number of susceptible individuals to become exposed as adults rather than as children. This problem does not attain unmanageable proportions, since the incidence of measles in the older age groups has remained lower in the United States than it was before the vaccination era. A proportional shift of the remaining cases to older age groups did occur and this was predictable, as it was with other diseases that the young are vaccinated against. From the reports to the Center for Disease Control, Atlanta, it appears that in 1960-4 37% of measles cases occurred under the age of 5 years, 53% at 5-9 years, 7% at 10-14 years, and 3% at and above 15 years of age. In 1971-5, the figures were 35%, 34%, 18%, and 14% respectively, and in 1976-8 16%, 25%, 36%, and 24%. During the prevaccine era, about 500 000 cases of measles were reported each year.² In 1979, only 13 000 cases were reported.³ On the basis of these figures, before vaccine was used about 50 000 reported cases of measles occurred after 10 years of age, compared with only about 8000 in this age group in 1979. Similarly, before vaccine was used 15 000 cases were reported in persons over 15 years of age, compared with about 3000 in 1979. If the present trend continues, there should be less than 10 000 reported cases of measles in the United States in 1980. The number of cases in adults will thus continue to be much less than in the prevaccine era.

A country can always decide to further decrease virus circulation, and exposure of adults, by more intensive vaccination of the young, as has been the effect of the US policy. For all these reasons it is not justified to withhold the personal benefit of the vaccine from the average child in any developed country. Of course, adult measles is highly visible owing to the absence of cases in the vaccinated young. Adult measles should be an incentive not to limit vaccination programmes to the recommended age of 15 months, but to extend them up to the age of 12 years in children who have never had measles or the vaccine.

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¹ Weibel RE, Bunyak EB, McLean AA, Hilleman MR. *Proc Soc Exp Biol Med* 1979;162:328-32.

² Orenstein WA, Halsey NA, Hayden GE, et al. *J Inf Dis* 1978;137:847-53.

³ Anonymous. *Morb Mort Wkly Rep* 1979;28:410-1.

SIR,—Dr Hillas Smith (15 March, p 766) has drawn attention to *selective* immunisation against measles, which was proposed in 1968 as an alternative to *routine* introduction of vaccine.¹ As he rightly points out, with the present acceptance rates of immunisation of the child population, measles is moving into the older age groups as was predicted.^{1,2} While the vaccine appears to be about 95% effective, the duration of protection is not known, nor is it known if revaccination may be required for adults (in whom vaccine reactions are more severe). We also know very little about possible teratogenic effects of "wild" or vaccine viruses in pregnant women.

Even before vaccine was introduced, measles appeared to be becoming a trivial disease in civilised communities, and it seems

not unreasonable to hope "that it will rapidly become as mild as rubella and chickenpox with a negligible mortality."³ There is something to be said for allowing a mild "wild" measles virus to give a natural life-long protection to the healthy children of the community and to offer vaccine *selectively* to those among whom the greatest morbidity and mortality occurs or who have escaped a natural infection in the early years of childhood.

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² Rand KH, Emmons RW, Merigan TC. *JAMA* 1976;236:1028.

³ Paul H. *The control of diseases*. Edinburgh: ES Livingstone, 1964:93.

Tuberculosis in patients having dialysis

SIR,—We believe that the recommendations you proposed in your leading article (9 February, p 349) for the treatment of patients on regular dialysis are misleading and potentially dangerous.

Firstly, we think that the dosage of isoniazid should not be decreased from 300 mg a day. Isoniazid is predominantly eliminated by acetylation in the liver and as a consequence the unchanged drug does not accumulate in renal failure. From estimates of the proportions of the dose excreted unchanged in the urine by normal subjects,¹ we calculate that the half life of isoniazid in slow acetylators is likely to be increased only from about three to four hours in complete renal failure, while in rapid acetylators changes in its rate of elimination would be minimal. Acetylisoniazid is eventually converted to diacetylhydrazine and isonicotinylglycine and in our experience the accumulation of these non-toxic terminal metabolites between dialyses does no harm.² Loss of renal function would have a negligible effect on peak isoniazid plasma concentrations, with which the antituberculous efficacy of the drug is correlated.³ In contrast, lowering the isoniazid dose size would certainly result in suboptimal drug concentrations and, if the patient were particularly heavy, a dose of 150 mg, as recommended, might even be ineffective.

Secondly, if it were considered important to add a third drug to the combination of isoniazid and rifampicin for the treatment of dialysis patients, it would be unwise to prescribe ethambutol at a daily dose of 5 mg/kg. Although the average plasma concentrations attained after several days of this dosage would probably be similar to those following dosage with 25 mg/kg/day in patients with normal renal function,³ the concentrations during the first one to two days would be much lower. As ethambutol in a daily dose of 6 mg/kg/day is only partially effective,⁵ a patient typically being dialysed three times a week and given 5 mg/kg/day would be unlikely to be getting fully effective therapy. We would therefore recommend giving substantially larger doses of ethambutol four to six hours before each dialysis as a safe and effective way of using this drug in renal failure. For patients being dialysed three times or more each week a dose of 25 mg/kg ethambutol might be employed, the dose being increased to 45 mg/kg for twice-weekly dialysis and 90 mg/kg for once-weekly dialysis. Daily doses of 25 mg/kg ethambutol are routinely used for the initial treatment of normal patients and the larger doses have been

shown to be well tolerated and efficacious in controlled clinical trials when given intermittently.^{6,7}

Since the efficacy of ethambutol in dialysed patients has not been established, it might be preferable to give streptomycin, an inherently more potent drug, in its place. Streptomycin could be given at a conventional dosage of 0.75 g four to six hours before each dialysis. The clinical efficacy of intermittent streptomycin treatment in patients with normal renal function has been well documented⁸ and since such a regimen is likely to be well tolerated in dialysis patients it can be utilised without recourse to serum streptomycin measurements. In brief, we recommend that tuberculous patients having dialysis should receive daily isoniazid and rifampicin at full conventional dosages, supplemented if it is thought necessary by streptomycin or ethambutol given four to six hours before dialysis, neither drug being administered in a reduced dosage.

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¹ *J Pharmacokinet Biopharm* 1976;4:83-113.

² Ellard GA. *Bull Int Union Tuberc* 1976;51:143-54.

³ Mitchison DA. In: Davies DS, Prichard BNC, eds. *Biological effects of drugs in relation to their plasma concentration* (British Pharmacological Society). London: Macmillan, 1973.

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⁶ Sbarbaro JA, Hudson LD. *Am Rev Respir Dis* 1974;110:91-4.

⁷ Tripathy SP. In: *Symposium on Rifampicin in Tuberculosis Treatment*. Helsinki: Uudenmaan Kirjapaino Oy, 1974:91-102.

⁸ Fox W. *Chest* 1979;76, suppl:785-96.

* * * Is it legitimate to accept a calculated change in the half life of isoniazid in renal failure from three to four hours on the basis of data from normal subjects? Maher¹ reported an increase in half life of isoniazid from the normal two to six hours to up to 17 hours in renal failure. On the basis of this prolonged half life, most recommend the limitation of dose to 150 mg daily in view of the risk of peripheral neuropathy.² But, as we said in our leading article, higher doses may be used if plasma concentrations are measured,³ and the larger patient would usually warrant a higher dose. In their comments on ethambutol Drs Mitchison and Ellard give their own answer to their criticism of our recommendations. If the drug is given in the dose of 5 mg/kg continuously in renal failure concentrations will be low on the first day after dialysis but will reach satisfactory concentrations before the next dialysis; and, as they say, intermittent peaks are efficacious. Anderson *et al*⁴ recommended that ethambutol should be given either in a dose of 18 mg/kg between dialyses or in a daily dose of 5 mg/kg. We recommend the latter because most patients find it easier to remember to take a regular daily dose.

Drs Mitchison and Ellard's suggestions about streptomycin would create practical problems. The patient with tuberculosis who is on dialysis will often have poor muscle bulk, which makes intramuscular injection difficult and painful. In addition, anticoagulation is necessary for dialysis and if an intramuscular injection has been given within the previous six hours a haematoma is likely. Furthermore, nephrologists are only too aware of the long-term ototoxicity associated with streptomycin,

since errors in dosage can occur even in the best units. The other practical problem in the case of outpatients is that the patient has to be brought up to hospital six hours before the dialysis.—Ed, *BMJ*.

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Haemodynamic monitoring in the intensive care unit

SIR,—In acute myocardial infarction a low-cardiac-output condition can be caused by inadequate intravascular volume, and an inappropriately low left ventricular filling pressure is an important diagnostic feature. Your leading article (12 April, p 1035) suggests that the incidence of the condition is small, but as long ago as 1974 Sobel¹ reported that nearly 25% of patients sent to his unit from community hospitals for the treatment of cardiogenic shock and power failure after myocardial infarction had this hypovolaemic disorder. It can kill within an hour or two of its onset if it is not treated by volume expansion, and so many patients must have died before they could reach the community hospitals or arrive at Sobel's unit.

More patients might be recovered if the condition was suspected more often, and if the diagnosis was not thought to depend on direct or indirect measurement of the left atrial pressure. The diagnosis can usually be made from the patient's response to intravenous test infusions of 200-400 ml 5% dextrose, and special equipment is not required to detect the recovery of palpable arterial pulses and recordable blood pressure, the improvement in the peripheral cutaneous circulation, the wakening from unconsciousness, and the resumption of urine flow, which are achieved when the circulation gets the fluid it needs. The ensuing diuresis commonly brings the left ventricular filling pressure below the effective threshold and so the infusion may need to be repeated over and over again during a period of one to seven days. Occasionally an inotropic agent requires to be used, and adrenaline is excellent.²⁻⁶

The infusions cause variable central venous pressure responses. When venous constriction is severe an infusion of 200 ml 5% dextrose may cause the pressure to rise by 20 cm of water, but the level quickly falls as the veins relax, and the infusion of 200 ml 5% dextrose when the hands are pink and warm may cause a pressure rise of less than 2 cm water.³⁻⁶

The majority of patients resuscitated by volume expansion at Charing Cross Hospital had inferior myocardial infarction and presented two remarkable features. Firstly, the heart block which was commonly present disappeared with the first test doses of infusion, but pacemaking without infusion did not relieve the shock. Secondly, the magnitude of the infarction seemed small for such a catastrophic illness when it was judged subsequently from the patient's physical ability and freedom from heart failure.

The diagnosis of hypovolaemic shock in acute myocardial infarction can be excluded when the test doses of infusion fail to produce a rapid and obviously favourable clinical response. The myocardial injury is usually a

severe anterior infarction, and adrenaline infusion may occasionally improve the left ventricular function to a level which enables the patient to recover.

The principles which encouraged the rational investigation and treatment of the low output states in acute myocardial infarction were clearly stated in your leading article—namely: (1) "Changes in [right] atrial pressure may be due to alterations in venous tone. . . ." (2) "In a small [sic] but important group of patients with low-output states complicating myocardial infarction the left atrial pressure is normal or even low." (3) "The use of diuretics to promote the flow of urine may be dangerous. . . ." These principles were waiting to be observed by anyone who turned his attention from the problems of open-heart surgery to acute myocardial infarction, and probably were discovered in many parts of the world at the same time; but I do think they were first published in England.²⁻⁶

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¹ Sobel E. In: Braunwald E, ed. *The myocardium: failure and infarction*. New York: HP Publishing Co, 1974:285-93.

² Nixon PGF, Ikram H, Morton S. *Lancet* 1966;i:1077-9.

³ Nixon PGF, Ikram H, Morton S. *Am Heart J* 1967;73:843-5.

⁴ Nixon PGF, Taylor DJE, Morton SD. *Lancet* 1968;i:1230-2.

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Hypokalaemia and diuretics

SIR,—We would like to congratulate Drs D B Morgan and C Davidson for their painstaking analysis of publications on hypokalaemia and diuretics (29 March, p 905). We would, however, like to make a few comments particularly relevant to the older population, 37.4% of whom are on regular diuretic therapy.¹

We surveyed 400 consecutive admissions to our unit; 85 patients were taking diuretics for more than three months and 17 of these were hypokalaemic (see accompanying table). It is interesting to note that 33% of the patients on frusemide alone were hypokalaemic as compared to 4% of those receiving frusemide in combination with potassium supplements or potassium-sparing diuretics. We therefore disagree with the authors' suggestion that the risks of hypokalaemia are small when loop diuretics are administered. Elderly patients are likely to develop hypokalaemia for several reasons: their dietary intake of potassium tends to be reduced,^{2,3} the gastrointestinal absorption may be diminished,⁴ and the reduced muscle bulk may further diminish the total body potassium reserves.^{5,6} If in addition they are challenged by a diuretic that increases the urinary potassium loss, hypokalaemia may develop.

It is interesting to note that in our survey, 27% of the patients on Navidrex K (cyclopentiazide and potassium chloride) became hypokalaemic. In elderly patients therefore the amount of potassium

supplements incorporated in these tablets may either be insufficient to replace the amount lost or not be completely absorbed from the gastrointestinal tract. From our data it may also be argued that even the potassium-sparing diuretics may lead to hypokalaemia: 18% of our patients on 50 mg hydrochlorothiazide and 5 mg amiloride (combined in one tablet) became hypokalaemic. Our findings regarding this combination are, however, in agreement with those of another study⁷ and it has been suggested that the formulation amiloride 5 mg and hydrochlorothiazide 50 mg may in some way interfere with the biological availability of amiloride, as when these two compounds are taken separately no significant drop in the serum potassium could be detected.⁷ On the other hand, the combination of 25 mg hydrochlorothiazide and 50 mg triamterene seems more effective in preventing potassium loss: several hundred elderly patients on this formulation are closely followed by the European Working Party on Hypertension in the Elderly, and no significant drop in their serum potassium has been reported. In another series of 484 patients treated with a combination of hydrochlorothiazide (25 mg) and triamterene (50 mg), only 6% developed hypokalaemia.⁸

We consider unacceptable the statement that "Hypokalaemia would almost disappear as an important complication of diuretic treatment if it was defined as a value less than 3.0 mmol[mEq]/l rather than as a value less than 3.5 mmol/l." Hypokalaemia in the elderly may be associated with postural hypotension and giddiness on standing up. In our series the hypokalaemic patients exhibited an average drop in systolic blood pressure on standing up of 20 mm Hg (from 148 to 128 mm Hg) despite the fact that none had a serum level below 3.0 mmol/l. Apart from the other known manifestations, hypokalaemia may also present in a non-specific manner with lethargy, apathy, and easy fatigability; whereas these manifestations may not be "harmful," the quality of life of older patients may be improved by preventing hypokalaemia from developing.

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¹ Williamson J. *Practitioner* 1978;220:749-55.

² Macleod CC, Judge TG, Caird FI. *Age Ageing*, 1975;4:49-51.

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⁵ Lye MDW, Tucker JS. *Proceedings of the Annual Meeting of the British Geriatric Society* 1978: abstract 21.

⁶ Cox R. *Geriatr Med* 1980;10:(4):22.

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⁸ Hansen KB, Bender AD. *Clin Pharmacol Therap* 1967;8:392-9.

Beta-blockers in immediate treatment of myocardial infarction

SIR,—On behalf of my colleagues, may I thank Professor G A Rose for his comments? He rightly points out that it is not possible to conclude from our results (29 March, p 885)

Diuretic treatment and hypokalaemia in 85 elderly patients

Diuretic agent	No of patients	Average age (years)	No with hypokalaemia
Frusemide	12	83	4
Frusemide and potassium supplement or potassium-sparing diuretics	23	81	1
Navidrex K (cyclopentiazide and potassium chloride)	26	79	7
Moduretic (amiloride hydrochloride and hydrochlorothiazide)	17	80	3
Others	7	81	2