placebo to the diet of 22 obese, poorly controlled diabetic outpatients. Over a three-month period, there was no significant reduction in body weight or of fasting or postprandial blood glucose concentration. The type of patient studied differed, as Jenkins *et al* had only two patients significantly above the desired body weight; but obese, poorly controlled patients would have been expected to benefit from any long-term effect of fibre additive. We would suggest that optimistic reports of the use of fibre supplementation in the therapy of diabetes mellitus should be confirmed by careful long-term studies.

M COHEN
F I R MARTIN

Department of Endocrinology,
Royal Melbourne Hospital,
Melbourne, Australia

Conservation surgery for laryngeal cancer

SIR,—Although I fully agree with your leading article (11 November, p 1318) that early vocal cord tumours are best treated with radiotherapy, I disagree with your statement that with conservative surgery the cure rate for small supraglottic tumours (presumably T1 and early T2 N0 lesions) is higher than with radiotherapy. Regrettably, you have failed to mention one of the largest series of supraglottic cancer treated by irradiation. This is the series from the Fondation Curie in Paris. It is an unfortunate omission, since this is one of the most prestigious radiotherapy centres in the world, where treatment of laryngeal cancer was pioneered several decades ago. In its recent studies^{1,2} (its series is one of the largest in the world), which have been published in English, the absolute and determinate survivals at three years were 80% and 87% respectively for these early stages. The preservation of the voice was excellent in over 90% of the patients. It should be pointed out that conservative surgery can be performed only on a very select and favourable group of early cancers, whereas such a selection does not apply for patients referred to the radiotherapist. Furthermore, because of the high incidence of occult nodal metastases in supraglottic cancers, the neck nodes bilaterally have to be treated electively with radiotherapy, even if conservative surgery has been performed.^{3,4}

You have quoted the results from centres in New York, Texas, St Louis, etc, but not from Paris, which is a stone's throw from London—or is it? I hope that you will be able to correct this unfortunate omission in your editorial.

N A GHOSSEIN

Department of Radiology,
Albert Einstein College of Medicine,
New York

¹ Bataini, J P, *et al*, *Cancer*, 1974, **33**, 1253.

² Ghossein, N A, *et al*, *Radiology*, 1974, **112**, 187.

³ Agazzi, C, *Matinées Carcinologiques ORL de l'Institut Gustave Roussy*, 1-5, October 1970.

⁴ Leroux-Robert, J, *Annals of Otolaryngology*, 1965, **82**, 305.

Typhoid fever

SIR,—Your leading article on typhoid fever (27 January, p 213) comments on isolation of *Salmonella typhi* from the blood stream for up to 10 days after the start of treatment and that there is no apparent explanation for this. In fact, the presence of *S typhi* in blood clot

of patients on treatment with chloramphenicol can be demonstrated much later than this. We have seen it in patients after 17 days' treatment and it is probable that such isolation may be obtained at any stage of illness in spite of therapy.¹

The reason almost certainly relates to the intracellular location of the organism in reticuloendothelial cells and to their ability to survive there and reinvade the blood stream periodically. We have shown that such intravascular shedding occurs in typhoid carriers and indeed may be the only manifestation of the carrier state.² Such isolations may also be made from patients with no previous history of clinical typhoid fever.² Both in this group and in patients with clinical relapse during the acute disease release of intracellular organisms will result in positive blood cultures. In the latter group sufficient organisms are released to provoke clinical signs and symptoms. The nature of the host-parasite relationship in typhoid fever is such that phagocytic uptake and release of organisms probably occurs continuously during the acute disease. Blood sampling will then detect those organisms that have just recently been released and which have not yet been destroyed or inhibited by antibiotic. Once removed by antibiotic or by antibody and complement mechanisms they are replaced from the reticuloendothelial sites. It has also been shown that both penicillin and streptomycin are capable of stimulating phagocytic uptake of bacteria⁴ and it is possible that antibiotic treatment may increase the potential reservoir of organisms in reticuloendothelial sites capable of reinvading the blood stream.

K C WATSON

Central Microbiological Laboratories,
Western General Hospital,
Edinburgh

¹ Watson, K C, *American Journal of Tropical Medicine and Hygiene*, 1957, **6**, 72.

² Watson, K C, *Lancet*, 1967, **2**, 332.

³ Linz, R, *Annales de l'Institut Pasteur*, 1953, **85**, 295.

Beta-blockers, blood sugar control, and renal function

SIR,—I was interested to read the paper from Dr A D Wright and his colleagues comparing metoprolol and propranolol in diabetics (20 January, p 159). I would agree that on their evidence there is no strong reason for choosing a cardioselective beta-blocker from the point of view of the minor differences in hyperglycaemia associated with their use. However, I think that they should have emphasised more the benefits of cardioselectivity in the recovery from insulin-induced hypoglycaemia, the evidence for which they review in their introduction.

My main purpose in writing is to confirm their observation of a greater deterioration in renal function during treatment with a non-selective compared with a cardioselective beta-blocking drug. We have recently completed a study comparing propranolol and atenolol in the treatment of 15 patients with essential hypertension in an open crossover trial. In doses producing equal reduction in blood pressure the creatinine clearance fell from 162 ± 9.4 (SE) l/24 h in the untreated state to 132 ± 8.5 l/24 h during propranolol treatment ($P < 0.01$), but only to 152 ± 13.9 l/24 h during atenolol treatment ($P = 0.05$). The reduction in function during propranolol

treatment was significantly greater than that during atenolol treatment ($P < 0.0125$). It is well known that non-selective beta-blocking drugs reduce creatinine clearance,¹⁻³ and it is of interest that there is now evidence that both of the most cardioselective drugs available cause less reduction in renal function. These differences in effect on renal function are, of course, of little importance in essential hypertension, but may be important in patients with renal disease.

R WILKINSON

Department of Medicine and Nephrology,
Freeman Hospital,
Newcastle upon Tyne

¹ Nayler, W G, *et al*, *American Heart Journal*, 1967, **73**, 207.

² Schirmeister, J, *et al*, *Arzneimittel Forschung*, 1966, **16**, 847.

³ Ibsen, H, and Sederberg-Olsen, P, *Clinical Science*, 1972, **44**, 129.

Mechanisms of sudden death

SIR,—Your leading article (23-30 December, p 1734) suggested that platelet embolism could be the precipitating factor for sudden death. I think this must be rarely so. Roberts has shown that, with few exceptions, neither sudden death nor myocardial infarction occur until two of the three main coronary arteries are narrowed by 75%.¹ It seems unlikely that platelet embolism would be delayed until this critical stage had been reached. Moreover, if platelet embolism were to blame, sudden death would occur more often during exertion or stress rather than at rest. An explanation more directly related to the degree of coronary narrowing is required.

Roberts argues that blood stasis from reduced perfusion is the initiating mechanism for ischaemia leading to heart attack. For ventricular fibrillation then to occur, the work of Lubbe *et al*² suggests that critical metabolic gradients must develop between well and poorly perfused myocardium. If fibrillation does not occur and ischaemia should persist, myocardial infarction could develop with or without thrombosis, depending on duration of survival.¹

The question now arises: what causes the reduced perfusion? Given the prerequisite of 75% coronary narrowing of two vessels, which are presumably rigid and virtually incapable of dilatation in response to demand, elementary principles of physics should apply. Quite small falls in blood pressure could reduce coronary perfusion critically and predispose to a heart attack if collateral circulation is stretched. It may be relevant that the following circumstances are associated with a poor prognosis: (a) when blood pressure falls as a result of exercise in patients with known ischaemic heart disease^{3,4}; (b) After recovery from myocardial infarction, if the blood pressure remains more than a few mm Hg lower than its preinfarction level^{5,6}; (c) When the blood pressure falls over the months or years following recovery from myocardial infarction.⁷

It may also be relevant that smokers have a lower blood pressure than non-smokers,⁸⁻¹⁰ which in the practolol trial persisted for about a year after giving up smoking.¹⁰ An increased mortality also persists for some time after giving up smoking. Finally, heart attacks often occur during sleep when oxygen requirements are minimal but when blood pressure is at its lowest.

Blood pressure reduction may, of course, be an expression of existing cardiac damage, as in the first three studies cited above.¹⁻³ But

the fact that death is usually due to acute arrhythmia rather than pump failure points to (fresh) ischaemia as the cause. Lowering of blood pressure may be the actual mechanism responsible for initiating this. However, increased blood viscosity and platelet adhesiveness could well raise the threshold of blood pressure which is operative.

K G GREEN

ICI Pharmaceuticals Division,
Macclesfield, Cheshire

- ¹ Roberts, W C, *Circulation*, 1974, **49**, 1.
- ² Lubbe, W F, *et al*, *Cardiovascular Research*, 1974, **8**, 478.
- ³ Irving, J B, *et al*, *American Journal of Cardiology*, 1976, **37**, 144.
- ⁴ Irving, J B, and Bruce, R A, *American Journal of Cardiology*, 1977, **39**, 849.
- ⁵ Kannel, W B, Sorlie, P, and Castelli, W P, *American Journal of Cardiology*, 1978, **41**, 407.
- ⁶ Kannel, W B, *et al*, *In press*.
- ⁷ Mulcahy, R, *et al*, *British Heart Journal*, 1975, **37**, 158.
- ⁸ Seltzer, C C, *American Heart Journal*, 1974, **87**, 558.
- ⁹ Royal College of Physicians, *Smoking or Health*. London, Pitman Medical, 1977.
- ¹⁰ Green, K G, *Principals and Problems of Controlled Clinical Trials in Cardiovascular Diseases*, ed J P Boissel and C R Klimt. Paris, INSERM.

Preventive genetic registers

SIR,—It was with great interest that I read the leading article (27 January, p 215) on registers for the prevention of genetic disease. You are clearly anxious that such a register should have an acceptable image, so that it will be widely used. I agree that such a register could be a valuable aid in reducing suffering associated with genetic disease, but feel that if suffering is to be genuinely reduced, rather than changed, certain questions must be taken into consideration.

You point out that discovering that one carries such a gene is distressing and that support should be available. The painful ramifications of discovering such a fact before or after one gets married, or of discovering, after one has had a handicapped child exactly which parent "caused" the disease are indeed distressing.

Not every carrier of genetic disease is destined to produce affected children, especially in a society where families are small; so a fair amount of this suffering would be needless, as also the suffering associated with having some healthy, and wanted, boy children aborted. I would like to think that the process suggested would not be initiated unless there was clear evidence that support was available to the person in question, or he or she had asked for it.

The other question concerns the freedom of the parents to decide whether or not to have a child, or an abortion. "There but for the grace of God go I" is not a phrase that comes easily to the mind of the common man. Already parents of handicapped children find themselves isolated from a rather critical society. This can only get worse if it becomes generally known that they could have found out and had the child aborted. It is one thing to worry about having to look after a handicapped child but quite another matter to discover that it is "me and him" against the rest of society, as so often happens. So people are being forced by social pressure to opt for sexing and abortion, while society leaves them to take the responsibility.

Finally, taking up the point that the frequency of these genes in the population would increase, I must ask what you mean by prevention. I thought that it had to do with the elimination of the cause of the disease, in this case a gene. Some responsible and intelligent

adults, faced with accurate information about their carrier status and appreciating the problems of carriers as well as affected children, will limit their families accordingly. Others, having had an affected child, feel little inclination to have more of the same. If nothing else were done, the gene frequency would decrease, and the small number of affected children born should be accepted by all as an inevitable, unalterable fact of life. What seems to be suggested here is that we solve our immediate problems regarding the care of children handicapped by hereditary disease by, quite literally, passing them on to our children.

T VAN DEN BERG

London N6

Severe hyponatraemia in hospital inpatients

SIR,—Dr P G E Kennedy and others (13 January, p 122), in replying to correspondence about their paper (4 November 1978, p 1251), criticise our letter of 9 December (p 1640). We gave three references¹⁻³ which cited evidence for water intoxication on the basis of appropriate biochemical tests. We feel it may be appropriate for us to quote from one of these references.³ "With euvoalaemia, hyponatraemia and hypertonic urine, inappropriate anti-diuretic hormone excess was diagnosed. The patient's fluids were restricted, but after 24 hours without improvement 5% saline and frusemide were given. This therapy resulted in dramatic improvement. Upon correction of the hyponatraemia the patient's electroencephalogram reverted to normal. Follow up one year later revealed a functional, active female with no neurological symptoms or signs." Dr Kennedy and his colleagues feel that management of this patient "may possibly have been a disadvantage." Clearly our objectives about patient management are different from theirs.

Kennedy *et al* in their paper of 4 November placed their diuretic-treated group of patients into the "depletional" group of hyponatraemia, but now in their letter of 13 January suggest that this may be "dilutional." They have no evidence to substantiate their placing this group of patients in either depletional or dilutional categories. They either disregard other mechanisms suggested (Dr C T G Flear *et al*, 9 December, p 1640) or do not consider other pathogenic mechanisms which may be involved.⁴

It has been suggested that serum sodium concentration is routinely measured in almost every hospital patient, being of value in only a minute proportion of these cases.⁵ It is not surprising therefore that hyponatraemia has been associated with a wide variety of clinical conditions. This is often difficult to interpret because in many instances it is multifactorial, and indeed the pathogenic mechanisms involved are not yet fully agreed on. We feel that this is often an epiphenomenon in otherwise ill patients. It is fortunate, however, that in many of these cases specific therapeutic intervention is rarely required. But when primary sodium and water disturbances do lead to encephalopathy then therapeutic measures may be undertaken only following appropriate biochemical tests on blood and urine.

From their selected group of hyponatraemic patients Kennedy *et al* still cannot justify their final conclusion that "Analysis of blood and

urine was of no value in distinguishing the different diagnostic groups in an emergency."

S JAVED IQBAL
P J OJWANG

Department of Biochemical Medicine,
Ninewells Hospital,
Dundee

- ¹ De Trayner, A, and Domenet, J C, *Quarterly Journal of Medicine*, 1976, **45**, 521.
- ² Ashton, G, *et al*, *British Medical Journal*, 1977, **1**, 1134.
- ³ Ruby, J R, and Burton, R, *Lancet*, 1977, **1**, 1212.
- ⁴ Ghose, R R, *British Medical Journal*, 1977, **2**, 1063.
- ⁵ Swales, J D, *Sodium Metabolism in Disease*. London, Lloyd-Luke, 1975.

Doctors, physiotherapists, and placebo pharmacology

SIR,—I appreciate the critical interest in my paper (23-30 December, p 1761). Some correspondents (3 February, p 341) wondered whether our seminar was very local and atypical of physiotherapists generally. The members came from all over London—all except two from different hospitals. I ask only the scientific status of travellers' tales for our findings, pending more careful and extensive explorations. We are convening another seminar with a different leader and recruits would be welcome. Inquiries should be sent to me please.

The paper was exceedingly condensed and meant chiefly to awaken doctors to the way they use physiotherapists. It would require a book to do justice to the subject and to the questions raised in letters. The book is written and awaits an imaginative publisher out to lose money.

S BOURNE

Tavistock Clinic,
London NW3

Cimetidine and duodenal ulcer

SIR,—We are appalled by the suggestion of Dr V W M Drury (10 February, p 410) that cimetidine should be used as a diagnostic rather than a therapeutic drug in the management of duodenal ulcer disease and symptomatic reflux oesophagitis. Many reports have shown that it is virtually impossible to diagnose accurately the cause of upper abdominal pain from the patient's history and physical signs, and cimetidine is not in any way a specific test, relieving as it does symptoms caused by duodenal ulcer, duodenitis, gastric ulcer, gastritis, and peptic oesophagitis. In addition, any form of treatment may have a placebo effect on abdominal pain, at least in the short term.

Much more dangerously, a number of cases have been reported¹⁻⁴ when carcinomatous or lymphomatous gastric ulceration has partially or totally healed endoscopically with complete symptomatic relief during cimetidine treatment, with consequent delay in appropriate surgical management. A patient whom we have recently seen serves to emphasise this point.

A 35-year-old man developed dyspeptic symptoms with epigastric pain as the principal complaint. Over 18 months he had three separate month-long courses of cimetidine with the first two providing complete symptomatic relief. He was investigated when the third course failed to relieve symptoms and was found to have a gastric lymphoma requiring extensive surgery and radiotherapy.

Unfortunately the course that Dr Drury has advocated is already being widely followed