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.

W F KELLY

University Hospital of South
Manchester,
West Didsbury, Manchester 20 8LR

G F JOPLIN
F H DOYLE
K MASHITER
L M BANKS

Departments of Medicine and
Radiology,
Hammersmith Hospital,
London W12 0HS

H GORDON

Department of Obstetrics and
Gynaecology,
Northwick Park Hospital,
Harrow, Middx HA1 3UJ

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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.

E J IMMELMAN
P JEFFERY
S R BENATAR

Groote Schuur Hospital Thromboembolus Study Group,
Groote Schuur Hospital, Cape Town

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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.

GUGLIELMO CURTARELLI
CARLO FERRARI

Second Department of Medicine,
Fatebenefratelli Hospital,
Milan 20121, Italy

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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