major histocompatibility complex. Chronic stimulation of host lymphoid tissue by this antigen may play a part in the development of lymphoma in syngeneic graft recipients.

Even in autologous hosts it was possible to induce malignant lymphoma⁵ by first exposing the

graft tissue, skin, to an abnormal culture atmosphere (45% CO₂ in air) for various periods (7-48 h). Normally-cultured skin grafts caused no lymphoid malignancy. Immunogenicity of exposed grafts as a result of modification of cell-surface proteins and production of "altered self" structures may be a factor in the subsequent appearance of lymphoma in these autologous hosts.

In the animal models described above, malignant lymphoma develops as a late sequela of transplantations in the absence of exogenous immunosuppressants; chronic antigenic stimulation appears to be a possible common factor. Significantly, only lymphoid neoplasms developed despite the grafting of four different tissues—lymph node, mammary gland, skin, and bone marrow. Bone marrow is the only tissue that did not induce lymphoma in its recipients even following exposure to an unphysiological environment. This raises the question whether the T lymphocytes in the graft tissues are involved in the malignant processes in these animal models.

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¹ Armstrong, M Y K, Schwartz, R S, and Beldotti, L, *Transplantation*, 1967, **5**, 1380.

² Goldsmith, A E, and Ryan, G F, in *Prevention and Detection of Cancer*, ed H E Nieburgs, p 971. New York, Marcel Dekker, 1977.

³ Von Boehmer, H, and Byrd, W J, *Nature New Biology*, 1972, **235**, 50.

⁴ Von Boehmer, H, and Adams, P B, *Journal of Immunology*, 1973, **110**, 376.

⁵ Goldsmith, A E, and Narvaez, R, *Oncology*, 1975, **32**, 247.

Polymyalgia rheumatica and primary biliary cirrhosis

SIR,—May we comment on the paper by Dr J C Robertson and others (21 October, p 1128)? We have reported the careful rheumatological examination of 88 patients suffering from biopsy-proved primary biliary cirrhosis.¹ We found a much higher prevalence of rheumatic disorders than Sherlock and Scheuer² but did not find any patient who had the classical polymyalgia rheumatica syndrome. Polymyalgia rheumatica can be a difficult condition to diagnose, especially in patients who already have many other problems, but we took special care to elicit symptoms of stiffness and pain in the joints and muscles.

We did see three main rheumatological complications: scleroderma, avascular necrosis of the femoral or humeral head, and inflammatory arthritis. At that time we felt that the inflammatory arthritis was probably no greater than would be seen in a comparable population of middle-aged women. Further experience has suggested to us that we may not have been correct in this assessment and we hope to be reporting further on the inflammatory arthritis in primary biliary cirrhosis; but we doubt that the polymyalgic syndrome occurs sufficiently frequently in primary biliary cirrhosis to be an important association. We would also offer a word of caution about treating patients with corticosteroids with a doubtful diagnosis of polymyalgia as there is a real danger of accelerated osteoporosis.

However, we would make the point that

patients presenting with a somewhat atypical rheumatological complaint should have, among other investigations, liver function tests performed with a view to the possibility that this might be an unusual manifestation of primary biliary cirrhosis.

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¹ Clarke, A K, *et al*, *Annals of Rheumatic Diseases*, 1978, **37**, 42.

² Sherlock, S, and Scheuer, M D, *New England Journal of Medicine*, 1973, **289**, 674.

Homoeopathic medicine

SIR,—Dr Hamish W Boyd's letter (24 March, p 821) is an extension of the old homoeopathic search for respectability.

Formation of a faculty, registration by Parliament, or registrable diplomas do not remove homoeopathy from fringe medicine. Those who feel that there may be a scientific basis for it should read recent publications on the subject such as those by Blackie¹ and by Ruthven Mitchell.² Both of these books speak a different language and indicate how little insight homoeopathic practitioners have into the powers of suggestion.

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¹ Blackie, M, *The Patient Not the Cure*. London, MacDonald and James, 1977.

² Mitchell, G R, *Homoeopathy*. London, W H Allan, 1977.

Postpartum haemorrhage and induction of labour

SIR,—We presented a paper (23 September 1978, p 855) showing an increased incidence of postpartum haemorrhage following induced labour compared with spontaneous labour. Additional data for the years 1975-7 from St Mary's Maternity Hospital, Portsmouth, confirm this finding.

A total of 10 320 spontaneous vaginal deliveries occurred in this three-year period, of which 6462 were spontaneous labours and 3858 were induced or accelerated labours. The accompanying table shows the figures for each year with the overall postpartum haemorrhage rate for the 10 320 cases. Multiparous and primiparous patients have been analysed separately, as they were in the initial study. The difference in postpartum haemorrhage rates between the induced and spontaneous groups is striking.

There has been no major change in the management of labour since our original paper was published. Intravenous prostaglandins have been used rarely for induction of labour. The oxytocin regimen remains unchanged and Syntometrine (ergometrine maleate and oxytocin) continues to be given for the third stage of labour.

MacKenzie (17 March, p 750) has confirmed our findings in his survey of delivery figures

from Oxford. He has in addition been able to show the figures for accelerated labour as a separate category, which show a postpartum haemorrhage rate between that of spontaneous and induced labours.

We present these figures in support of our previous submission that postpartum haemorrhage should be considered as a serious complication of induction of labour, especially in primigravidae, and that it is probably related to the dosage of oxytocin infused.

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Male sexual dysfunction and cimetidine

SIR,—I read with interest Dr N R Peden and colleagues' report (10 March, p 659) about three patients with sexual dysfunction after cimetidine and their postulation of an anti-androgenic action for cimetidine in man. It is worthy of comment that in two patients (cases 1 and 3) the luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels were higher off cimetidine treatment and that the level of these hormones fluctuated at three and seven months after treatment in case 2. The data presented seem rather sparse to suggest overall trends.

Dr A M Hoare and I¹ were unable to find any differences in prolactin, total androgen, and oestradiol levels, or in the response of LH, FSH, and thyroid-stimulating hormone to appropriate releasing-hormone stimulation in 10 male subjects tested before and at completion of a 12-week course of cimetidine (1600 mg per day). Patients' ages ranged from 29 to 76 years (mean 50). Moreover, the lack of significant change is not altered by omitting those patients who were less than 40 years old.

It seems unlikely therefore that there is an endocrinological basis for the impotence reported by Peden *et al*, although other mechanisms may indeed be operating in the aetiology of this distressing complaint.

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¹ Barber, S G, and Hoare, A M, *Hormone and Metabolic Research*, 1979, **11**, in press.

Cimetidine and erythrosis-like lesions

SIR,—A 36-year-old man was admitted to our clinic on 2 November 1978 with a history of epigastric pain. Over the past 10 years he had had recurrent epigastric pain and three episodes of gastrointestinal bleeding after taking anti-inflammatory drugs.

Postpartum haemorrhage (PPH) rates in induced and spontaneous labours: Portsmouth, 1975-7

Year	Spontaneous labour				Induced labour				Total
	Primiparae		Multiparae		Primiparae		Multiparae		
	Total No	No (%) with PPH	Total No	No (%) with PPH	Total No	No (%) with PPH	Total No	No (%) with PPH	
1975	731	27 (3.7)	1217	46 (3.8)	629	46 (7.3)	931	57 (6.1)	3508
1976	908	40 (4.4)	1451	62 (4.3)	448	37 (8.2)	702	49 (7.0)	3509
1977	838	33 (3.9)	1317	44 (3.3)	436	35 (8.0)	712	39 (5.5)	3303
Total	2477	100 (4.0)	3985	152 (3.8)	1513	118 (7.8)	2345	145 (6.2)	10320