Contrary to some recent measurements of the half life of methadone,² we found that the half life of this drug in four healthy volunteers varied between 12 and 30 hours, with a mean of 23 hours. (Measurements were made on two separate occasions in the same subject.) From our data we have calculated that if methadone is given in a fixed dose every 12 h the steady-state plasma concentration will be twice as high in a patient with a methadone half life of 30 h when compared with that in a patient with a half life of 12 h. From these calculations it is evident also that the shorter the dosing interval in relation to the drug half life, the greater will be the accumulation.

We would also like to comment on the pharmacokinetics of the controlled-release methadone tablets that were used. The marked peaking of plasma concentrations that occurred in all three subjects would appear to be inconsistent with the characteristics of such a tablet preparation, and it is difficult to understand how the authors can report that a satisfactory plateau level was obtained when their accompanying figure shows evidence of both peaks and valleys. The plasma concentration versus time curves which we obtained following the administration of standard 10-mg methadone hydrochloride tablets to our volunteers are very similar to those depicted. This suggests that there is no substantial difference between the two tablet preparations.

Finally, may we point out that in quoting one of us (DR) the name was incorrectly spelt twice.

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¹ Gibaldi, M, and Perrier, D, *Pharmacokinetics*. New York, Marcel Dekker Inc, 1975.

² Verebely, K, et al, *Clinical Pharmacology and Therapeutics*, 1975, **18**, 180.

Carbenoxolone, diuretic treatment, and body potassium

SIR,—It appears misleading that Dr C Descamps and his colleagues (29 January, p 272) should describe their case of acute tubular necrosis associated with rhabdomyolysis and potassium depletion as "a new complication of carbenoxolone." The patient was also taking chlorthalidone and so the events might equally, and misleadingly, be regarded as a new complication of chlorthalidone. There is no reported instance, so far as I know, of carbenoxolone itself causing acute tubular necrosis. As the authors imply, their patient's condition was very probably a consequence of myoglobinuria, itself a consequence of severe potassium depletion.

Soon after the introduction of oral diuretics it was shown that their kaliuretic properties were considerably increased by mineralocorticoids.¹ Carbenoxolone 300 mg daily has a mineralocorticoid activity in man of about 200-300 µg daily of 9-α-fluorocortisol.² Since the physiological replacement dose of the latter used in adrenal insufficiency is 50-100 µg daily, this dose of carbenoxolone produces a chronic state of mild mineralocorticoidism. The recommended maintenance dose of carbenoxolone, 150 mg daily, is obviously preferable in reducing the effect and although some fall of serum potassium concentration

occurs in some individuals on this dose, significant depletion of intracellular potassium is rarely produced.² On prolonged use of the larger dose of 300 mg daily some patients develop potassium depletion, elderly patients and those with hypertensive or cardiac disease being especially at risk. As with other substances having mineralocorticoid activity, carbenoxolone, especially at the higher dose level, markedly potentiates the kaliuretic action of diuretics so that considerable potassium depletion may occur during prolonged treatment.² The additional administration of adequate potassium supplements or of a potassium-sparing diuretic such as amiloride can prevent potassium depletion.² Spironolactone, which seems at first to be particularly suitable, cannot, unfortunately, be used with carbenoxolone as it interferes with the healing effect.³

Despite the fact that carbenoxolone is widely used being now the mainstay of outpatient treatment of gastric ulcer⁴ relatively few cases of severe potassium depletion have occurred. Less than 20 have been reported in the UK since 1966 and in the majority carbenoxolone was clearly misused, the patients being very elderly, given much too prolonged a course, or inadequately supervised despite the presence of recognised risk factors such as hypertensive disease or concurrent diuretic administration.

The unhappy course of events described by Dr Descamps and his colleagues illustrates the consequences of the failure to give proper supervision of drug therapy, particularly when there is considerable deviation from the recommended course of treatment. It also re-emphasises the importance of recognising that considerable potassium loss may result from combining diuretic therapy with a drug having mineralocorticoid activity and that, lacking sufficient awareness, potassium depletion may progress unrecognised to reach gross proportions.

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¹ Edmonds, C J, and Wilson, G M, *Lancet*, 1960, **1**, 505.

² Edmonds, C J, and Tomkins, A M, in *Fourth Symposium of Carbenoxolone*, ed Sir F Avery Jones and D V Parke, p 129. London, Butterworths, 1975.

³ Doll, R, Langman, M J S, and Shawdon, H H, *Gut*, 1968, **9**, 42.

⁴ Montgomery, R D, *Journal of the Royal College of Physicians*, 1976, **11**, 181.

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

SIR,—Dr Edmonds's comments are in complete agreement with our thesis that in our patient acute tubular necrosis resulted from myoglobinuria produced by severe potassium depletion. Nor does he dispute that the potassium deficiency itself was the consequence of the excessive dosage of carbenoxolone and the diuretic used. Thus we do not see why Dr Edmonds feels that it is misleading to relate carbenoxolone with acute tubular necrosis.

Carbenoxolone alone, even at an appropriate dosage, can induce myoglobinuria, as documented by several case reports.¹⁻⁴ By contrast, to our knowledge, no such complication has ever been demonstrated after chlorthalidone 50 mg every other day, the dosage used in our patient. Admittedly, as we pointed out in our report, it is likely that the deleterious effect of carbenoxolone in our patient was markedly enhanced by the addition of the diuretic.

It may be anticipated that sooner or later all factors capable of producing myoglobinuria will induce acute tubular necrosis. This has already been demonstrated for heavy exercise, McArdle's disease, viral infections, grand mal seizures, etc.⁵ Our report adds only another factor to this list.

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¹ Mohamed, S D, Chapman, R S, and Crooks, J, *British Medical Journal*, 1966, **1**, 1581.

² Forshaw, J, *British Medical Journal*, 1969, **1**, 674.

³ Mitchell, A B S, *Postgraduate Medical Journal*, 1971, **47**, 807.

⁴ Barnes, P C, and Leonard, J H C, *Postgraduate Medical Journal*, 1971, **47**, 813.

⁵ Grossman, R A, et al, *New England Journal of Medicine*, 1974, **291**, 807.

Geriatricians to the gas chamber?

SIR,—I was dismayed that Professor Ian Donald, in his admirable Simpson Oration (26 February, p 555), should have introduced the concept of "geriatricide" (the slaughter of geriatricians). Even Dr J Leonard ("Can geriatrics survive?", 29 May, 1976, p 1335) did not go so far as that!

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Ophthalmic services for the elderly

SIR,—We should like to add support to Dr P A Gardiner's comments on the large number of elderly people who attend eye outpatient departments (19 February, p 513). In Oxfordshire we found that 20% of all new outpatient bookings for patients aged 65 years and over and 24% of all (new and repeat) bookings in this age group were to ophthalmology clinics.¹ The corresponding figure for new outpatients in a study from Chesterfield² was 16%, which, though a little lower than ours, is none the less considerable. These data emphasise the frequency of eye conditions in the elderly as a reason for hospital outpatient referral and underline the importance of considering new ways, such as Dr Gardiner suggests, of meeting the ophthalmic needs of the elderly closer to their homes when possible.

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¹ Goldacre, M J, and Gatherer, A, *Hospital and Health Services Review*, 1977, **73**, 14.

² Trout, K, and Martindale, A, *An Experiment in Outpatient Information*. Sheffield, Trent Regional Health Authority, 1974.

Insurance companies' attitude to psychiatric illness

SIR,—Recently two former patients of mine have complained to me that insurance companies have made it difficult for them to take out life insurance because they had a history of psychiatric treatment. Both patients were male; one was a young adult and the other was middle-aged. Both were treated for mild

anxiety states arising from domestic crises. Treatment was given to them as outpatients and recovery was obtained with the use of mild anxiolytic drugs and a small number of interviews. The younger man had a life policy offered to him with such a heavily loaded premium that he could not afford it. The older man was turned down completely by one insurance company. In neither case was I asked for my opinion by an insurance company. In any event I did not consider that either patient was a suicidal risk.

I have not come across this practice before in patients with such minor psychiatric histories as these two had. I would be interested to know if other colleagues have had similar experiences. If this practice is widespread it would be useful to know which prognostic criteria are being used by the insurance companies in the assessment of psychiatric illness.

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Ascaris infection

SIR,—Your leading article on *Ascaris lumbricoides* (12 February, p 406) was interesting and timely as infestation with this worm is becoming more frequent in Britain owing to the arrival of people from endemic areas. However, there is one point which needs clarifying, and that concerns intestinal perforation. There is doubt whether the worm can perforate normal bowel,¹ but it does penetrate lesions such as typhoid ulcers.² More important, the worm will perforate intestinal or biliary anastomoses giving rise to fistulae or peritonitis.³ These serious surgical complications occur because the worms seem to be attracted to the site of an anastomosis and digest the suture material.

We have recently seen and presented⁴ four patients who, after routine abdominal surgery, developed biliary or intestinal fistulae through which an ascaris emerged. These complications can be avoided by giving patients with definite evidence of infestation or from high-incidence areas piperazine adipate (up to 4 g) the day before operation.

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¹ Cole, G J, *British Journal of Surgery*, 1965, **52**, 444.
² Van Rensburg, L C J, and Kark, A E, *Medical Proceedings*, 1958, **4**, 522.

³ Milwidsky, H, *Acta Medica Orientalia*, 1945, **4**, 370.

⁴ Franklin, A, *Proceedings of the Royal Society of Medicine*, In press.

Breast size and cancer

SIR,—It seems curious that in all the thousands of papers written on the subject of breast cancer little if any attention has been devoted to the significance of the size of the breast in which a malignant tumour develops. It must be the experience of all surgeons that the extremes occur—of large tumours developing in small atrophic breasts and yet the patients survive for many years after appropriate local treatment, while tiny tumours in large, fatty breasts may quickly prove fatal despite all treatment.

Is the amount of fat in a breast developing a carcinoma a disadvantage or is the prognosis totally independent of the size of the host breast with regard to both breast tissue and

fat? Is the incidence of carcinomas in fat, medium, and small breasts different?

Should we accept that the behaviour of the seed is uninfluenced by the size of the flower-pot in which it grows?

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Underweight breast-fed babies

SIR,—Now that both breast-feeding and not weighing babies are becoming more fashionable I would like to draw your attention to a condition that is now appearing in child health clinics. In the past 2½ years I have seen three infants who were well below their birth weight when they first appeared at the clinic. All three were breast-fed and all were first-born children.

I would like to impress upon all medical colleagues, health visitors, and clinic nurses the necessity of keeping a careful eye on breast-fed babies now that older relatives and neighbours have no practical experience to go on.

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Suicidal behaviour syndrome with low CSF 5-HIAA

SIR,—Predictors of suicidal behaviour have largely been derived from epidemiological studies which have concentrated on demographic variables such as sex, age, and social isolation. Such factors have low predictive power for suicidal behaviour in individual patients¹ and are of limited help to the clinician at the bedside.

Suicidal behaviour remains a serious problem which ties up a large number of beds and manpower in acute medical and psychiatric units besides causing considerable suffering, morbidity, and mortality. Epidemiological studies have demonstrated the size of the problem, but the kind of predictors they yield are of limited value for the clinicians' assessment of the suicidal risk in an individual. Perhaps a more fruitful approach would be to identify subgroups of suicidal behaviour using clinical observations and biochemical procedures which have a higher predictive ability and could ultimately allow the development of specific treatments.

Recent cerebrospinal fluid (CSF) studies^{2,3} have identified one possible subgroup among depressive patients. A low concentration of 5-hydroxyindoleacetic acid (5-HIAA) in the CSF is associated with a very high (40%) rate of serious suicidal attempts. This finding is surprising and raises the question whether lumbar punctures should be reintroduced into psychiatric practice. It is our impression that members of this group have sufficient clinical features in common for the condition to be described as a syndrome. People with this syndrome exude an unspoken hostility and give the impression that they might have outbursts, but these are in fact not common. They display little concern for themselves and lack empathy towards others. They tend to avoid close emotional relationships, but in spite of their aloofness they may perform well in certain social spheres. They may come to medical attention after a suicidal attempt which

is often surprisingly violent, and there is a discrepancy between the seriousness of the attempt and their smiling denial. They may give a history of depressive episodes, but often do not at the time appear clinically depressed. They are not attention-seeking and accept treatment reluctantly or with indifference.

The hypothesis of a relationship between this clinical picture and a low 5-HIAA concentration in the CSF needs to be tested and should be studied together with further psychological and biochemical investigations aimed at the development of more effective treatment.

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¹ Murphy, G E, in *The Prediction of Suicide*, ed A T Beck, H L P Resnik, and D J Lettieri. Maryland, Charles Press, 1974.

² Åsberg, M, *et al*, *Science*, 1976, **191**, 478.

³ Åsberg, M, Träskman, L, and Thoren, P, *Archives of General Psychiatry*, 1976, **33**, 1193.

Oxprenolol overdose with survival

SIR,—With reference to the report by Drs A Khan and J M Muscat-Baron of a fatal case of oxprenolol overdosage (26 February, p 552) I would like to record a similar case in which the patient made a full recovery following a period of cardiac massage lasting two hours.

A 39-year-old woman was admitted to the casualty department having ingested an estimated 2.5–3 g of oxprenolol. During a stomach washout she had a brief respiratory arrest and probably inhaled vomit. A mild generalised convulsion occurred, lasting about 15 s. An endotracheal tube was passed and 500 mg of hydrocortisone was given intravenously. The blood pressure was unrecordable and the pulse very feeble, but spontaneous respiration returned and the cardiac monitor showed sinus rhythm with a rate of 60/min. Two further brief convulsions occurred.

Shortly after transfer to the intensive care unit she had a respiratory and cardiac arrest and the cardiac monitor now showed a bradycardia of about 20/min. She was connected to a ventilator and external cardiac massage was started and performed continuously for two hours. During this time she was given: 1.2 mg atropine, 3 ml adrenaline (1/1000), and 20 ml 10% calcium gluconate intravenously; 1 ml adrenaline (1/1000) by intracardiac injection; 13 mg isoprenaline as an infusion in a total of 1.5 l of isotonic saline; 150 ml 8.4% sodium bicarbonate; and 1 l of dextran 70.

Extreme bradycardia persisted and no pulses were palpable whenever cardiac massage was stopped. The pupils were dilated and unreactive. A transvenous pacing wire was inserted and pacing was easily obtained, but there were still no palpable pulses. However, after two hours the femoral pulses became weakly palpable and cardiac massage was discontinued. Mannitol was given and she was started on dexamethasone and antibiotics.

During the next two hours the blood pressure became recordable at 130/100 mm Hg and she reverted to sinus rhythm at 80/min. Within 48 h she was fully conscious but required the pacemaker periodically. After 72 h assisted ventilation was discontinued. After this she recovered rapidly and there was no gross cerebral impairment. When seen as an outpatient seven weeks later she appeared to have made a full recovery.

This case demonstrates that recovery from oxprenolol poisoning may follow prolonged