source of uncertainty and even scepticism about the applicability of the result of such a trial to a population in general and to a single patient in particular.

We suggest that participating clinicians should be prepared to enter *all* their patients into the selection process and, with a minimum of exclusion clauses, that the *whole* population be documented. The results should then be reported in two parts—those for patients who have been randomised and those for patients who have been excluded from the trial. This comprehensive approach would allow would-be followers of new methods to have greater confidence in deciding whether an individual might benefit from the results of a reported investigation.

Although this would increase the task, perhaps it is a necessary bridge between the scientist's wish to study populations and the clinician's drive to identify the best treatment for the individual patient.

L P FIELDING
L BLESOVSKY
SARAH STEWART-BROWN

Surgical Unit,
St Mary's Hospital,
London W2

Localisation of vipoma

SIR,—I was interested to read the short report on the localisation of a vipoma by Dr J G C Kingham and others (16 December, p 1682). In this paper the authors state that the vasoactive intestinal peptide (VIP) concentrations in the portal and systemic veins around the head of the pancreas fell dramatically 10 minutes after removal of the small tumour which was presumed to be the site of VIP secretion. Presumably this fall in concentration was not known to the surgeon until several days later, when the radioimmunoassay results were known.

Can the authors advise us on the use of any preoperative techniques which may aid the surgeon in localising a vipoma or the presence of micrometastases? Could they also comment on how they would have managed this case had the VIP concentrations not been reduced by the resection of this tumour—this fact only being known several days after laparotomy?

It seems to me that there is still the need for a rapid assay, which perhaps could be performed in an operating theatre side room in order to provide the surgeon with information regarding the adequacy of resection of a hormone-secreting tumour. Perhaps the further development of cytochemical bioassays will have a part to play in this context.

R W HOILE

Surgical Unit,
Westminster Medical School,
London SW1

* *We sent a copy of this letter to the authors, whose reply is printed below.—Ed, *BMJ*.

SIR,—In reply to Mr Hoile's comments, he presumes correctly the surgeon was unaware of the rapid fall of VIP levels after tumour excision. The VIP radioimmunoassay used in the management of this case¹ takes four days and therefore is not of value as a theatre side room assay in its present form. It is possible that a highly modified VIP radioimmunoassay, as has been described for insulin,² may be of use preoperatively. Such an assay has not yet been

developed, but our VIP assay could be performed in two hours at the expense of considerable loss of sensitivity. Most bioassays for VIP are not sufficiently sensitive to detect physiological levels of VIP or even levels in the vipoma range. However, a bioassay has been reported recently that is sensitive to 10 pmol/l VIP,³ though its complexities would make it unsuitable as a side room technique.

If tumour excision had cured this man's symptoms but not reduced his VIP levels to normal, then further treatment would not have been warranted. If excision had neither cured the symptoms nor reduced VIP levels despite the tumour's being a histologically proved vipoma, then metastases would have been presumed responsible and we would have considered a trial of streptozocin rather than continued high-dose steroids.

We know of no currently available technique for localising tumour or micrometastases preoperatively and agree that there is need for one.

J G C KINGHAM

Gastroenterology Department,
St Bartholomew's Hospital,
London EC1

R DICK

Diagnostic Radiology Department,
Royal Free Hospital,
London NW3

STEPHEN BLOOM

Royal Postgraduate Medical School,
London W12

R J FRANKEL

Department of Endocrinology,
Frimley Park Hospital,
Frimley, Surrey

¹ Mitchell, S J, and Bloom, S R, *Gut*, 1978, **19**, 1043.
² Turner, R C, *et al*, *Lancet*, 1976, **1**, 515.
³ Waldman, D B, *et al*, *Gastroenterology*, 1977, **73**, 518.

Iodine and acetone-containing plastic spray dressing

SIR,—We read with interest the letter from Dr J C Morgan-Hughes and Mr R A Bray (26 August, p 639) on the suggested hazard of using an acetone-containing spray (Op-Site) in conjunction with tincture of iodine, and would like to offer some information which may help to interpret their observations.

It is known that iodine can react with acetone under appropriate experimental conditions,¹ as Dr E Powell pointed out (25 November, p 1500); and it has been postulated that iodoacetone may be formed in an aqueous acetone solution of iodine.² In our opinion it is unlikely that such a reaction could occur to a significant extent under the conditions of an acetone-containing spray dressing being applied to iodine-treated skin, and no evidence of such a reaction has been put forward in the current correspondence.

Clinically, it is well known that solutions of iodine applied to the skin should not be covered with an occlusive dressing,³ a view supported by Dr Morgan-Hughes's observations¹ that "erythema occurred in all areas painted with tincture of iodine and covered by Sleek" (an occlusive strapping). The "more severe" reaction demonstrated when iodine, Op-Site spray, and Sleek were used suggests an exaggeration of the effects of occluding iodine on the skin. The combination of Op-Site and Sleek failed to produce skin reactions, and it is unfortunate that the effect of Op-Site spray alone on iodine-prepared skin was not investigated by Dr Morgan-Hughes, since the film formed by the Op-Site spray is highly permeable and not occlusive.

In a recent communication Dr P R W Lanham (30 September, p 961) has indicated that, in his experience, Op-Site spray on iodine-prepared skin does not cause a reaction since a gauze swab is used to protect the iodine- and Op-Site-prepared skin from the occlusive Sleek strapping. We have demonstrated that Op-Site spray itself, when applied directly to iodine-treated skin, does not give rise to any complications.⁴ Thus we conclude that the essential factor in the skin reactions reported by Dr Morgan-Hughes was occlusion of the iodine-prepared skin by an occlusive strapping. Op-Site spray alone over iodine-prepared skin does not constitute a hazard.

J G B HOWES

Smith and Nephew Research Ltd,
Harlow, Essex

P KIRWAN

Smith and Nephew Ltd,
Welwyn Garden City, Herts

¹ Benesi, H A, and Hildebrand, J H, *Journal of the American Chemical Society*, 1949, **71**, 2703.

² Dawson, H M, and Leslie, M S, *Journal of the Chemical Society*, 1909, **95**, 1860.

³ Wade, E (editor), *Martindale: The Extra Pharmacopoeia*, 27th edn, p 826. London, Pharmaceutical Press, 1977.

⁴ Smith and Nephew Research Ltd, internal report, October 1978.

Long-term parenteral nutrition

SIR,—With reference to the paper by Drs Karin Ladefoged and Stig Jarnum (22 July, p 262) I would like to comment on table IV, "Complications unrelated to long-term parenteral nutrition."

The authors mention two patients with paresis of the peroneal nerve without giving any explanation of this. I too observed in a patient undergoing long-term total parenteral nutrition the onset of a bilateral paresis of the peroneal nerve after seven to eight months of completely intravenous nutrition. Paralysis was associated with "burning" feelings and sensations of heat, which affected mainly the soles of the feet and less frequently the dorsal aspect of the feet as well. Sometimes the pain took the form of a dull, constant ache in the feet or sometimes in the entire leg; it was often sharp and lancinating, even if momentary in duration. Neurological examination revealed a severe bilateral motor, reflex, and sensory loss confined to the legs and feet. No cardiac abnormality was found on the electrocardiogram except sinus tachycardia unresponsive to digoxin.

Since the patient had been maintained on a daily dosage of 3.2 mg thiamine for seven months and balance studies¹ indicate a minimum daily requirement of approximately 1 mg, a thiamine deficiency was not initially suspected and high dose of pantothenic acid was administered. Subsequently, owing to the persistent symptoms, I suspected that this patient, who had been receiving parenterally about 600-750 g dextrose a day, might have a high consumption of thiamine since it is an important cofactor in carbohydrate metabolism: thiamine in fact is required for the oxidative decarboxylation of both pyruvate and α -ketoglutarate and also participates in the transketolase reaction of the pentose shunt. I administered, therefore, 100 mg thiamine a day, and the patient experienced a prompt and progressive resolution of his pain and an improvement of the sensory function, though only a slight recovery of the motor activity.

While a survey of reports on this topic showed no mention of peripheral nerve paresis during TPN parenteral nutrition, I found two cases of Wernicke encephalopathy after prolonged intravenous therapy that were probably due to thiamine deficiency.² Since the patients mentioned by Dr Ladefoged and Dr Jarum received only 9.7 mg thiamine once or twice a week, I think that a thiamine deficiency could probably explain the paresis of the peroneal nerves and perhaps of the radial nerves too.

These facts should alert the clinician to suspect a "parenteral-nutrition-related beri beri" if polyneuropathy without any evident cause appears in patients fed intravenously (the determination of transketolase levels might prove a reliable laboratory test in this case). They suggest that about 0.3 mg thiamine/kg/day should be given to patients receiving parenteral nutrition as has been recently advocated.³

FEDERICO BOZZETTI

Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

¹ Ziporin, Z. Z., *et al*, *Journal of Nutrition*, 1965, **85**, 297.
² Nadel, A. M., and Burger, P. C., *Journal of the American Medical Association*, 1976, **235**, 2403.

³ Wretling, A., *Surgical Clinics of North America*, 1978, **58**, 1055.

How to take a clinical examination

SIR,—I started to read the article by Dr J F Stokes (13 January, p 98) with interest because he has been concerned with the clinical examination of the MRCP for a number of years, but as I read my disappointment and later annoyance grew. Regarding the Adie pupil, he suggests that the examiner will have arranged for the pupil to be dilated if the daylight in the ward is bright and suggests that the candidate should ask the patient if he has had drops in his eye, which would presumably have been homatropine. He does not seem to appreciate that the drops should be 2.5% mecholyl, which constricts the Adie pupil but not the normal pupil.¹ If homatropine had been put into the eye to dilate the pupil, it is doubtful if it would be possible to recognise the Adie pupil anyhow. Nowhere in the article does he suggest that the urine should be tested or a sample asked for or that the blood pressure should be measured.

Towards the end of the article, Dr Stokes remarks that it is better not to appear obviously pregnant, which must be offensive to female candidates. Many of the most distinguished doctors in Britain today are women and it is irrelevant if they took the MRCP when pregnant.

K N V PALMER

Department of Medicine, University of Aberdeen

¹ Beeson, P. B., and McDermott, W., *Textbook of Medicine*, p 328. Philadelphia, Saunders, 1971.

* * * We sent a copy of this letter to Dr Stokes, whose reply is printed below.—Ed, *BMJ*.

SIR,—The lines are crossed. I had tried to put myself in the position of a candidate who found a patient with unequal pupils and was uncertain whether one had been dilated to make it easier for him to see the fundus or whether he was faced with a case of Adie's syndrome. The question of whether I am able or unable to distinguish between the uses of homatropine and mecholyl does not arise.

I do not undervalue the importance of the blood pressure or of urine testing. In an article of limited length it seemed best to concentrate on points which might be less generally recognised.

If susceptibilities have been offended by a reference, in what I had hoped might be helpful terms, to the variable reactions I have observed in examiners to a physiological state (which may be met at graduating as well as postgraduate examinations), it is a matter for regret—though I do find it difficult to see how it can be interpreted as being denigratory to our admirable company of medical women.

J F STOKES

Nr Henley-on-Thames, Oxon

Early growth retardation in diabetic pregnancy

SIR,—The observation of Drs Jan Fog Pedersen and Lars Mølsted-Pedersen (6 January, p 18) that in a group of insulin-dependent diabetics 10 of 35 patients whose fetuses were "small for dates," by ultrasound measurement of the crown-rump length between 7 and 14 weeks postmenstrual age, subsequently delivered smaller babies than patients in whom the fetal crown-rump length measurements were appropriate for dates is interesting. However, fuller clinical detail is required before their hypothesis that there is a different pattern of growth retardation in diabetic pregnancies can be accepted.

In considering such a small number of cases the mean birth weight can readily be biased by an uneven distribution of the fetal sex, birth rank, maternal size, cigarette use, and the presence of complications such as pre-eclampsia. For example, the average effect of the first three factors at term would be as follows: male *v* female, +150 g; first pregnancy *v* subsequent pregnancies, -150 g; 175 cm/70 kg mothers *v* 150 cm/45 kg mothers, +600 g.¹ Also babies with congenital abnormalities should be excluded in view of their common association with intrauterine growth retardation. If after these factors are allowed for a significant difference in the mean birth weights remains, the hypothesis that the fetal age is less than the postmenstrual age in the "small" group cannot simply be dismissed as unlikely because the menstrual history was certain. There is considerable evidence to suggest that ovulation is not nearly as constant as implied in Naegle's rule. Boyce *et al*² studied 317 pregnancies with reliable basal body temperature charts and found that in 30% conception occurred more than two weeks beyond the usual day of ovulation calculated by Naegle's rule. The gestational age and birth-weight limits used in compiling the control series would be expected to exclude such cases and could account for the different distributions of crown-rump length measurements in the control and diabetic series.

Ultrasonic fetal measurement in early pregnancy has repeatedly been shown to predict the onset of spontaneous labour resulting in the delivery of a mature fetus more precisely than an impeccable menstrual history.³ Experience shows that when a fetal measurement falls below the normal range for the gestation age because of growth retardation the growth rate usually remains below normal. But a small measurement associated with a normal growth rate (as in Pederson and Mølsted-Pederson's cases)

indicates incorrect assignment of the gestational age.³

If our hypothesis is correct that the fetal age of the "small" group was on average 12 days less than that of the "normal-size" group, then a simple calculation from normal birth-weight data¹ suggests that this could account for a 300-500 g weight difference.

We are particularly concerned that obstetricians may be persuaded to disregard the possibility of an error in the expected date of delivery predicted by the menstrual history and deliver such fetuses earlier than would be their normal practice in diabetic pregnancy.

D J LITTLE

S M STUBBS

MICHAEL BRUDENELL

STUART CAMPBELL

Department of Obstetrics and Gynaecology, King's College Hospital, London SE5

¹ Thomson, A. M., *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1968, **75**, 903.

² Boyce, A., *et al*, *American Journal of Obstetrics and Gynecology*, 1976, **125**, 911.

³ Campbell, S., in *Fetal Physiology and Medicine*, ed R W Beard and P Nathanielsz. London, W B Saunders Co. Ltd, 1976.

Ergotamine tartrate overdose

SIR,—It is interesting to note that the difficulties of giving an effective treatment with ergotamine tartrate in migraine are given publicity. I refer to a letter from some well-known physicians with an interest in migraine whose signatures are headed by Dr J N Blau (27 January, p 265).

Most surprisingly, hypnosis and autohypnosis are seldom mentioned in connection with this distressing complaint—it is without doubt the treatment of choice when simple analgesics fail. Much of the poor reputation of hypnosis of past years has been due to poor patient selection, setting of unrealistic goals, and uncertainty of application; but none of these apply where the treatment of migraine is concerned. Impressive results have been reported by Harding,¹ Cedercreutz,² and Perkins.³

I was involved in a multicentre trial to compare hypnosis and autohypnosis with prophylactic prochlorperazine mesylate (Stemetil) and therapeutic ergotamine tartrate.⁴ Independent assessment was applied by a "blind" observer so far as possible after a 12-month trial period. It was found that those having hypnosis or autohypnosis had significantly fewer attacks in the first six months of the trial than the six months preceding the trial, and in the last six months than the first six months. The chemotherapy group showed no significant change for either the period prior to the trial or the two six-month trial periods.

There were 13 patients having grade IV attacks prior to the trial in the hypnosis group. This was reduced to five in the last three months of the trial. Ten patients were having grade IV attacks in the chemotherapy group, which went up to 14 after chemotherapy. Finally, out of 23 patients having hypnotherapy, 10 patients had complete remission with no attacks in the last three months, while only three of the 24 chemotherapy patients showed similar remission.

While it is perfectly true that there is a tremendous variability in hypnotic susceptibility, the majority of patients can be