to medical schools should include measures to detect vulnerability, and the curriculum should embody programmes which will help the student to cope with later professional stresses. Faculty advisors, tutors, and organised peer groups should be aware of their duty to recognise and intervene at an early stage rather than to wait for the GMC to take action when problems may be ineradicably established.

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¹ Sakinofsky I. Suicide in doctors and wives of doctors. *Can Fam Physician* 1980;26:837-47.

² Office of Population Censuses and Surveys, England and Wales.

Beta-blockers in the treatment of myocardial infarction

SIR,—Professor Geoffrey Rose in his letter (19 April, p 1099) rightly drew attention to the need to give confidence limits in “negative” trials such as that recently reported with beta-blockers in the secondary prevention of myocardial infarction (29 March, p 885), and Dr N S Baber and Mr J A Lewis (5 July, p 59) have performed a useful service in drawing further attention to this point. They would have done better, however, to have quoted the references and omitted the names of the beta-blockers, since no comparative conclusions can possibly be drawn from the data. Their illustrative examples tend to confuse rather than clarify the situation; since their list is incomplete, it mixes studies of entirely different design and duration, and the results given arise from different types of analysis.

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* * * The omission of the full reference list from the letter by Dr Baber and Mr Lewis was an editorial suggestion, made regretfully to save space. The authors do, however, say in their letter that the references will be supplied on request.—ED, *BMJ*.

Hypertensive response to labetalol in phaeochromocytoma

SIR,—Dr G Reach and others (31 May, p 1300), reporting the effects of labetalol in three patients with phaeochromocytoma, conclude that the drug “could be useful in the preoperative management of patients with phaeochromocytoma provided the blood pressure was carefully monitored.” Careful blood pressure recording is required since a paradoxical rise in blood pressure has been described in two patients with phaeochromocytoma following the oral administration of labetalol.^{1,2} We have learnt caution with this drug by experiencing a similar case.

A 46-year-old man, who was admitted (day 1) with a supine blood pressure of 150/100 mm Hg rising to 260/150 mm Hg on standing, was shown preoperatively to have a phaeochromocytoma (24-h urinary conjugated metanephrine excretion 130 μ mol; normal < 3 μ mol) that was subsequently confirmed at laparotomy. Supine blood pressure readings over the first four days of admission ranged from 110/70 mm Hg to 150/100 mm Hg with the exception of an isolated reading of 220/140 mm Hg. Oral labetalol was commenced on day 5 in a dose of 200 mg 8 hourly (600 mg daily) resulting in sustained hypertension

(210/150 mm Hg), which was not abolished by increasing the dose of labetalol to 400 mg 8 hourly (1200 mg daily) on day 6 (280/160 mm Hg). Satisfactory blood pressure control was achieved by withdrawal of labetalol and the oral administration of phenoxybenzamine 10 mg 6 hourly (40 mg daily) from day 7 onwards (110/80 mm Hg). In addition propranolol was commenced from day 9 with no adverse effect on blood pressure control (120/80 mm Hg).

Hypertension in phaeochromocytoma may be aggravated by the administration of a β -adrenoreceptor blocker before adequate α -adrenoreceptor blockade is established.³ While labetalol has both α - and β -adrenoreceptor blocking actions it has predominantly β -adrenoreceptor blocking activity.⁴ Thus the administration of this drug may provoke a paradoxical rise in blood pressure in patients with phaeochromocytoma, particularly if the tumour is secreting adrenaline as its predominant catecholamine.¹ Labetalol should therefore be used with caution in patients with phaeochromocytoma and may have no advantage over conventional preparations with α -adrenoreceptor blockade followed by additional β -adrenoreceptor blockade.

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¹ Rosei EA, Brown JJ, Lever AF, et al. *Br J Clin Pharmacol (Suppl)* 1976;3:809-15.

² Briggs RSJ, Birtwell AJ, Pohl JEF. *Lancet* 1978;i:1045-6.

³ Ross EJ, Prichard BNC, Kaufman L, Robertson AIG, Harris BJ. *Br Med J* 1967;i:191-8.

⁴ Brittain RJ, Levey GP. *Br J Clin Pharmacol (Suppl)* 1976;3:681-94.

Asthma and enkephalin

SIR,—Dr R D G Leslie and others (5 January, p 16) reported five patients with asthma induced by chlorpropamide alcohol (CPA). This was partially blocked in one patient by a high dose of naloxone but in another there was no definite effect. In the former patient the enkephalin analogue DAMME (250 μ g) produced tightness of the chest, breathlessness, and a fall in forced expiratory volume in one second (FEV₁), which had largely resolved by 20 minutes. They did not attempt to block this effect with naloxone. The one asthmatic patient tested experienced no change in FEV₁ with CPA or DAMME. They concluded that CPA asthma is mediated by enkephalins.

We have studied minute ventilation, FEV₁, and forced vital capacity (FVC) in six normal (non-asthmatic) subjects infused with 250 μ g of DAMME. No change in FEV₁ or FVC was recorded in any subject. In one subject hyperventilation occurred in association with a feeling of oppression in the chest, breathlessness, and anxiety (fig). Hyperventilation may precipitate an asthmatic attack¹ and it is possible that DAMME-induced hyperventilation may be responsible for the fall in FEV₁ in the asthmatic patient of Dr Leslie and his colleagues. Enkephalin-induced asthma may therefore be no more than a non-specific consequence of anxiety and hyperventilation.

A feeling of oppression in the chest lasting 20-30 minutes in about 20% of subjects given DAMME 250 μ g has previously been reported.^{2,3} The facial flushing, analgesia, and hormonal effects which occur in nearly all subjects last about two hours. The time course of the fall in FEV₁ in the asthmatic patient reported therefore approximates better

Hyperventilation in a normal subject given the enkephalin analogue DAMME.

Conversion: SI to traditional units PACO₂:—1 kPa=7.5 mm Hg.

to that of the feeling of chest oppression, anxiety, and hyperventilation. The case for CPA-induced asthma mediated by enkephalin-like substances is thus not proved. Nevertheless care should be exercised in giving DAMME to asthmatic subjects; but our initial results suggest that it is safe in normal subjects.

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¹ McFadden ER, Ingram RH. *N Engl J Med* 1979;301:763-9.

² Krebs E, Roubicek J. *Pharmacopsychiat* 1979;12:86-93.

³ Graffenried B, Dol Pozo E, Roubicek J, et al. *Nature* 1978;272:729-30.

Effect of plasma exchange in rhesus immunisation

SIR,—Regarding the article by Mr G R Barclay and others (28 June, p 1569) on the apparent adverse effect of plasma exchange on anti-D production in rhesus immunisation, we do feel that their conclusions are unduly pessimistic. We have treated 18 similar cases with a 64% success rate (report on 14 in press).

It has been shown in animal experiments by Branda and his co-workers¹ that plasma exchange following secondary immunisation results in a permanent lowering of the antibody level. However, in a recently published article Branda² now states that when antigen is continuously present only a temporary lowering of antibody can be achieved, with a prompt return to high levels. This finding is significant with regard to the case in question.

The circumstances outlined by Mr Barclay and colleagues would strongly suggest that their patient was being regularly subjected to the Rh antigen and therefore the immunological response was “switched on.” The Rh-positive antigen could well have got into the mother’s circulation in the replacement plasma, as a result of the amniocentesis, or during intra-uterine transfusion.

From our experience stillbirths are particularly likely to occur as a direct result of restimulation by Rh-positive antigen early in the pregnancy. Once this has occurred the rate of anti-D production can exceed the rate at which it can be removed and even intrauterine transfusion in these circumstances does not prevent the intrauterine death. For this reason we recommend that amniocentesis is delayed until at least 28 weeks' gestation, particularly for the first amniocentesis, and that any other manipulative or invasive procedure is avoided. If secondary stimulation can be avoided in the Rh-alloimmunised pregnant woman, the chances of a successful outcome using intensive plasma exchange can be high, even when there is a history of stillbirth.

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¹ Branda RF, Moldow CF, McCulloch JJ, Jacob HS. *Transfusion* 1975;15:570-6.

² Branda RF. *Plasma Therapy* 1979;1:43-8.

Quality of prescribing for children

SIR,—Dr J C Catford in his paper on quality of prescribing for children (14 June, p 1435) argues that improvements in pharmacy practice are necessary. Most pharmacists would agree that what is really required is an improvement in prescriber-pharmacist relationships.

My suspicion, based on anecdotal evidence, is that many pharmacists would be rebuffed by the prescriber when offering the views expressed by Dr Catford. Until prescribers recognise the contribution which pharmacists can make to improving patient care and help to establish a relationship in which information can be exchanged prescriptions for hazardous and undesirable drugs will from time to time be dispensed.

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Pelvic inflammatory disease and intrauterine contraception

SIR,—The paper by Margaret Booth and others (12 July, p 114) does nothing to increase our knowledge of the hazards (if any) of intrauterine contraceptive devices in relation to salpingitis. In the first place, the diagnosis of pelvic inflammation in their cases was made on clinical criteria (pain and tenderness), which are even less reliable in users of intrauterine contraceptive devices than in other women.

The paper appeared to show that nulliparous women attending the Margaret Pyke centre for contraception became less likely to acquire salpingitis as they got older. Most venereal disease clinics would endorse this probability. The paper also showed that symptoms diagnosed as pelvic inflammation became less frequent with the passage of time after fitting, which suggests that in many cases they were caused directly by the device and not by infection.

It has been shown repeatedly that in any population in which venereal disease is common there will be an increased incidence of pelvic infection in users of intrauterine contraceptive devices. On the other hand, my personal experience of parous married women

in a hospital clinic using a variety of plastic devices failed to show any significant evidence of pelvic inflammatory disease and I believe that in the absence of venereal disease it is rare for an intrauterine contraceptive device to cause salpingitis. If there is indeed evidence to the contrary it would surely be necessary to discover whether such infection were introduced at fitting or facilitated by the thread in the cervical canal. Appropriate steps could then be taken towards its avoidance rather than suggesting that young nulliparous women should have "careful counselling."

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¹ Mills WG. Further experience with intra-uterine contraceptive devices. *Lancet* 1970;ii:921.

Lipids and vegetarians

SIR,—The data of Dr J S Gear and others (14 June, p 1415) confirm that a vegetarian diet can produce a significant decrease in total blood cholesterol. This decrease primarily involves LDL-cholesterol and does not result in a substantial decrease in HDL-cholesterol. This fact could explain the low rate of ischaemic heart disease observed in such people.

A vegetarian diet is not always, however, synonymous with a low-lipid diet in that eggs and dairy products are often included. Eating two eggs and a pint of milk daily is equal to the ingestion of approximately 500 mg of cholesterol. This is in contrast to an average steak (200 g) containing about 200 mg of cholesterol.

It would be more interesting if the authors gave more details about the dietary habits of the studied subjects and specifically about the blood lipid values and the egg and dairy intake of the vegetarians subjects. There is still a lack of information about the actual value of various vegetarian diets and how they may affect the development of atherosclerosis.

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* * We sent a copy of this letter to the authors, whose reply appears below.—ED, *BMJ*.

SIR,—The diets have not, in fact, been analysed for cholesterol content. This would certainly be worth doing, and we hope to get it done. I would certainly agree with Dr Mannarino's last sentence, and we have started a major prospective study hopefully aimed at answering this question. The blood lipid values of the vegetarians were in fact given in our short report.

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Controlling the spread of acinetobacter infection

SIR,—The outbreak of multiply-resistant acinetobacter infection described by Drs Mary Anne L Burrow and Penelope J Redding (14 June, p 1451), which included two patients with positive blood cultures (presumably not

skin contaminants?), highlights the need for a clearer understanding of the epidemiology of this opportunist Gram-negative species in order to answer the important question "How can we best prevent its spread throughout the hospital?"

Our own findings in an outbreak of antibiotic-resistant *Acinetobacter calcoaceticus* var *anitratus* among 40 patients in six wards of St Thomas's Hospital will be described fully elsewhere,¹ but our investigations do suggest that these outbreaks can be controlled by strict handwashing. The epidemic strain, sensitive only to amikacin and tobramycin, was isolated from the hands of 11 (29%) of 38 staff examined on affected wards, but from none of 38 staff on other wards. The two microbiologists investigating the outbreak also became inadvertent carriers. Affected patients often developed skin, but not bowel, carriage; and we were able to demonstrate the experimental transmission of the epidemic strain from patients to the hands of staff. After the implementation of strict handwashing with chlorhexidine skin cleanser after any contact with affected patients the outbreak came to a close. Although the organism was isolated from a few environmental sites, attention to environmental hygiene failed obviously to alter the course of the outbreak.

Our results suggest that, as with *Klebsiella* species,^{2,3} colonisation of patients' skin and transmission via the hands of staff are of greater importance than the environmental contamination stressed in some other reports.⁴⁻⁷

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¹ French GL, Casewell MW, Roncoroni AJ, et al. *J Hosp Infect* 1980 (in press).

² Casewell MW, Phillips I. *Br Med J* 1977;iii:1315-7.

³ Casewell MW, Dalton MT, Webster M, et al. *Lancet* 1977;iii:1315-7.

⁴ Ramphal R, Kluge RM. *Am J Med Sci* 1979;277:57-66.

⁵ Abrutyn E, Goodhart GL, Roos K, et al. *Am J Epidemiol* 1978;107:328-35.

⁶ Castle M, Tenney JH, Weinstein MP, et al. *Heart and Lung* 1978;7:641-4.

⁷ Lowes JA, Smith J, Tabaqchali, et al. *Br Med J* 1980;280:722.

Emphysema: beginning of an understanding

SIR,—I was interested to read your leading article on emphysema (5 April, p 961), which rightly draws attention to the relationship between tobacco smoke and emphysema. It seems established that there is an increased release of elastase from human alveolar macrophages in smokers and that the condition can be produced in animals by intratracheal instillation of papain, elastase, or leucocyte homogenates—"all of which seem to act by degradation of pulmonary elastic tissue, an action inhibited by α_1 -antitrypsin."¹

No mention is made, however, of the extensive animal studies showing that emphysema results from the inhalation of nitrous fumes²⁻⁴ or of the high concentration of oxides of nitrogen in tobacco smoke.^{5,6} It would certainly seem probable that it is the nitrous fume component of tobacco smoke that is responsible for the "beginning" or start of the changes in the alveolar macrophages and the degradation of pulmonary elastic tissue. In fact, the Hunter Committee's second report acknowledges that oxides of nitrogen con-