include frequent visits to wards to discuss problems relating to individual patients. As you point out, few doctors have opportunity to work with pathologists during their undergraduate course and the preregistration year, and in consequence they are usually unaware of how satisfying and rewarding a career in pathology can be. You refer to a paper of mine which was unfortunately published in incomplete form.² These matters are discussed in a subsequent complete version.³

Finally, the nature of the pathologist's work allows of some flexibility in its performance. It is well suited to part-time training and consultant practice, and the part-timer can usually make arrangements which are compatible with other demands. For this reason, and also because of the relative availability of senior registrar and consultant posts, pathology has particular advantages for doctors whose working hours and mobility are restricted by domestic duties.

JOHN ANDERSON
President, Royal College
of Pathologists

London SW1Y 5AF

¹ Institute for Manpower Studies, *The Determinants of Doctors' Career Decisions*, 1979.

² Anderson, J R, *BMA News Review*, 1979, 5 (4), 26.

³ Anderson, J R, *BMA News Review*, 1979, 5 (6), 72.

Dangerous antihypertensive treatment

SIR,—I refer to your leading article (28 July, p 228), the report by Dr D H Cove and others (p 245), and the following case report.

In July 1978 a 24-year-old housewife was admitted as an emergency to the National Hospital of Iceland. She had sinus tachycardia of 120 beats/min, blood pressure of 300/200 mm Hg, haematuria, and blurred sight of the left eye, but no cardiac enlargement or focal neurological signs. Fundoscopy showed grade IV hypertensive retinopathy. She was twice given diazoxide 300 mg intravenously, with a one-hour interval, together with frusemide; after this the blood pressure fell by one-third only to rise again. Sodium nitroprusside infusion¹ was then commenced, the drip rate being adjusted according to the blood pressure. This was discontinued eight hours later, the blood pressure being 120/80 mm Hg, and from then she received atenolol 100 mg twice daily and diuretics. Ten hours later, when her blood pressure was 110/75 mm Hg and she had sinus bradycardia, she complained of total visual loss. On examination, she did not perceive light, her pupils were bilaterally dilated and unresponsive to light, and fundoscopy showed grade IV hypertensive retinopathy with a macular star.

Assuming that the cause of her blindness was imbalance between the perfusion pressure to her eyes and the intraocular pressure, I immediately commenced a 25% mannitol infusion, and she received 300 ml within 15 minutes in order to reduce the intraocular pressure and so restore the balance between the two pressures. Within 20 minutes the pupils began to react to light and the patient reported that she was seeing again.

Three hours later the patient again lost her sight, her blood pressure being 90/60 mm Hg, when the same treatment was unsuccessfully repeated together with intravenous dexamethasone. After 24 hours' duration of blindness, by the time her blood pressure was 180/130 mm Hg the patient again reported that she was perceiving light and she continued to improve from then on. The underlying cause for her hypertensive crisis was not found, and she has been well controlled on antihypertensive treatment. Visual acuity is 6/6 in each eye, the visual fields are full, and eight months later hypertensive retinopathy was no longer present.

I would like to suggest that in conditions like this lowering of the intraocular pressure

might be considered, with either mannitol or acetazolamide sodium intravenously.

Visual loss in temporal arteritis is considered to be associated with a fall in the perfusion pressure of the extraocular arteries with subsequent imbalance between this and the intraocular pressure.² In that particular disease there are reports suggesting that regaining sight after visual loss of more than 24 hours' duration is unusual.^{3 4}

FRIDBERT JONASSON

Eye Department,
Landakot Hospital,
Reykjavik, Iceland

¹ Cohn, J N, and Franciosa, J A, *New England Journal of Medicine*, 1977, 297, 27.

² Hayreh, S S, *British Journal of Ophthalmology*, 1974, 58, 955.

³ Cullen, J F, *British Journal of Ophthalmology*, 1967, 51, 513.

⁴ Jonasson, F, Cullen, J F, and Elton, R A, *Scottish Medical Journal*, 1979, 24, 111.

Renal artery stenosis and hypertension

SIR,—Reporting the development of renal artery stenosis in two hypertensive patients with previously normal renal angiograms, Dr Mattias Aurell (5 May, p 1180) suggested that "the vascular disease caused the hypertension." A similar sequence of events in a patient of ours has led us to the opposite conclusion.

The patient presented at the age of 54 with a short history of symptoms of uraemia and left ventricular failure. Her blood pressure was 260/140 and her fundi showed bilateral papilloedema with haemorrhages and exudates. Her blood urea was 66 mmol/l and creatinine clearance 1.3 ml/min. The kidneys were normal in size and shape radiologically, so a kidney biopsy was carried out and the histology showed hypertensive nephrosclerosis. Because of clinical features suggesting the possibility of a pheochromocytoma, bilateral selective renal angiography was done. There was no evidence of a pheochromocytoma and the major renal arteries were normal, but there was an intrarenal arteriovenous fistula at the site of biopsy in the left kidney.

During three years of haemodialysis and treatment with antihypertensive drugs her hypertension was never well controlled and her blood pressure ranged from 160/100 to 210/210. Since the iatrogenic arteriovenous fistula could have been contributing towards her hypertension we considered surgical treatment and a second renal angiogram was carried out. The fistula had disappeared and the kidney had shrunk to 10 cm in length, but there was now a tight stricture of the left main renal artery 1.5 cm from its origin with poststenotic dilatation. On the right there were multiple stenoses of the right main and intrarenal arteries.

This patient had radiologically normal main renal arteries at the time of her presentation with hypertension, as did one of Aurell's patients. We do not know the pathology of the stenosis she later developed, but it seems reasonable to postulate that her continuing hypertension may have been the cause. Although many patients have been cured of hypertension by correction of their renal artery stenosis, we wonder whether some of the surgical failures may have been because their hypertension was the cause rather than the consequence of their renal artery stenosis.

PAUL SHARPSTONE
ANTHONY TRAFFORD
RICHARD MCGONIGLE

Royal East Sussex County
Hospital,
Brighton BN2 5BE

Burning and the inadequate management of epilepsy

SIR,—Burning is a potentially fatal hazard faced often by the poorly controlled epileptic. We have been impressed—and depressed—by the poor quality of previous management of epilepsy in patients admitted to the regional burns unit in this infirmary. Admission is sought for patients with especially large burns, burns involving important areas such as hands or face, skin grafting, etc. We studied the management of 10 consecutive patients with epilepsy admitted to the burns unit and offer a brief summary of two cases together with comment on the others.

A 51-year-old man had a three-year history of tonic-clonic seizures following skull fracture. Despite taking phenytoin sodium regularly in a dose of 100 mg thrice daily control remained poor. During a seizure he sustained an extensive full-thickness burn to his right foot from an electric fire. The serum phenytoin sodium level of admission was 10 µmol/l (therapeutic range 40–80 µmol/l) and he required increase in dose to 700 mg daily to obtain control.

A 26-year-old man had an eight-year history of tonic-clonic seizures of idiopathic type. Despite taking, or claiming to take, phenobarbitone 60 mg thrice daily control remained poor but specialist help was not sought. During a seizure he sustained a full-thickness burn to his left leg. The serum phenobarbitone levels were below the therapeutic range of 40–120 µmol/l.

Of the eight other patients, one was untreated, two were on inappropriate therapy, one failed to take all doses of the prescribed anticonvulsant, two had inadequate doses of an appropriate anticonvulsant (judged by continuing seizures in the presence of low serum levels), and two were taking several anticonvulsants at inadequate doses. Of the ten patients, only one had been seen by a neurologist and two had been admitted to general medical wards to seek better control.

The risks of anticonvulsant therapy have become increasingly apparent.^{1 2} The lack of benefit and hazards which often result from therapy with several anticonvulsants have been brought to our attention.² We agree with a policy of seeking control on minimum effective therapy, and with the reluctance to use more than one anticonvulsant until all appropriate drugs have been tried alone in adequate doses. However, undertreatment, including inappropriate treatment, also carries risks, of which severe burning is an especially dramatic example.

At the risk of being thought patronising and pompous, we wish to remind our colleagues that optimal control of correctly diagnosed epilepsy depends on the selection of an appropriate anticonvulsant which is then given in adequate dose. Specialist advice should be sought for refractory cases; we would arbitrarily define as such the failure to respond to a single anticonvulsant.

W F DURWARD
M G HARRINGTON

Royal Infirmary,
Glasgow G4 0SF

¹ Richens, A, in *Drug Treatment of Epilepsy*, ed A Robin. London, Henry Kimpton, 1976.

² Reynolds, E H, *Lancet*, 1978, 2, 721.

Poisoning with chlormethiazole

SIR,—We were interested in the report by Dr R N Illingworth and others (13 October, p 902) of severe poisoning with chlormethiazole. All their patients had taken oral overdoses, and while the previously noted effect of this

drug on respiratory function¹ was prominent cardiac rhythm was unaffected. Chlormethiazole toxicity is not confined to excessive oral administration but has been reported after parenteral use¹ and recently we have seen two patients who had cardiac arrests during chlormethiazole infusion at the recommended dose.

Case 1—A 65-year-old man with a history of alcohol abuse was drinking heavily until one day before admission following a haematemesis. There was no clinical evidence of hepatic decompensation although serum enzymes were markedly elevated. Vital signs and concentrations of serum electrolytes and haemoglobin were satisfactory. Delirium tremens developed 24 hours after admission. When treatment with parenteral diazepam and chlorpromazine proved unsuccessful, satisfactory control of symptoms was achieved by chlormethiazole 0.8% infusion alone. Sixteen hours after the infusion was commenced he developed ventricular tachycardia, from which he was resuscitated and made an uneventful recovery.

Case 2—A 54-year-old man was admitted with severe facial bone fractures following an assault outside a bar. His clinical state was stable although biochemical studies revealed raised serum enzymes and low serum albumin. Soon after admission he became increasingly restless, parenteral diazepam and chlorpromazine again proving ineffectual. Intermittent infusions of chlormethiazole 0.8% controlled his symptoms but cardiac arrest followed a one-hour infusion of 100 ml, its only administration for 24 hours. Resuscitation was unsuccessful. The only other drug treatment was diazepam 10 mg in divided doses over the six hours before death. Necropsy revealed an insignificant pulmonary embolus and fatty hepatic degeneration consistent with chronic alcoholism.

These cases demonstrate that potentially lethal cardiac dysrhythmias may complicate chlormethiazole infusion at the manufacturer's recommended maintenance dose (333-1333 mg/h). At the times of cardiac arrest the infusion rates were 667 mg/h and 660 mg/h respectively. There was no evidence, prior to arrest, of the respiratory depression noted by Dr Illingworth and his colleagues and by others.¹

The extensive hepatic biotransformation of chlormethiazole² should be emphasised. Although neither of our patients nor those of Dr Illingworth and his colleagues had clinically overt liver dysfunction, hepatic enzyme activity might be expected to be abnormal in chronic alcoholics, as in our patients and in the six alcoholics in their series. Presumably as a result of age-related changes in hepatic clearance,² the terminal phase half-life of chlormethiazole is longer in the elderly² than in healthy young adults.³ Acute ingestion of alcohol, which accompanied the overdose in at least six of the subjects reported, might also be expected to inhibit the metabolism of drugs with high presystemic extraction, such as chlormethiazole, when they are taken orally.⁴ The likely influence of alcohol on chlormethiazole toxicity has previously been reported in animals⁵ and in man.¹ The plasma half-life in the patients described by Dr Illingworth and colleagues was rather longer than in previously reported cases,^{2,3} from which it may be inferred that the above factors were indeed relevant.

Chlormethiazole is a useful drug which may be employed successfully in the management of the acute symptoms of alcohol withdrawal when other drugs are less satisfactory, as in our cases. However, this report and other recent case studies^{1,6} emphasise that the drug should be administered with caution. Particular attention should be paid not only to the patient's respiratory function and age but also

to alcohol intake and hepatic and cardiac function when chlormethiazole is prescribed for oral or intravenous use.

G T MCINNES
R E YOUNG
B S AVERY

Department of Medicine,
Western Infirmary
Glasgow G11 6NT

¹ Pentikainen, P J, Valtanen, V V, and Miettinen, T A, *International Journal of Clinical Pharmacology*, 1976, **14**, 225.

² National, R L, et al, *European Journal of Clinical Pharmacology*, 1976, **10**, 407.

³ Moore, R G, et al, *European Journal of Clinical Pharmacology*, 1975, **8**, 353.

⁴ Bircher, J, and Zysset, T, paper presented to International Conference on Drug Absorption, Edinburgh, 1979.

⁵ Vapaatalo, H, and Karppanen, H, *Agents Act and Actions*, 1969, **1**, 43.

⁶ Horder, J M, *British Medical Journal*, 1978, **1**, 693.

SIR—In his discussion of severe poisoning with chlormethiazole (13 October, p 902) Dr R N Illingworth and others question its safety in elderly patients and in patients with chronic bronchitis.

Having acquired wide experience in the use of chlormethiazole, orally as a premedicant, intravenously for sedation during surgical procedures under local anaesthesia, and in combination with a variety of narcotics as a general anaesthetic for minor surgical procedures, I feel Dr Illingworth has overstated his case.

The patients who received oral premedication and intravenous sedation with chlormethiazole were invariably elderly with some degree of pulmonary dysfunction and at no time have I experienced any untoward respiratory complication. Even in combination with narcotics the degree of respiratory depression has never exceeded that expected from the narcotic alone. The conclusions drawn from Dr Illingworth's case histories should include: (1) caution should be employed whenever any pharmacological preparation is prescribed for the elderly; (2) the long-term prescription of large doses of chlormethiazole to outpatients is contrary to the manufacturer's advice; (3) despite massive overdosage with chlormethiazole all the patients survived.

R W MORRIS

Bridgend General Hospital,
Mid Glamorgan CF31 1JP

Neutropenia associated with metronidazole

SIR—It is not without astonishment that I read the letter by Drs M W McKendrick and A M Geddes (29 September, p 795) describing a patient who developed neutropenia while taking metronidazole. Since azathioprine was given simultaneously, it is highly questionable whether the warning against metronidazole in connection with neutropenia has a shred of evidence to support it. Azathioprine is well known as an agent capable of inducing neutropenia—alone. In this country a general warning is included in the annual prescriber's handbook, including all pharmaceutical products accepted by the Norwegian authorities, to the effect that haematological side effects (leucopenia, thrombocytopenia, and pancytopenia) are so important that regular monitoring must be carried out at least weekly during the first eight weeks of azathioprine treatment.

Metronidazole—or any other agent—given together with a drug which regularly may precipitate leucopenia cannot be incriminated

on the basis reported by Dr McKendrick and Dr Geddes. If you observe leucopenia in a patient who has received chloramphenicol and distilled water, would there be any reason to suspect the water to be the cause?

TOM BERGAN

Institute of Pharmacy,
University of Oslo,
Oslo 3

SIR—It was with interest that we read that a combination of metronidazole and azathioprine was found to cause neutropenia¹ (29 September, p 795). We believe that a combination of metronidazole and fluorouracil may also give rise to such an effect.

In a trial of adjuvant chemotherapy with fluorouracil in this department, patients with colorectal cancer have received 12 mg/kg fluorouracil intravenously after surgery and on the first two postoperative days followed by weekly fluorouracil at a dose of 15 mg/kg. An initial pilot study performed one year ago demonstrated no adverse side effects of this regimen in the 20 patients included. However, of the 12 patients admitted to the present trial four have developed a leucopenia with leucocyte counts of $1 \times 10^9/l$ or less. This has been caused by a reduction in neutrophils and was not observed earlier than eight days after commencement of therapy. The neutropenia lasted from one to three weeks. The time of onset led us to believe that the dose of fluorouracil at one week was responsible, but withdrawal of this dose has not eliminated the occurrence of neutropenia. The only difference in therapy between the two studies has been our recent use of metronidazole at a dose of 400 mg orally three times daily for three days before surgery and 500 mg intravenously three times daily for five days after surgery.

Reversible neutropenia has been reported following the use of metronidazole alone,² and McKendrick and Geddes¹ suggested that the neutropenia may be akin to that observed following treatment with levamisole because of their like chemical structures. However, we have not observed a greater incidence of neutropenia in patients who have received in addition to fluorouracil and metronidazole 150 mg of levamisole on the first three postoperative days. In addition, a combination of levamisole and fluorouracil (without metronidazole) has not, in our hands, been found to cause neutropenia.

The mechanism of the neutropenia remains obscure; however, our findings suggest that caution must be exercised in giving metronidazole with fluorouracil to postoperative patients.

R WINDLE
S MACPHERSON
P R F BELL

University Department of Surgery,
Leicester Royal Infirmary,
Leicester LE2 7LX

¹ McKendrick, M W, and Geddes, A M, *British Medical Journal*, 1979, **2**, 795.

² George, R H, *Prescribers' Journal*, 1979, **19**, 18.

Withdrawal of cyanocobalamin

SIR—Dr A H Goodspeed (3 November, p 1142) misses my point, which is that occasional patients with cyanide toxicity syndromes may be harmed by the use of cyanocobalamin, whether incidental or therapeutic (but erroneous).

The chance that a patient who has had a sensitivity reaction ("rare," according to the data sheet) or anaphylaxis ("exceptional") will not be equally sensitive to hydroxocor-