a journal. Shelley advises painting the axillae at bedtime with a 20% solution of aluminium chloride hexahydrate in absolute ethyl alcohol. The axilla is then occluded for the night with polyethylene (Saran wrap). I use polyethylene bags with the ends cut off. It is important that the axilla should be dry and the pH of the solution less than 1. In the morning the polyethylene is removed and the axilla washed.

I have treated five patients in whom all local treatment had failed, and four can control axillary sweating with monthly applications, having started treatment two to three times a week 10 months ago. Our pharmacist had difficulties because 20% of aluminium chloride hexahydrate will not dissolve in absolute alcohol and he uses a saturated solution, which is nearer 15%. The only drawback to the technique has been slight soreness of the axillary folds until the patient has mastered the method of painting only the sweating area. As Shelley states in his book, Try it, the patients like it.

I am grateful to the pharmacists at the Sheffield Royal Infirmary for their help in overcoming the difficulties of making the solution.

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¹ Shelley, W B, *Consultations in Dermatology II*, p 259. Philadelphia, London, and Toronto, Saunders, 1974.

Prescribe British

SIR,—Mr David Ennals, in a speech on 7 November in Norwich, has stated that attempts should be made to reduce the costs of drug prescriptions. This is obviously desirable. A further logical step would be for all doctors to use as far as possible only those drugs which are made in Britain by British pharmaceutical companies. This habit would have the dual advantages of reducing imports and promoting expansion of the British pharmaceutical industry.

I realise that in some clinical conditions this is impossible—for example, there is no British high-potency "loop" diuretic such as frusemide. However, in the antibiotic and beta-blocker groups of drugs there can be only a very few circumstances when imported compounds are essential.

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Addictive abuse of dipipanone

SIR,—The combination of dipipanone hydrochloride and cyclizine in tablet form (Diconal) is used by many doctors as an effective analgesic in terminal cases of carcinoma and other cases of severe chronic pain. However, dipipanone is an addictive synthetic narcotic drug (controlled under the Misuse of Drugs Act 1971 and subject to the prescribing and other regulations of this Act) which is now increasingly favoured and used by young narcotic addicts and other multiple drug abusers.¹ Most such addicts crush up the tablets and inject the drug, with all the consequent hazards of the intravenous injection of a preparation intended for oral use. It is uncertain why this drug has become so popular among young addicts, but it may well be a consequence of the pharmacy thefts which

have become a major source of illicit narcotic drugs in recent years.²

Any doctor approached by a young person whom he does not know, as a "temporary resident" or in other circumstances, with a request or demand for a prescription for Diconal may be well advised to consider seriously whether the real reason for such a request is simply in order to satisfy the patient's addiction. In 1975 more persons were convicted in this country of criminal offences involved with the drug dipipanone than with either heroin or cocaine.³

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¹ Bishop, B P, *et al*, *British Journal of Psychiatry*, 1976, **129**, 465.

² James, I P, *Medicine, Science and the Law*, 1973, **13**, 246.

³ Home Office, *1975 Statistics of Misuse of Drugs in the UK*. Press release, 1976.

Atenolol eye drops

SIR,—Atenolol, a new beta-adrenergic blocker without sympathomimetic or local anaesthetic effects, has been shown to reduce ocular tension in humans when given by mouth,^{1 2} as discussed in the *BMJ* recently.^{3 4}

The great advantages of administration as eye drops prompted us to conduct a double-blind controlled trial on eight healthy young volunteers; the volunteer study was conceived to establish reasonable and independent evidence that trials of atenolol eye drops on glaucoma patients would not be unethical. The experiment followed a crossover design whereby four subjects, chosen at random, received guttae atenolol 4% in the right eye on day 1 and guttae saline in the left eye, the treatments being crossed over on day 2. The remaining four subjects were given guttae saline in the right eye and guttae atenolol 4% in the left eye on day 1, with a crossover of treatments on day 2. On each experimental day drops were administered to volunteers immediately after a reference applanation tonometry at 0900. Tension was taken at 1030, 1230, and 1430. Observations on propranolol and practolol eye drops^{5 6} (as well as tablets by mouth^{2 7}) and a report of the efficacy of guttae pindolol⁸ gave grounds for optimism.

Ocular tension fell in the course of the day in both eyes relative to their 0900 reference pressures. The mean fall (based on readings at 1½, 3½, and 5½ h after the instillation of drops) was compared for atenolol and saline within volunteers by the Wilcoxon matched pairs signed ranks test applied to the pooled data from days 1 and 2. Seven of the eight differences in mean fall in pressure were non-zero; of these, only the smallest absolute difference showed that one subject benefited more from saline. We thus conclude that the mean pressure fall was significantly greater in the atenolol-treated than in the saline-treated eye ($P < 0.05$), albeit the difference was small; the median of the observed pressure fall was 2.2 mm (range 1.3-3.7) for the atenolol-treated eye and 1.2 mm (range -0.3-3.5) in the saline-treated eye. The median difference in pressure fall (atenolol-saline) within volunteers was 0.8 mm (range -0.2-2.0).

This finding was lower than we had expected based on prior knowledge of atenolol eye drops and might have been due to a systemic effect of atenolol being absorbed from the one eye and reducing pressure in the control (saline-treated)

eye. Accordingly a second volunteer study was done. Four subjects, selected at random from eight, were given guttae atenolol 4% in both eyes on day 1, crossing over to guttae saline in both eyes on day 2, while the remaining four volunteers received guttae saline on day 1 and guttae atenolol 4% on day 2 in both eyes. The difference between the two treatments did not reach statistical significance (by Wilcoxon matched pairs signed ranks test), but the design had the defect that it was not replicated over two or more pairs of experimental days, which, though desirable, was unpopular with volunteers.

Although these observations suggest that the efficacy of atenolol eye drops in volunteers may be small, the statistically significant difference in pressure fall in atenolol-treated and saline-treated eyes in the first study, whose design is the more powerful, constitutes reasonable evidence that a trial on glaucoma patients is not unethical. Such a study has been instigated.

Our volunteers were young (20-30 years) and normal, and so had relatively low initial pressures; a greater effect can be expected in glaucoma patients and this may be therapeutically useful. Volunteer studies cannot predict the magnitude of treatment effect on patients. Preliminary inspection of data on glaucoma patients is encouraging.

We are grateful to ICI (Pharmaceuticals) Ltd for supplies of guttae atenolol (Tenormin, ICI) and to Dr A Rushton for helpful discussion.

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¹ Elliot, M J, Cullen, P M, and Phillips, C I, *British Journal of Ophthalmology*, 1975, **59**, 296.

² Wettrell, K, and Pandolfi, M, *Experimental Eye Research*, 1975, **21**, 451.

³ *British Medical Journal*, 1976, **1**, 180.

⁴ Phillips, C I, *British Medical Journal*, 1976, **1**, 584.

⁵ Vale, J, Gibbs, A C C, and Phillips, C I, *British Journal of Ophthalmology*, 1972, **56**, 770.

⁶ Vale, J, and Phillips, C I, *British Journal of Ophthalmology*, 1973, **57**, 210.

⁷ Phillips, C I, Howitt, G, and Rowland, D J, *British Journal of Ophthalmology*, 1967, **51**, 222.

⁸ Bonomi, L, and Steindler, P, *British Journal of Ophthalmology*, 1975, **59**, 301.

Fatal ovarian haemorrhage associated with haemodialysis

SIR,—One of the causes of death in haemodialysis patients is haemorrhage. We report a patient who died as a result of haemorrhage from a corpus luteum.

A 21-year-old woman with chronic renal failure due to chronic pyelonephritis had been maintained on twice-weekly haemodialysis for six months. Recurrent clotting of the arteriovenous shunt had necessitated continuous anticoagulation. Hypertension was controlled with a beta-blocker.

At night the patient developed persistent, severe, colicky, central abdominal pain. There had been no vaginal loss. Her menstrual cycle was 5/28 and the last menstrual period had been 25 days previously. On examination blood pressure was 150/70 mm Hg, which later fell to 90/60 mm Hg. There was vague, generalised, abdominal tenderness. Subsequently guarding and rebound tenderness developed in the left iliac fossa. The cervix was very tender.

At laparotomy there was 800 ml of blood in the peritoneal cavity and bleeding from a corpus luteum on the right ovary was found. Right salpingo-oophorectomy and left salpingectomy were performed. On the second postoperative day she required dialysis, during which she had

respiratory arrest and died. No additional information was obtained at post-mortem examination.

Presumably in our patient the normal blood loss from the corpus luteum was magnified by anticoagulation. Menorrhagia and irregular prolonged menstrual cycles are common in renal failure, but some of these cycles are ovulatory.¹ Often an oral contraceptive agent is advised to reduce the menstrual blood loss in these patients, who are already anaemic. A more simple approach would be to use medroxyprogesterone 150 mg intramuscularly three-monthly. This would prevent ovulation and conception and would perhaps abolish menstruation. There may therefore be a place for the regular use of a long-acting progesterone in some menstruating women being treated by chronic haemodialysis.

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¹ Goodwin, N J, *et al*, *American Journal of Obstetrics and Gynecology*, 1968, **100**, 528.

Low-nicotine cigarettes and health

SIR,—It was with great interest that I read the contribution by Dr S Freedman and Professor C M Fletcher (12 June, p 1427) because Kirsch¹ has run similar experiments in our research department. In these almost 45 000 cigarettes from four different test brands of varying nicotine content were smoked blind-fold by 47 heavy smokers over a total test period of 1400 days. In our experiments with cigarettes of especially low nicotine content (so-called nicotine-free cigarettes) the majority of smokers smoked their regular brands on the side, although the nicotine content of the test cigarettes was unknown and they were handed out in unlimited quantities at no cost. We see this as further confirmation of the generally known fact that tobacco is smoked instead of lettuce solely because of its nicotine content.

Dr Freedman and Professor Fletcher deduce from their experiments that the dangers of smoking could be neutralised by lowering the content of nicotine. The submitted findings do not, however, justify such a conclusion: (1) The poison intake from smoking is only slightly influenced by the poison content of the respective cigarette brand. Depth of inhalation is much more important. According to experiments carried out by Harke² in the research institute of the German cigarette industry the nicotine intake varies in the ratio of 1:100 from smoker to smoker. Compared with this a reduction of nicotine in one cigarette by a factor of 0.3—as in Dr Freedman and Professor Fletcher's experiments—is so small as to be practically meaningless because it can be compensated or even over-compensated without the slightest difficulty by merely inhaling a little more deeply, something which most smokers usually do unconsciously. (2) Depth of inhalation was not measured in the authors' experiments. (3) Evidently only those cigarettes smoked during the test were counted. According to our experience one important source of error in such tests—neglected by the authors—is from people continuing to smoke their own regular brand. (4) The evaluation of the frequency of coughing was evidently based on the purely subjective statements of the smokers themselves during the monthly visits. This is a completely

unscientific method which cannot be acknowledged.

Thus not even the results obtained by Dr Freedman and Professor Fletcher can alter the fact that, until we have definite proof to the contrary, we must continue to assume that the hope of "desharpened" smoking by reducing the cigarette poison content is for the present unfounded and probably even an illusion.

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¹ Kirsch, E, Dissertation, Clinical Faculty Mannheim, University of Heidelberg, 1975.

² Schmidt, F, *Kassenarzt*, 1976, **16**, 1964.

³ Harke, H-P, *Münchener medizinische Wochenschrift*, 1970, **112**, 2328.

Definition of preterm delivery

SIR,—In the article on the contribution of preterm delivery to perinatal mortality by Dr R W Rush and others (23 October, p 965) it is stated that "infants born before the onset of the 37th week of pregnancy—that is, three weeks or more before the expected date of delivery—are now described as preterm."

If normal pregnancy lasts for 40 weeks from the first day of the last menstrual period, the interval between the onset of the 37th week and the end of the 40th week is four weeks and not three.

I would be grateful if this apparent discrepancy could be explained, as it obviously affects the definition of "preterm" in a large number of infants.

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*.*We sent a copy of this letter to Dr Rush and his colleagues, whose reply is printed below.—ED, *BMJ*.

SIR,—Dr Rush is now in South Africa and we are replying on his behalf.

Oxford, like several other centres in the UK, does not calculate the length of pregnancy in the way described by Dr Dennison. In Oxford the expected date of delivery is taken as the beginning of the 40th week rather than the end, the patient completing 39 weeks plus 6 days from the first day of her last menstrual period before entering the 40th week of pregnancy. There is thus no discrepancy in our definition of "preterm," that being delivery before the onset of the 37th week or three weeks or more before the expected date of delivery.

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Chiropody services

SIR,—Your leading article "Boots, boots, boots" (20 November, p 1214) illustrates well the present need for further assessment of so-called medical sociology. I know from personal experience that there is a growing tendency, for example, for chiropodists to work autonomously instead of accepting necessary guidance from a patient's general practitioner.

This is a dangerous practice. Particularly in the case of the chronically sick or physically disabled chiropody treatment should be available as and when indicated by the condition of the feet at the time and not merely as a routine, say two-monthly, service. The patient's whole bodily health needs to be taken into account. In this group of patients sepsis following too heroic chiropody treatment can be a great hazard to those with poor resistance to infection coupled with delayed healing power. The decision as to when chiropody treatment should be given or suspended is surely the doctor's responsibility. There needs to be a healthier relationship between paramedical and medical personnel. This is essential if community medicine is to function satisfactorily.¹

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¹ *Seminars in Community Medicine*, ed R M Acheson and L Aird, vol 1, ch 1. London, Oxford University Press, 1976.

Salbutamol by various routes

SIR,—Drs M R Hetzel and T J H Clark (16 October, p 919), comparing intravenous and aerosol salbutamol in stable asthmatics, found the aerosol to have a more prolonged bronchodilator effect. However, the parenteral and aerosol routes are used in different clinical situations. The patient with severe asthma may have insufficient vital capacity for satisfactory inhalation of aerosol. In this situation bronchodilatation should be effected by intermittent positive-pressure ventilation¹ or parenterally. The response to intravenous salbutamol compares favourably with that to intravenous aminophylline.²

When dealing with severe asthmatics at home the family doctor is restricted to parenteral therapy, but there may be difficulties in administering drugs intravenously to a distressed asthmatic patient. Recently the effects of intramuscular salbutamol have been assessed in a dose-response study³ and in patients with acute asthma.⁴ Following administration of a single intramuscular injection of salbutamol (8 or 12 µg/kg body weight) to 10 asthmatic patients admitted urgently to hospital there was a rapid increase in the FEV₁ over baseline values in nine subjects. A mean maximum increase in FEV₁ of 41% and a sustained increase in nine of the 10 patients at two hours were observed. In those nine patients there were varying degrees of clinical improvement.

Judging from its effect on this small number of patients and because of the ease of administration we feel intramuscular salbutamol may represent an advance in the emergency treatment of asthma. At present the effect of repeated injections has not been assessed. Though not yet marketed, we feel a dose of 10 µg/kg (700 µg for the average 70-kg man) would be appropriate.

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¹ Choo-Kang, Y F G, Parker, S S, and Grant, I W B, *British Medical Journal*, 1970, **4**, 465.

² Williams, S J, Parrish, R W, and Seaton, A, *British Medical Journal*, 1975, **4**, 685.

³ Ingram, J, *et al*, *British Journal of Clinical Pharmacology*, 1975, **2**, 263.

⁴ Semple, P d'A, Legge, J S, and Habeshaw, T, *British Journal of Clinical Pharmacology*, 1976, **3**, 935.