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.

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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-

tribute to the overall pathological changes induced by smoke in the lung parenchyma leading to emphysema. Drs M J Jarvis and M A H Russell (also 5 April, p 994) comment on the Hunter Committee's second report and rightly plead for advice on control and regulation of all harmful constituents of tobacco smoke. They specifically mention that current cigarette brands have an eightfold variation in delivery of oxides of nitrogen. Surely the industry should be paying as much attention to reducing these fume levels as to reducing tar yields?

The statement that "while emphysema occurs in non-smokers it is usually mild, almost never being of clinical importance" may be true of some communities, but does certainly not apply to foundry workers or coalminers. The incidence of postmortem emphysema in coalminers is much higher than in non-miners,^{7, 8} and there is good evidence that this occurs as the result of the high nitrous fume content of mine air.⁹

Coalminers who smoke and live in polluted urban areas may be exposed to nitrous fumes from three sources and are at special risk. In recent years the Clean Air Act and improved ventilation in mines with less shotfiring have reduced two sources of nitrous fume. However, there are still many miners with a clear history of excessive exposure to fumes who are severely disabled with emphysema yet have difficulty in getting certified as suffering from poisoning by nitrous fumes (prescribed disease No 17) in its currently prescribed form. Ten years ago I advocated in your columns a review and suitable amendment of the prescription of this disease.¹⁰ It is hoped that the Department of Health and Social Security may now do this in the light of the further evidence which has accrued.

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- ⁷ Ryder R, Lyons JP, Campbell H, Gough J. *Br Med J* 1970;iii:481-7.
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- ¹⁰ Kennedy MCS. *Br Med J* 1970;iv:805.

Recurrent abdominal pain in childhood

SIR,—In his letter concerning recurrent abdominal pain in childhood (7 June, p 1377), Professor J S McCormick comments on the lack of objective markers in the closely related disorders of abdominal migraine, periodic syndrome, and cyclical vomiting.

Russell¹ studied a number of these children and found that some had decreased ornithine carbamyl transferase activity. This enzyme catalyses the second of the five steps of the urea cycle. Its complete absence would be incompatible with life. A number of children with very low enzyme activity (about 5% of normal) have also been described, generally presenting in the first few months of life with episodic vomiting, psychomotor retardation, and hyperammonaemia. The identical twin of one such infant was well until the age of 9,

with normal growth and development, when she presented with headache, malaise, and lethargy. The child had mildly elevated fasting blood ammonia levels and a prolonged rise of blood ammonia following protein ingestion or an ammonia load. Her mother and mother's sister, who also had an infant with hyperammonaemia, had high fasting blood ammonia levels and disliked protein-rich food.^{2, 3} Similarly, Levin *et al*⁴ described the mother of a child with hyperammonaemia who had an ornithine carbamyl transferase activity only 50% of normal. Ingestion of protein foods induced nausea and vomiting. Her fasting blood ammonia levels were again elevated with an abnormal rise after a protein load. She was otherwise mentally and physically normal.

Liver biopsy is obviously best avoided in children. Fasting blood ammonia levels, response to a protein load, and urinary glutamine excretion may provide diagnostic clues. Reduced ornithine carbamyl transferase activity has also been found in some patients on biopsy of the jejunal mucosa.³ As the enzyme deficiency is only partial, blood urea levels are, unfortunately, normal and not decreased.

Despite Russell's findings, I am unaware of further similar studies in children with abdominal migraine or cyclical vomiting. Similar studies do not appear to have been undertaken on those young adults with the "irritable bowel syndrome" in whom abdominal pain is prominent and many of whom have a history extending back to childhood or adolescence.

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- ¹ Russell A. In: Allen JD, Holt KS, Ireland JT, Pollitt RJ, eds. *Enzymopenic anaemias, lysosomes and other disorders*. London: E and S Livingstone, 1969:134.
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- ⁴ Levin B, Abraham JM, Oberholzer VG, Burgess EA. *Arch Dis Child* 1969;44:152-61.

The liver and halothane—again

SIR,—Your correspondent Dr M E Sinclair rightly points out (28 June, p 1617) that during and after anaesthesia with enflurane less than 3% of the agent is metabolised in the body. He suggests that its breakdown to form potentially toxic fluoride might be induced by other drugs and by previous exposure to the anaesthetic itself. As evidence he cites a paper¹ in which the authors suggest that "enflurane may cause induction of hepatic microsomal enzymes." This work was carried out in six experimental subjects having very prolonged (9.5 MAC (minimum alveolar concentration) hours) anaesthetics, during which extensive investigatory procedures were undertaken. It has not, to my knowledge, been repeated or confirmed.

Your correspondent did not mention a recent prospective study² of the problem in 102 patients, some of whom had more than one exposure to enflurane, and who were submitted to a variety of surgical procedures and were under treatment with a variety of drugs, including phenobarbitone. No evidence of significant increases in serum inorganic fluoride levels due to enzyme induction was found after more than 2 MAC hours of enflurane anaesthesia. Serum inorganic fluoride

levels rose only to a mean level of 17 $\mu\text{mol/l}$ in six hours in this group.

The patient with "renal failure" mentioned by Dr Sinclair had oliguria on the second, third, and fourth days following a six-hour operation for the creation of an ileal loop bladder for bladder carcinoma under enflurane anaesthesia.³ A single high inorganic fluoride level was found in the second postoperative day's blood specimen; the third and subsequent day's blood fluoride levels were relatively low. The characteristic presentation of fluoride-induced disorder is a high-output polyuric syndrome, due to a tubular rather than a glomerular nephropathy. The exposure to enflurane during the preliminary cystoscopy and biopsy undertaken in this patient was presumably brief and occurred six weeks prior to the main anaesthetic. The suggestion that subsequent biodegradation of the anaesthetic was induced by this exposure is purely speculative. A prospective human study found no evidence that this occurs in practice following repeated exposure after one week.⁴ It is not unknown for transient periods of oliguria to occur postoperatively following abdominal surgery of the length and gravity discussed in Eichhorn's paper—particularly for a procedure involving the urinary tract and in a patient with heart disease, in whom fluid replacement on the operation day was understandably conservative. Retained fluoride was rapidly cleared when diuresis commenced; and this single case, in which rapid and full recovery occurred, can hardly be regarded as sufficient to merit Dr Sinclair's concern about repeated enflurane anaesthesia.

Although there is clinical evidence confirming that enflurane anaesthesia and the small increases in serum inorganic fluoride levels it usually produces are not harmful to patients with glomerular or tubular renal disease⁵ further confirmation from good prospective clinical studies is greatly needed. Until this work has been satisfactorily carried out, Abbott Laboratories Ltd will continue to recommend caution in the choice of this agent for anaesthesia for such cases.

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Graduated compression stockings

SIR,—It is with interest that we have read the articles on graduated compression stockings (22 March, p 818 and 820). These stockings have been available to us from an American source for two years now and while they have been advertised for use in deep venous insufficiency and are by implication useful in preventing limb ulcers, our main use has been in patients with postural hypotension.

The standard elastic stocking is seldom long enough and not specific in size for the individual patient. It is essential that some abdominal compression be applied to help with control of postural hypotension as well as in the legs. Venous pooling is prevented