blown into his face. After he replaced the original Gramoxone container with a new plastic container he had no further symptoms. His chest x-radiograph during these episodes of fever was not significantly altered.

As in the case reported by Drs George and Hedworth-Whitty, it was not possible to investigate this further as my patient was not seen soon after exposure; but his story strongly suggests that inhalation of paraquat was responsible for his symptoms.

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Ectopic production of methionine enkephalin and beta-endorphin

SIR,—In the paper by Dr P T Pullan and others (15 March, p 758) three met-enkephalin- and β -endorphin-producing tumours, recognised histologically as carcinoids, are nevertheless described as *non-endocrine*. This view is surely insupportable.

In terms of their admittedly not invariable production of amines carcinoids have been regarded as endocrine for over a quarter of a century and in most parts of the world they are now recognised as apudomas, and therefore as "neuroendocrine,"¹ derived from cells which are "endocrinologically totipotent with respect to both amines and peptides."² They can thus be defined as endocrine or neuroendocrine tumours capable of producing "any of the 35 APUD peptides, or variations of the correct sequences of any of the known or presently unknown prohormones and pre-prohormones, or fragments thereof."³

Beta-endorphin and met-enkephalin are integral parts of pro-opiocortin, the adrenocorticotrophic hormone-lipotropin precursor.⁴ Their postulated production by small-cell carcinoma of the lung, another apudoma, is virtually certain⁵ and the secretion of β -endorphin by yet another apudoma (islet-cell tumour) is hardly surprising. Only in the sense originally used by Liddle *et al*⁶ is this function ectopic—an interpretation opposed by Rees and Ratcliffe,⁷ who maintained that a hormone is ectopic only when its *normal* sites of synthesis are known (which they are not). I consider that it is misleading and wrong to interpret the three tumours as non-endocrine and that current use of the word ectopic should be qualified by a note in the text of any paper in which it is used.

I have no quarrel with the proposition that ectopic peptides secreted by endocrine tumours, even if they are not called apudomas, may be responsible for much otherwise inexplicable symptomatology.

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¹ Pearse AGE, Polak JM, Heath CM. *Virchows Archiv B* 1974;16:95-100.

² Pearse AGE. *Z Krebsforsch* 1975;84:1-18.

³ Pearse AGE. *Clin Endocrinol Metab* (in press).

⁴ Eipper BA, Mains RE. *J Biol Chem* 1978;253:5732-44.

⁵ Bertagna XY, Nicholson WE, Sorenson GD, Pettengill OS, Mount CD, Orth DN. *Proc Natl Acad Sci USA* 1978;75:5160-4.

⁶ Liddle GW, Nicholson WE, Island DP, Orth DN, Abe K, Lowder SC. *Rec Prog Horm Res* 1969;25:283-314.

⁷ Rees LH, Ratcliffe JG. *Clin Endocrinol* 1974;3:263-99.

SIR,—I read with interest the paper by Dr P T Pullan and others (15 March, p 758) reporting the presence of methionine enke-

phalin and beta-endorphin in carcinoid tumours in three patients with the ectopic-adrenocorticotrophin syndrome, and I noted your interesting leading article (p 741) on this topic. All three patients had affective disorders—one mania and two depression—and these resolved when the tumours were removed. I have recently published¹ a psychiatric study of 29 patients with Cushing's syndrome: one of my conclusions was that since the depressive symptoms were relieved by removal of the adrenal glands and were not related to the concentration of plasma cortisol we needed to consider whether "an as yet unknown substance produced by the adrenals is responsible for the depression of Cushing's syndrome." Could it be that opioid peptides are responsible? Might it even be possible that the very rapid remission of psychiatric symptoms after operation was the result of removal of the adrenal medulla rather than the cortex, since enkephalin is normally found in the medulla as Dr Pullan and others state?

A second finding which I reported was that patients whose Cushing's syndrome was the result of an adrenal tumour were considerably less likely to be psychiatrically disturbed than patients with pituitary-dependent Cushing's syndrome, and, indeed, there was a three-in-four chance that a patient who was absolutely free from psychiatric symptoms might have a tumour: of four patients without psychiatric symptoms, three had a tumour and one had hyperplasia, whereas of 25 patients with psychiatric symptoms, five had a tumour and 20 hyperplasia ($\chi^2=5.22$; $n=1$; $0.025 > p > 0.02$). It would be interesting to compare observations on the opioid peptides in patients with Cushing's syndrome with and without affective disorders.

Finally, I should like to emphasise that if further work is undertaken in this field it is of the utmost importance that an appropriate description of the patient's psychiatric features should accompany the other clinical details.

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¹ Cohen SI. *Br J Psychiatry* 1980;136:120-4.

Is severe restriction of food really a very-high-fat diet?

SIR,—Your inquirer (*Any Questions?* 1 March, p 628) correctly states that "severe restriction of food intake in obesity effectively puts the patient on a very high-fat diet," and asks if the harmful effects said to follow a very high-fat diet in Europeans have been observed. Your expert missed the point of this intelligent question—namely, that severe restriction of food intake in obesity causes body fat to be mobilised for energy, in effect a very high-fat diet.

The fat that is mobilised will alter in composition according to the previous diet. For instance, Edinburgh men aged 40 years had in their adipose tissue 7.3% linoleic acid (an essential fatty acid, EFA) and a polyunsaturated: saturated fat (P:S) ratio of 0.30; comparable men in Stockholm, who have only about a third of the incidence of coronary heart disease, had 11.8% linoleic acid and a P:S ratio of 0.44.¹ I normally eat considerable amounts of linoleic acid daily, and my adipose tissue has about 29% of this EFA, with a P:S ratio of 1.3. In the Finnish hospital study² dietary alteration to increase linoleic acid while keeping total dietary fat constant increased

the percentage of this in adipose tissue so that the experimental hospital had 26.9% of this near the end of the first period and the control 10.2%; when the hospitals were reversed the experimental one now had 32.5% linoleic acid and the control 9.8. The change in diet decreased thrombotic tendency of blood.

So for most people in this country severe restriction of food intake will cause fat to be mobilised that is relatively saturated and very low in EFA. Acute starvation usually produces a slight rise in plasma cholesterol whereas partial starvation usually produces a slight fall. When three epileptics were acutely starved for 11 days this therapy was not successful: one died after a rise in plasma cholesterol of about 90%.³ At the end of the second world war Swiss investigators noted frequent venous thrombosis with occasional pulmonary infarction in undernutrition,⁴ and extensive investigations by French investigators found frequent venous thrombi at necropsy, some associated with atheroma⁵; indeed, they emphasised that atheroma occurred at a much earlier age than usual. However, in more severe starvation in the siege of Leningrad and, as so brilliantly studied in tragic circumstances, in the Warsaw ghetto⁶ atheroma was conspicuously absent at necropsy. Stress, like severe restriction of food, mobilises fatty acids from adipose tissue. Stressed Americans have increases in catecholamines and in plasma cholesterol, and shortened clotting time.⁷

Severe restriction of food in ordinary persons in this country may therefore be similar to a very high-fat diet in increasing the amount of saturated fatty acids in blood. In a reducing diet fat must be kept low (as your expert states) but it should be relatively rich in EFA. More important, however, is to increase the ratio of EFA to non-EFA by dietary means⁸ in the ordinary diet, and then adipose tissue will be relatively rich in the former.

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¹ Logan RL, Riemersma RA, Thomson M, *et al*. *Lancet* 1978;i:949-56.

² Turpeinen O, Karvonen MJ, Pekkarinen M, *et al*. *Internat J Epidemiol* 1979;8:99-118.

³ Lennox WG, O'Connor M, Bellinger M. *Arch Intern Med* 1926;38:553-65.

⁴ Uehlinger E. In: Hottinger A, Gsell O, Uehlinger E, *et al*, eds. *Hungerkrankheit, Hungerödem, Hungertuberkulose*. Basel: Benno Schwabe, 1948:181-246.

⁵ Lamy M, Lamotte M, Lamotte-Barrillon S. *La dénutrition, clinique-biologie-thérapeutique*. Paris: Doin, 1948.

⁶ Apfelbaum E. *Maladie de famine. Recherches cliniques sur la famine exécutées dans le Ghetto de Varsovie en 1942*. Warsaw: Am Joint Distribution Committee, 1946.

⁷ Friedman M, Rosenman RH. *Circulation* 1957;16:339-47.

⁸ Sinclair HM. *Lancet* 1980;i:414-5.

*Our expert writes: "Dr Sinclair correctly points to the abrupt changes brought about by starvation, the hazards of which are well recognised. During fasting adipose tissue is mobilised to glycerol and fatty acids and the concentration of free fatty acids in the blood is increased.¹ Sometimes during total starvation excessive mobilisation of fatty acids may result in the deposition of triglycerides in the liver producing a fatty liver. Reduction of weight, however, regularly causes a fall in serum cholesterol and serum triglyceride concentrations.² Moreover, the improvement sometimes persists when a normal-calorie diet is resumed, suggesting that plasma lipoprotein metabolism is influenced not only by the calorie balance but by the total adipose tissue mass. Even in hyper-beta-lipoproteinaemia cholesterol levels may fall during fasting.³ In this famous Framingham study the serum cholesterol was shown to have a linear correlation with weight change. The

blood concentrations of lipids are only a guide in the "steady state" to what is actually happening to lipid metabolism in the body. The correlation between atheroma and abnormal blood lipids is indirect; the relationship is likely to be with the overall complex of lipid metabolism. There is certainly no evidence to suggest that arterial disease is worsened by weight reduction, and much evidence to the contrary."—Ed, *BMJ*.

¹ Glennon JA, Breech WJ, Gordon ES. *Metabolism* 1967;16:503-6.

² Levy RI, Bonne EL, Ernst NO. *J Am Diet Assoc* 1971;58:406-16.

³ Ashley FW, jun, Kannel WB. *J Chronic Dis* 1974;27:103-14.

Traction tears of the spleen

SIR,—I read with interest Mr D Ernst's report "Ruptured spleen after electric convulsion therapy" (15 March, p 763). This case would indeed fulfil Orloff and Peskin's four criteria for spontaneous rupture of the spleen,¹ but I strongly suspect that this patient suffered a traction tear of the spleen following the ECT. We reported a similar case which followed a prolonged period of vomiting,² and suggested that violent contractions of the diaphragm caused a traction tear where the diaphragmatic peritoneal reflection met the splenic capsule. Such a traction tear may well be the explanation of a number of otherwise classified "spontaneous ruptures of the spleen."

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¹ Orloff MJ, Peskin GW. *Int Abstr Surg* 1958;106:1-11.

² Thomas WEG. *Br Med J* 1978;i:409-10.

Career prospects in geriatric medicine

SIR,—My recent letter (15 March, 1980) on the subject of the excellent career prospects in geriatric medicine mentioned a bursary scheme to enable doctors already appointed to a senior registrar post in general medicine or related subspecialties to gain experience in geriatric medicine. Unfortunately, the reference was omitted and correspondence I have had suggests that doctors would certainly like to know more about the scheme. Details are available from all regional and area medical officers, who were informed about the bursary scheme in a letter from the DHSS medical manpower division; this was dated 24 May 1979, and has the reference code D/M 169/6D.

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Postgraduate education and the doctor

SIR,—Dr David C Evered and Hilary D Williams (1 March, p 626) were guilty in their paper of two basic errors of scientific research.

Firstly, they selected for review only those papers included in "continuing medical education" in which the title suggested some methodological evaluation. As a result they omitted from consideration the work of Maguire *et al*,¹ who demonstrated that the use of audiovisual material was the most effective method of teaching medical students

the skills of interviewing techniques. It would seem likely that a method that was successful in undergraduates would also be of use in postgraduate medical education. Indeed, we have demonstrated a positive effect in a controlled trial among experienced general practitioners² and a trend among trainee general practitioners.³ We have also prepared a paper describing, on the basis of our experience, some of the problems inherent in the use of this new educational technology.⁴

Secondly, Drs Evered and Williams, having limited their material artificially, were guilty of extrapolating beyond their data. Hence their conclusions are probably not only wrong but, more importantly, dangerous in that they may deter the use of valuable techniques.

Audiovisual technology provides a unique and acceptable method of observing and providing feedback of a central part of the clinical process of the consultation. Commerce has been rather quicker than the medical profession to recognise its usefulness in training. The value of this paper by Drs Evered and Williams is that it highlights the inadequacy of a great deal of currently published work.

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¹ Maguire P, Rowe P, Goldberg D, Jones S, Hyde C, O'Dowd T. *Psychol Med* 1978;8:695.

² Verby JE, Holden P, Davis RH. *Br Med J* 1979;i:1686-8.

³ Verby JE, Davis RH, Holden P. *Excerpta Medica* (in press).

⁴ Davis RH, Jenkins M, Smail SA, Stott NCH, Verby J, Wallace BB. *J R Coll Gen Pract* (in press).

Interaction between lithium and carbamazepine

SIR,—I was interested to see that Dr W A G MacCallum's patient, during maintained lithium therapy, not only tolerated carbamazepine, but was better with this treatment (1 March, p 610). Dr E Perruca and Dr A Riches suggested that this could be due to carbamazepine's antidiuretic property (22 March, p 863). My clinical experience, however, is somewhat different.

It has been suggested that lithium inhibits the vasopressin-stimulated adenylylase and that the distal renal tubules become relatively insensitive to antidiuretic hormone (ADH).¹ Meinders *et al* suggested that carbamazepine's antidiuretic effect may be related to this drug's ability to increase renal responsiveness to endogenous ADH.² Hence, it is likely that carbamazepine will be beneficial in lithium-induced polyuria. In an initial open study, this drug apparently produced some relief within one week in one 50-year-old man with bipolar manic depression. In view of that a placebo-controlled (double-blind crossover) investigation involving 10 patients with unipolar and bipolar disease was carried out.³ Oral carbamazepine (300-600 mg daily for six weeks) was observed to have no pharmacological effect either in alleviating subjective symptoms or in improving renal responsiveness to subcutaneous Pitressin injection. Half of the patients dropped out during the active phase of the treatment. Most developed various central symptoms like ataxia, dizziness, blackout, agitation, restlessness, confusion, and feelings of unreality during carbamazepine therapy, and these symptoms disappeared with discontinuation of this medication. It appeared that lithium exacerbated carbamazepine-induced central side effects, or vice versa. There was no significant fluctuation in plasma lithium concentrations, but it was not possible to measure

the plasma concentrations of carbamazepine during this investigation because of a methodological problem. It should be emphasised that these patients were all maintained on lithium for 2-12 years: their affective states were fairly well controlled, many of them were holding responsible jobs, and they had satisfactory therapeutic relationships with the clinic.

Prolonged lithium therapy is known to be associated with negative sodium balance and central sodium depletion,⁴ and further unbalance in sodium metabolism (either by reducing sodium or by retaining water) may be fatal in these patients.⁵ Lithium is also known to reduce nervous conduction velocity.⁶ Although the mechanism of increased incidence of various central symptoms in these patients during carbamazepine therapy was not very clear, it could be related to the drugs' mutual effect on sodium metabolism or on nervous conduction velocity. Since, however, the above investigation was carried out in a limited number of patients in an outpatient department, it will be interesting to see the outcome of further controlled trials involving larger number of patients.

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¹ Dousa T, Hechter O. *Life Sci* 1970;9:765-6.

² Meinders AE, Ceika V, Robertson GL. *Clin Sci Mol Med* 1974;47:289-99.

³ Ghose K. *Pharmacopsychiatr Neuropsychopharmacol* 1978;11:241-5.

⁴ Edelfors S. *Acta Pharmacol Toxicol* 1975;37:387-8.

⁵ Ghose K. *Br J Hosp Med* 1977;18:578-80.

⁶ Girke W, Krebs FA, Muller-Oerlinghausen B. *Int Pharmacopsychiatry* 1975;10:24-36.

Epidemiology and clinical practice

SIR,—Since June 1979 we have met on a number of occasions to consider the relationship of epidemiology to clinical practice. We think that the present separation of the two disciplines is to the disadvantage of both. The conclusions from our meetings are: (1) There is a demand for training in epidemiology among doctors at registrar and senior registrar level who wish to develop epidemiological skills and use them in a subsequent career in hospital or general practice. In most specialties the rules for accreditation are too rigid to permit trainees to attend courses such as an MSc in epidemiology. (2) There is a demand for posts which combine clinical practice as a consultant or general practitioner with an opportunity to carry out epidemiological research. (3) There is a demand among men and women seeking a career in epidemiology for a training programme which does not require service experience in medical administration or health service planning. Such a programme could lead to a career within a subspecialty of community medicine.

A meeting to discuss these issues will be held in London in June. Will anyone wishing to attend please write to Professor ED Acheson, MRC Environmental Epidemiology Unit, South Academic Block, Southampton General Hospital, Southampton SO9 4XY.

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N J BLACKLOCK	M F OLIVER
R B COLE	G A ROSE
P C ELMES	M SHEPHERD
N S GALBRAITH	M D WARREN
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