nately and postnatally. In their absence, the strong available evidence supporting this concept is by no means invalidated by Professor Dobbing's criticism based on inconsistent interpretation of unsuitable data.

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¹ Dobbing, J, and Sands, J, *Early Human Development*, 1978, 2, 81.

² Gairdner, D, and Pearson, J, *Archives of Disease in Childhood*, 1971, 46, 783.

³ Dobbing, J, and Sands, J, *Archives of Disease in Childhood*, 1973, 48, 757.

⁴ Campbell, S, and Newman, G B, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, 78, 513.

The premature breech

SIR,—Mr St C Hopper (27 October, p 1074) and Mr J P Calvert (28 July, p 274), both advocate midline uterine incisions to avoid trauma to the head by the contracting thick uterine wall at caesarean section.

I would suggest that the administration of halothane will abolish uterine contractions and make the abdominal delivery of the premature fetus easier, especially when there is no liquor. Halothane is routinely used during caesarean section at this hospital and uterine haemorrhage is not a problem and when it occurs it responds to oxytocics. Halothane depresses the fetus but this is always temporary and responds to the usual remedies.

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Stress and premature labour

SIR,—We feel that the article by Dr Richard W Newton and others (18 August, p 411) is, because of methodological problems discussed below, unable to substantiate the claim made in it "that pregnancies resulting in premature labour are far more likely to have been stressful."

Many women after giving birth prematurely, especially those with very low birthweight infants or infants in special care, feel that the birth has been precipitated by something they themselves did, or omitted, or by something unpleasant that happened during pregnancy. In this situation then both their recall and their interpretation of life events in pregnancy are likely to be very different from those of the woman about to leave hospital with a healthy full-term infant. The "control" group could be the mothers excluded from consideration because they had "obstetric" causes of premature labour. These at least are in the same crisis of premature birth. If the obstetric cause is known to them, however, they may well feel less guilt and anxiety.

The paper does not report how many women were excluded because of obstetric causes for premature labour, nor what the causes were. It is not easy, however, to distinguish the group of women with idiopathic preterm labour. Rigorous definition of this group would require extensive investigation—for example, to exclude uterine abnormality. Another important question in

an investigation where the two extreme groups only differed by four weeks' gestation is how was gestation assessed and confirmed? How many women were excluded because of induction or communication problems to give an improbable incidence of 37% for all premature labours?

We heartily agree with the authors that antenatal care often leaves much to be desired in relation to the psychosocial needs of pregnant women, but we doubt whether it is easy in reality to provide "financial and emotional support" for women in need.

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Reproductive mortality

SIR,—It is not often that one finds an arresting new thought in a medical journal nowadays. When the idea is also simple and could lead to a better understanding of the health of a lot of people, the author deserves congratulation. Dr Valerie Beral's contribution to the interpretation of mortality data of young women does all that in her new index of reproductive mortality (15 September, p 632). By combining maternal mortality including that from abortion and deaths associated with contraception Dr Beral is aiming at a measure of several events surrounding reproduction using a firm outcome—death. It is a similar concept to that of perinatal mortality which takes all stillbirths and the neonatal deaths of the first week as a measure of obstetrical events. That index had its doubters in the early days for it was a mixture of divergently derived data but it has survived to be a useful basis of more refined analyses and standardisation. Some parts of the new index of reproductive mortality will be easier to collect than others and information may be less complete on deaths associated with contraception but this new idea deserves to be tried widely to assess its usefulness and correlation with other measures of health.

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Abnormal smears in pregnancy

SIR,—Dr J Elizabeth MacGregor's letter (20 October, p 1002) augments the conservative attitude to the pregnant patient with an abnormal cervical smear encouraged by your leading article (29 September, p 753).

To reduce the number of cone biopsies performed on pregnant patients it is reasonable to delay treatment until the postnatal period of those cervixes with cytological abnormality but normal appearance. I differ in the opinion that colposcopy should be deferred until the postnatal period, for who would be considered better qualified to judge whether a cervix appears non-malignant or otherwise than the experienced colposcopist?

Dr MacGregor is right to propose that cervical smears should be taken antenatally and any practitioner who has witnessed the tragedy of invasive disease in pregnancy would find this difficult to dispute. She is better qualified to argue that cost-effectiveness of cytological screening than I, but the proposal that for

economy's sake only those patients epidemiologically at risk should be screened antenatally would be most difficult to implement effectively. The only way we may safely economise would be to exclude from antenatal screening those women with recent normal cervical cytology. Patients may have had smears taken at a variety of institutions and clinics, and in larger cities these are often reported from more than one laboratory. The general practitioner's records are the sole source of ready access to this information, so perhaps if the result of the patient's last cervical smear could be included in the antenatal referral by the conscientious family doctor we might then achieve some economy in eliminating unnecessary duplication.

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Pregnancy in patients presenting with hyperprolactinaemia

SIR,—We read with interest the paper by Dr M O Thorner and others (29 September, p 771), in which the role of prophylactic external irradiation of the pituitary was discussed. A preliminary report from our group was cited,¹ and since we have just published² our most recent figures we would like to draw attention to these.

We observed 41 pregnancies in 27 patients who initially had infertility and raised serum prolactin concentrations. Associated symptoms were secondary amenorrhoea (81%) and galactorrhoea (81%); 19 patients (70%) had radiological evidence of pituitary tumours.³ Our policy is to implant the pituitary with yttrium-90 rods where there is a definite pituitary tumour, and we have stated our selection criteria.⁴ So far, 15 patients have had 21 pregnancies after such interstitial irradiation; 14 patients have had 20 pregnancies without prior pituitary implantation or any other attempt to prevent tumour expansion. Tumour expansion, as shown by diminished visual acuity, visual field defects, severe headaches, diabetes insipidus, and radiological changes, occurred in three of the 14 patients who had not had pituitary implants, but in none who had been treated by interstitial irradiation. Two patients who became pregnant both before and after pituitary implantation suffered tumour expansion in their pregnancies before the yttrium implants, but not when pregnant after the operation. From our literature survey² we found an incidence of tumour expansion during pregnancy of about 20% in those patients with definite (but untreated) pituitary tumours, and that significant further expansion of the pituitary was unlikely where radiological examination had been normal before the pregnancy. We also gave details of how fertility was achieved, and we can confirm that in our experience bromocriptine does not lead to multiple pregnancy, and is not teratogenic. There was no morbidity, whether surgical or endocrine, in our treated series. It will be of great interest to hear the results of endocrine testing in the series of Dr Thorner and his colleagues when the major effect of the irradiation has had time—say five years—to appear.

Thus, in general, our findings are in agreement with those of Thorner *et al*: we

recommend prophylactic treatment of the pituitary only where there is definite radiological evidence of a tumour. The early identification of those patients at risk of tumour expansion, and their treatment, clearly requires further study.

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² Kelly, W F, *et al*, *British Journal of Obstetrics and Gynaecology*, 1979, **86**, 698.
³ Doyle, F H, and McLachlin, M, *Clinics in Endocrinology and Metabolism*, 1977, **6**, 53.
⁴ Kelly, W F, *et al*, *Quarterly Journal of Medicine*, 1978, **47**, 473.

Preventing postoperative thromboembolism

SIR,—Before answering the specific questions directed to our report (2 June, p 1447) by Professor V V Kakkar and other correspondents (14 July, p 127), we wish to make it clear that the present study was mounted to fill what we considered to be a gap in currently available studies. To our knowledge, no previous low-dose heparin study of a comparable patient population has employed as comprehensive a surveillance protocol for either deep venous thrombosis (DVT) or pulmonary embolism (PE), and in particular most have relied almost entirely on ¹²⁵I-fibrinogen leg screening, the sensitivity of which has recently been called into question.¹ It is for these reasons that we believe a cautiously worded interim report justified.

It is misleading to suggest that sublethal thromboembolic events are unimportant and thus unworthy of study. A DVT involving the axial system with or without PE is certainly important if it leads to therapeutic anticoagulation, prolongation of hospital stay, and the long-term risk of post-phlebotic symptoms. End-points such as these occur with sufficient frequency to justify an objective single-centre study.

The question of beta-effect in relation to trial size has been raised by Dr C R M Prentice and others (p 128). A major part of our conclusions however is based on alpha, confirming a reduced incidence of DVT in heparin-treated patients and locating the source of this difference as a reduction in calf vein thrombosis. Apart from the relatively low observed frequency of proximal segment thrombosis a further point at which the comment regarding beta could be relevant would be if only patients scoring 6/6 for PE were to be considered in isolation ignoring all lesser scores. As scoring criteria were stringent we believe that scores of 4/6 or greater are highly likely to represent PE (6/68 control patients). If heparin were capable of reducing the PE rate by 50% the probability of encountering PE in 9/95 heparin patients would be low ($P=0.0052$). Even if heparin were capable of reducing PE by 25% the probability of the findings in the heparin patients would be 0.054. While nearly a quarter of patients in both groups developed new postoperative perfusion defects, the majority were allotted low scores because of the difficulty in assigning "without doubt" validity to perfusion defects in the presence

of obstructive airways disease. That it is likely that at least a proportion of these patients did indeed suffer a PE is attested to by the high degree of correlation between the presence of phlebographic DVT and postoperative perfusion defects. The absence of even a trend towards reduction at this event-rate frequency after the entry of 200 patients is of concern. We do, however, intend to continue this study until a sufficient number of patients has been entered to place the results beyond reasonable doubt.

In his letter Professor Kakkar points out that a number of patients in our study developed post-operative perfusion defects in the absence of phlebographically demonstrable DVT. This is in accordance with the findings of Knight and Metrewelli.² Emboli may originate from the pelvic veins or from discrete iliofemoral thrombi that have already embolised by the time the phlebogram is performed. This merely serves to highlight the importance of combining adequate PE and DVT surveillance in studies of prophylactic agents.

In the light of Professor Kakkar's criticism of our technique of diagnosing PE we find it surprising that he quotes the study of Buttermann *et al*³ as confirming that low-dose heparin reduces the incidence of non-fatal PE. We wish to correct his statement that this latter study utilised combined ventilation-perfusion scanning. Not only was perfusion lung scanning used alone, but this was only done postoperatively and was only performed in ¹²⁵I-fibrinogen-positive patients. In addition this study was not adequately randomised.

Few would deny that the major goal of prophylaxis lies in the prevention of fatal postoperative PE. The dilemma lies in the daunting logistics of proving this beyond doubt. Pulmonary embolus mortality probably varies worldwide and from centre to centre. Of the small proportion of patients who do succumb to this event, an appreciable number will be patients with a terminal illness. Thus fatal PE in patients who would otherwise recover is a rare event and it is precisely for this reason that many surgeons have questioned the benefit-to-risk ratio of applying a prophylactic regimen, with a small but unquestioned risk of bleeding complications to all their patients over the age of 40.

Like Dr Prentice and his colleagues we would welcome a definitive and independently confirmed multicentre study if this were possible. Until such time, we believe that objective studies of sublethal thromboembolic events have a part to play in furthering our understanding of the efficacy of prophylactic regimens.

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- ¹ Sautter, R D, *et al*, *Archives of Internal Medicine*, 1979, **139**, 148.
² Knight, M T N, and Metrewelli, C, *British Journal of Surgery*, 1977, **64**, 712.
³ Buttermann, G, *et al*, *Medizinische Klinik*, 1977, **72**, 1624.

Hyperprolactinaemia and cardiac disorders

SIR,—We were interested in the paper by Dr J Cohen and others (29 September, p 678) reporting two cases of life-threatening arrhythmias occurring during treatment with intravenous cimetidine. The authors have also seen two patients with prolactinomas and unexplained arrhythmia, and speculate on the possibility that hyperprolactinaemia might be involved in the pathogenesis of cimetidine-associated arrhythmias.

We have recently described a woman with long-standing prolactinoma who presented with unexplained cardiomegaly and heart failure, and eventually died suddenly.¹ A preliminary survey of 35 prolactinoma patients showed five with raised blood pressure and four (two of whom were normotensive) with cardiomegaly. We also speculated on the possible pathogenetic role of prolactin hypersecretion in cardiac disorders associated with pituitary tumours, but our data suggest that long-standing hyperprolactinaemia is required for any possible effect of the hormone on the heart to be manifested.¹

Sudden death has been reported in some patients chronically treated with phenothiazines,² drugs known to stimulate prolactin secretion. Several actions of prolactin on the heart have been described in animals. The hormone induces changes in rhythm and amplitude of cardiac contraction, and it has been suggested that stress-induced hyperprolactinaemia might contribute to cardiac arrhythmias during myocardial infarction³ or, alternatively, dampen the tachycardia-inducing effect of isoprenaline in experimentally-induced myocardial infarction in the rat.⁴ Although the possibility that drug-related hyperprolactinaemia of short duration may precipitate cardiac arrhythmias is far from established, further study is obviously needed on the cardiovascular effects of prolactin overproduction.

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² Leestma, J E, and Koenig, K L, *Archives of General Psychiatry*, 1968, **18**, 137.
³ Horrobin, D F, *et al*, in *Progress in Prolactin Physiology and Pathology*, ed C Robyn and M Harter, p 189. Amsterdam, Elsevier, 1978.
⁴ Lewis, B K, and Wexler, B C, *Proceedings of the Society for Experimental Biology and Medicine*, 1975, **150**, 712.

Vasodilators in senile dementia

SIR,—I would like to comment on your leading article (1 September, p 511) and certain letters in response to the editorial (6 October, p 866), in which a literature review of mine was quoted.¹

I am in complete agreement with your basic stance that "cerebral activators" are backed by more positive clinical studies than are "vasodilators." I would disagree, however, with your strong contrast between dihydroergotoxine mesylate (Hydergine) and naftidrofuryl (Praxilene, Nafronyl). The use of both of these compounds is supported by large numbers of positive double-blind clinical studies and neither seems to have serious side effects at recommended doses. It seems as though the side effects of ergotamine have been confused with those of dihydroergotoxine.

I do also share your concern for the "practical" impact of such compounds. Certainly they do not work miracles; nevertheless, they do seem to have some effect. In the attempt to increase the practical effects of such medications we have been concerned with finding the proper dosage for the individual, selecting drug-responsive patients, and combining these medications with psychotherapies aimed at improving cognitive function.² It is hoped that the application of some of the standard techniques of general