Poor energy intake is certainly not the only cause of growth retardation in chronic renal failure and may indeed not be the most important, for, while growth may improve with supplements, many children still grow poorly in spite of apparently adequate intakes.³ Provided the children accept them, feeding energy supplements would still seem to be justified. As the authors have demonstrated, they may have the advantage of limiting spontaneous intake of protein and other nutrients which may need to be reduced in renal failure.

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chronic renal insufficiency, suggesting that their reduced energy intake is a related but not necessarily causal factor. As we stressed in our last paragraph, we feel that if energy supplementation were to result in increased growth velocity, then this is more likely to occur when commenced in early childhood; indeed, the only child to show a significant increase in growth velocity with increased energy intake was aged 2.8 years when supplementation started.

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¹ Betts, P R, and Magrath, G, *British Medical Journal*, 1974, 2, 189.
² Chantler, C, et al, *Medizinische Mitteilungen*, 1976, 50, suppl 11, p 57.

¹ *Scientific Tables, Documenta Geigy*, ed K Diem, 6th edn, p 191. Manchester, Geigy Pharmaceutical Co Ltd.

² Betts, P R, and McGrath, G, *British Medical Journal*, 1974, 2, 189.

³ Chantler, C, et al, *Medizinische Mitteilungen*, 1976, 50, suppl 11, p 57.

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

SIR,—We thank Dr Chantler and his colleagues for their additional interpretation of our data (12 February, p 416). We agree that many of our children had only a moderate degree of renal insufficiency; nevertheless, nine of the 11 children who received energy supplementation were below the 50th centile for height and nine of 10 children had a height velocity below the 50th centile in the preceding year. Since growth velocity was determined over a 12-month period before the study this information was not available in case 7, who was only 0.6 years old on entry. We felt justified in including the two pubertal boys (cases 16 and 17) in our analysis since their energy intake and growth velocity did not parallel one another. Had they shown an increase in both these factors their data would have been difficult to interpret.

The questions we asked were whether an increased energy intake would result in (1) increased growth velocity and catch-up growth in children growing steadily along a given centile and (2) restoration of normal growth velocity in those in whom this was previously suboptimal. Dietary assessments were not made over a full year before the study as we had previously shown a relationship between energy intake and growth velocity.¹ Following supplementation it proved possible to increase the energy intake of four out of six children in whom this was previously suboptimal, yet only one of these four (case 8) showed significantly increased growth velocity. None of the five children with intakes greater than 80% of the recommended dietary allowance showed a significant increase or even reached the mean expected for their age. One of the six children (case 2) not receiving energy supplementation also significantly increased his growth velocity.

In answering the question whether the reduced energy intake of children with renal insufficiency is a causal or merely a related factor in their reduced growth velocity Dr Chantler and his colleagues have themselves shown that the provision of extra energy for children with terminal renal failure "did not ensure good growth."² We have shown similar results in children with milder degrees of

Timing of cervical smears

SIR,—I am most interested that Professor H C McLaren and Dr A J Lucas have found (12 February, p 445) that in some places in the USA it is obligatory to offer Papanicolaou tests to women under medical care in all hospital specialties. In this region, where screening for uterine cervical cancer is very comprehensive, cases of overt clinical cervical cancer still occur in the unscreened population and 75% of these women have previous hospital records. The taking of cervical smears should be part of routine hospital care.¹

I agree that carcinoma-in-situ is being diagnosed at an earlier age than it was 10 years ago, but this is relevant to the increase in the number of women under 25 years who are having smears taken. In this region, where 150 000 women have been screened, the detection rate is very low in women below 20 years of age. Very few cases occur at this age possibly because biopsy is seldom done as these young women can be followed with further smears. Only one case of microinvasive cancer has been found below 25 years of age, but four overt clinical cases have presented in women under 25 years who have never been screened. The detection rate of preclinical cancer is found to be 0.18% between 20 and 30 years, but rises steeply to 0.9% between 30 and 40 years, stays high, at 1.1%, between 40 and 50 years, and then begins to fall.

In addition to financial considerations, the frequency of repeating cervical smears must depend on the length of time, usually assumed to be about 10 years, that this disease remains at the in-situ stage, the efficiency of smear collection, and the reliability of the smear interpretation.

From 1968 to 1974 there were no deaths (Registrar General's figures) from cervical cancer in Scotland in women under 25 years.

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¹ *British Medical Journal*, 1976, 2, 659.

Vital follow-up of atypical cervical smears

SIR,—I should like to emphasise the importance of referring patients who have had two successive cervical smears showing abnormal cells for a gynaecological opinion.

I say this for the following reasons. Patients may have cervical smears taken by any or all of the following: their general practitioner, a family planning clinic, or at a routine gynaecological or postnatal clinic. Most of the laboratories associated with these clinics will suggest a six-month delay in repeating smears with "atypical or dyskariotic cells." It is easy to see that the cumulative effect of all these delays may add up to several years, sometimes with disastrous results for the patients. On the other hand it is often possible to pick up a carcinoma-in-situ from the second abnormal smear onwards.

It is therefore vital that the space on the smear form asking for the patient's general practitioner should be completed, together with the latter's correct address, even when the patient might not want to have her GP contacted. Ultimately it will be the GPs responsibility to be aware of this second abnormal report and to arrange appropriate and rapid referral.

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Voluntary Service Overseas

SIR,—Dr D C Morley and his colleagues (26 February, p 572) have eloquently put forward the case for the priority of socioeconomic development and preventive medicine in developing countries. No one would disagree with this, but their statement also actively discourages doctors trained in curative medicine from contributing. I believe that this is wrong.

At this moment people are dying in pain and misery from strangulated hernias, pneumococcal pneumonia, obstructed labour—the list is interminable. A health care system must be capable of relieving this suffering, not all of which is preventable. Western aid can help here, not just as a "pair of hands" but in training health workers, whether as doctors or as medical auxiliaries.

Let us encourage as many medical volunteers as possible to go to as many countries as possible. Even if some set out with the "wrong" motives and orientation I am certain that within a very few months they will appreciate the "real issues confronting those seeking to combat disease" and begin to tackle them, to the benefit of the communities they serve.

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Methadone: evidence of accumulation

SIR,—We are writing in consequence of the letter from Mr S T Leslie and others (5 February, p 375). From the results presented readers might have been confused into thinking that the accumulation of methadone in plasma is a continuous and indefinitely progressive process. However, this is not so, since the rate of accumulation decreases with each dose until a steady-state concentration is reached, after which no further accumulation occurs. The amount of drug that accumulates following multiple dosing can be calculated readily from a knowledge of both the drug half life and the dosing interval.¹

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