consider, however, that the risks of lactic acidosis make the use of phenformin undesirable.⁷ Stanozolol on the other hand has been shown to be effective when given alone for periods up to 30 months and it is relatively free from side effects.⁸ We should like to suggest that stanozolol is effective in reversing the deficiency of fibrinolysis found in Behçet's disease and that it deserves further consideration as long-term therapy to prevent the development of potentially serious thrombotic episodes in patients with this condition.

We would like to thank Dr B Colvin for advice and Professor R D Cohen for permission to report this case.

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¹ O'Duffey, J D, and Carney, J A, *Annals of Internal Medicine*, 1971, 75, 561.

² Chajek, T, Aronovski, E, and Izak, G, *Thrombosis et Diathesis Haemorrhagica*, 1973, 29, 610.

³ Davidson, J F, et al, *British Journal of Haematology*, 1972, 22, 543.

⁴ Jarrett, P E M, Morland, M, and Browse, N L, *British Medical Journal*, 1977, 1, 933.

⁵ Jarrett, P E M, Morland, M, and Browse, N L, *British Medical Journal*, 1978, 2, 523.

⁶ Fearnley, G R, Chakrabarti, R, and Hocking, E D, *Lancet*, 1967, 2, 1008.

⁷ Cohen, R D, and Woods, H F, *Clinical and Biochemical Aspects of Lactic Acidosis*. Oxford, Blackwell Scientific, 1976.

⁸ Davidson, J F, McDonald, G A, and Conkie, J A, in *Synthetic Fibrinolytic Agents*, ed K N von Kaula and J F Davidson, chap 24. Springfield, Illinois, Thomas, 1975.

Eyesight standard for driving

SIR,—As an ophthalmologist I am regularly seeing middle-aged patients who come in to have their reading glasses strengthened but who, I find, have been driving with visual acuity below the legal standard. None of these had realised that the distance vision was not good, so that there was no question of writing to the Vehicle Licensing Centre. There was also a driving instructor who worked for three months with substandard vision following the loss of his spectacles.

I would agree that poor vision is not one of the main causes of road accidents. However, I think that the legal standard is reasonable. It should be enforced by having the police carry out spot checks with the number-plate test in laybys when they check the lights, brakes, and tyres. We seldom hear of a prosecution for driving with inadequate vision. There could also be more publicity on this subject.

All my patients became "legal" by my prescribing a distance corrector for their hypermetropia.

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Hypotensive effect of propranolol and phenoperidine in tetanus

SIR,—Dr N Buchanan and others (22 July, p 254) describe a patient with tetanus who developed profound hypotension after receiving propranolol. I have recently seen a similar phenomenon in which both propranolol and the synthetic narcotic phenoperidine appeared to be implicated.

A previously very fit 71-year-old man developed tetanus six days after sustaining a penetrating injury of the forearm while gardening. Artificial ventilation

was established, D-tubocurarine and diazepam being used as relaxants. Heart rate and intra-arterial recordings of blood pressure were monitored continuously. Phenoperidine 2 mg was given intravenously for sedation on five occasions during the first 24 h, during which period the heart rate and blood pressure remained stable. On the second day after admission the heart rate rose gradually to 150/min with a blood pressure of around 150/70 mm Hg. After a short burst of supraventricular tachycardia propranolol 2 mg was given intravenously over 5 min. The heart rate fell to around 120/min with no change in blood pressure. An hour later phenoperidine 2 mg was given intravenously and the systolic blood pressure immediately fell to 30 mm Hg at a heart rate of 100-120/min. There was no evidence of reflex vasoconstriction and the hypotension persisted for 5-10 min until it was rapidly and completely reversed by the narcotic antagonist naloxone 0.4 mg intravenously. The patient appears to have suffered no ill effects during this episode.

There is little doubt that phenoperidine was the immediate cause of the fall in blood pressure in view of the sequence of events and the prompt response to naloxone. However, previous doses of phenoperidine had not produced hypotension in this patient and it appears that prior β -blockade with propranolol was an important contributory factor.

The autonomic manifestations of tetanus are complex and unpredictable. When a β -blocking drug is considered essential to control sympathetic overactivity it would seem advisable to use the minimum effective dose and the possibility of a synergistic hypotensive effect with narcotics should be borne in mind.

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Body weight and endocrine function in anorexia nervosa

SIR,—Dr R D G Leslie and his colleagues (19 August, p 526), in their study on the influence of weight gain on hypothalamic-pituitary-thyroid (HPT) function in anorexia nervosa report that pituitary thyroid-stimulating hormone (TSH) reserve, as assessed by a standard thyrotrophin-releasing hormone (TRH) test, was reduced at low body weight. In a previous letter (20 August 1977, p 521) they reported a similar finding for prolactin. They suggest that these results are in accord with the theory that there is excessive dopaminergic activity at central receptors in anorexia nervosa.

We have recently completed a study of 20 patients with anorexia nervosa with particular emphasis on interrelationships between body weight and concentrations of gonadotrophins, prolactin, TSH, and thyroid hormones.¹ Our results in relation to the HPT axis are in substantial agreement with those of Dr Leslie and his colleagues, as were the findings of normal resting prolactin concentrations, but we were unable to demonstrate any correlation between body weight and the prolactin response to TRH. Beumont *et al*² were also unable to show any effect of weight on prolactin responses to TRH. In our own study and that of Beumont *et al*, however, TRH tests were performed on patients of low weight only after they had been in hospital for at least five days and had resumed an adequate diet. It is important to know whether Dr Leslie and his colleagues studied their patients initially in the starvation phase or after a period of refeeding,

as it is known that prolonged fasting results in a blunting of prolactin response to TRH.³

Many of the endocrine changes in anorexia nervosa occur as a consequence of malnutrition and quickly resolve with either the resumption of a normal diet or restoration of normal weight.⁴ It is clearly inappropriate to accord such endocrine changes and their central mechanisms any primary significance in the aetiology of the disorder. Many patients, despite weight gain, retain the characteristic psychopathological features of anorexia nervosa. In order to attach primary aetiological significance to changes in endocrine function it would have to be demonstrated that such changes are not merely the secondary effects of a low body weight. The clearest evidence so far of failure to resume normal endocrine function after resumption of body weight relates to the hypothalamic-pituitary-gonadal axis.⁵ Findings in this area, however, are not yet sufficiently advanced to permit aetiological hypotheses in terms of central neurotransmitter activity.

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¹ Wakeling, A, et al, *Psychological Medicine*. In press.

² Beumont, P J V, et al, *Journal of Clinical Endocrinology and Metabolism*, 1976, 43, 487.

³ Vinik, A I, et al, *Hormone Metabolism Research*, 1974, 6, 499.

⁴ Russell, G M F, *Psychological Medicine*, 1977, 7, 363.

⁵ Wakeling, A, et al, *Psychological Medicine*, 1977, 7, 397.

Phenothiazine-induced dystonic reaction while swimming

SIR,—We wish to call attention to a rather unusual but potentially very serious situation in which a 24-year-old woman who had been admitted to hospital with a diagnosis of acute schizophrenia developed a dystonic reaction during a swim with other patients. Eight days previously she had experienced a dystonic reaction involving eye, neck, and lower extremity muscles approximately 26 h after she had received 20 mg of oral fluphenazine hydrochloride. The dystonia quickly subsided after 2 mg of intramuscular benztropine mesylate, which was continued orally at 1 mg twice daily. Oral fluphenazine hydrochloride was resumed at a dosage of 10 mg once daily at 9 pm.

Approximately 19 h after the patient had received her evening dose of fluphenazine and 7 h after her morning dose of benztropine mesylate she felt her legs "tighten up" while swimming in the deep end of the pool. She went under several times but managed to call out for help. She was pulled out almost immediately; one observer noted that her eyes "rolled back" several times, an apparent oculogyric crisis. She reported that after swimming 1½ lengths her legs had gone into spasm, making it impossible for her to stay afloat. After approximately 20 min these symptoms subsided completely.

We believe that this patient developed a phenothiazine-induced dystonic reaction of the lower extremities. We do not think that there is any association between swimming and dystonic reactions because many patients have participated in our swimming programme during the past four years without an incident

being reported. The physician should be aware that dystonic reactions can occur while swimming and could be potentially fatal.

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Persistence of barbiturate prescribing

SIR,—Drs J B and Elspeth T Macdonald in their paper on barbiturates and fractures (20 August 1977, p 483) commented that although it had been reported that barbiturate prescribing was declining at 7.5% a year their results indicated that this might be a complacent view. My experience when taking over a practice in south-east London earlier this year seems to confirm this opinion.

It was found that 47 patients, the majority being in the 61-80-year age group, asked for repeat prescriptions for barbiturates and, having very strong views on the use of these drugs as hypnotics, I refused them as a matter of policy to everyone except epileptics and patients with terminal illnesses. Instead they were given either nitrazepam or flurazepam. Of the 47 patients, 28 readily accepted flurazepam, seven accepted it with difficulty, and four preferred nitrazepam, while two refused both drugs. Of the remaining six patients, four left the practice because they were refused a prescription for barbiturates and the other two left the district.

In view of the authors' findings that the incidence of mental status questionnaire scores of under 12 dropped from 39% to 1% on stopping barbiturates and that the clinically important degree of confusion found in the old people following the use of barbiturates is reversible when the drugs are withdrawn the substitution of barbiturates by non-barbiturate hypnotics is a worthwhile exercise.

I would also agree with these authors (1 October 1977, p 891) that the lives of a large number of elderly people throughout the country would be made less confused and miserable if their barbiturates were stopped.

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Solving clinical questions by research

SIR,—Following the Horizon programme (BBC2, 8 September) your correspondent WFW (16 September, p 825) concludes that work on synthetic membranes is "just looking for the sake of looking with no practical benefit in sight." This conclusion undermines the fair-minded circumstances which stimulated it and is critical of teams tackling complex clinical questions, their funding, and the educational standards and pool of knowledge to which they contribute.

The programme appeared complicated but then so is the subject. How then are clinical questions solved in the supposedly utopian arena, outside the usual experience, but of which WFW writes, where funds seem plentiful and obsessions unrestrainedly pursued? A difficulty facing investigators and committees alike is to produce answers for man. Did WFW predict at the time of the solution of the molecular structure of DNA that it might be possible to produce a genetic

implant capable of producing insulin? It seemed clear from the programme that vision alone would not, for example, prove whether an artificial membrane approach could be used to render insulin injections unnecessary in diabetic patients, control coagulation defects, improve cancer chemotherapy, restore genetic mishaps, and so on. It is necessary to conceive and do the appropriate molecular experiments and clinical studies.

The critique appears also to be directed at the creation and funding of the right blend of clinical and biochemical talents to study such complex questions. Perhaps the programme did not emphasise enough this difficulty. An interdisciplinary team is probably the best instrument by which to hold a principal clinical question in constant perspective so that the eventual solution is clinically justified, ethically acceptable, and scientifically valid. By even appearing to argue against use of funds in this way WFW does a grave disservice to investigators and to the Medical Research Council, Department of Health, independent grant-awarding bodies, and pharmaceutical companies who supported studies mentioned in the programme. Further consequences of the implementation of such an uninformed constraint would be the strangulation of some of the best sources of future clinical, teaching, and research staff and the lowering of morale of present workers.

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Hypertension and oral contraceptives

SIR,—We have some comments about the letter from Dr F B Pipkin and others (22 July, p 278) on this subject. On the basis of their results with the infusion of the angiotensin II antagonist Saralasin they reach the conclusion that "the renin-angiotensin system is not immediately involved in the pathogenesis of this form [contraceptive] of hypertension." Their preliminary results add interesting information in connection with the pathophysiology of hypertension from oral contraceptives. However, we feel that there is an alternative explanation for their results.

A review of the literature and studies in our own laboratory lead us to conclude that there is more than one mechanism simultaneously at play in the production of contraceptive hypertension. Oestrogens increase the renin substrate and this in turn results in an associated increase in renin activity, angiotensin II, and aldosterone.¹ In addition, oestrogens have a mineralocorticoid effect directly on the renal tubules.² The direct mineralocorticoid action causes a decreased renal renin secretion. The net effect of these two countering actions is a normal or only slightly elevated plasma level of renin activity, angiotensin II, and aldosterone. In some patients the direct mineralocorticoid effect appears to be relatively greater than the effect of the oestrogens on the renin substrate and the renin activity levels tend to be in the low range.

In addition to those two effects of the oestrogens the synthetic progestational agents with an alpha side radical on carbon 17 of the steroid molecule have a direct mineralocorticoid effect.³ This action is in contrast to natural progesterone, which has an anti-mineralocorticoid effect.³ Synthetic gestogens

would thus tend to lower the actual values of renin activity and aldosterone even further.

A patient, then, who is taking an oral contraceptive agent would have a two-pronged attack on the renin-angiotensin-aldosterone system. One mechanism (oestrogen) increases the circulating angiotensin II and aldosterone; the other mechanism (oestrogen-synthetic gestogen) acts as a mineralocorticoid to suppress angiotensin and aldosterone. Which of these mechanisms is the cause of the hypertension? The answer is probably one or the other or both. It would depend on whether the patients were responding more to the stimulatory effect on the renin-angiotensin system with a high plasma renin activity or whether they were responding more to the mineralocorticoid activity of the contraceptives.

One would expect those who are hypertensive solely from the mineralocorticoid action of the oral contraceptive to respond to Saralasin with no change or a slight increase in blood pressure. On the other hand those who were hypertensive solely as a result of an inappropriately high level of angiotensin II would respond to Saralasin by a decrease in blood pressure. The patients who had hypertension from a combination of both mechanisms should not exhibit a drop in blood pressure from Saralasin.

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- ¹ Crane, M G, Harris, J J, and Winsor, W, *Annals of Internal Medicine*, 1971, **74**, 13.
- ² Thorn, G W, and Harrop, G A, *Science*, 1937, **86**, 40.
- ³ Crane, M G, and Harris, J J, in *Oral Contraceptives and High Blood Pressure*, ed M J Fregley and M S Fregley, p 100. Gainesville, Florida, Dolphin Press, 1974.

Patient package inserts

SIR,—Dr J Deane Collinge's comments on patient package inserts (30 September, p 958) prompt me as a pharmacist to put forward my own comments as follows:

With an increasing trend towards "original pack" dispensing of medicines, whether from hospital, general practice, health centre pharmacies, or dispensing practices, many medicinal products now reach the patient as supplied by the manufacturer. Often included in the pack, whether it be a dermatological preparation, inhaler, suppositories, course of tablets, etc, is literature, some of which is intended solely for the patient's benefit in addition to the labelling added by the pharmacist, so enabling optimum results to be obtained from the medication and which should therefore be left in the pack when issued to the patient at the time of dispensing. Many manufacturers, however, still include in their products literature intended only for the use of the medical and allied professions regarding indications, contraindications, dosage, etc, of the product. This literature should not, of course, reach the patient for various reasons, one example being quoted by Dr Collinge.

I feel that it is one of the duties of the pharmacist to ensure that the patient receives only that information which is necessary for the correct use of the medication prescribed together with any relevant precautions—for example, antihistamines and driving—and