validated treatment threshold (170/100 mm Hg, mean of three readings) and those with borderline pressures (90-99 mm Hg diastolic phase V, reviewed annually). Published evidence does not suggest that the effect of sodium restriction on blood pressure is large enough to control pressure in the former group without additional drug treatment. We chose to study the latter group because if treatment were shown to confer benefit in this range of blood pressures, these patients would have most to gain from a non-pharmacological method of lowering blood pressure.

Dr MacGregor and others raise but do not attempt to answer the important question of what is an acceptable clinical definition of mild hypertension. This problem was highlighted by the Australian mild hypertension trial in which half of the patients with pressures sustained twice above 95 mm Hg at entry showed a subsequent fall in pressure without treatment.² Our use of six casual pressures measured over five years was an attempt, which was partially successful, to select patients with more stable mild hypertension using data routinely available in any practice with an active blood pressure programme. That so few of our borderline patients had pressures in the range 95-99 mm Hg was an unexpected finding and may be an important consequence of applying a fixed treatment threshold in a continuously screened population for nearly 15 years.

Dr MacGregor and others point out that the mean diastolic pressure at the start of our study, measured under standard conditions, was lower than the mean diastolic pressure based on six casual pressures (91 mm Hg *v* 93 mm Hg). This difference was due to the inclusion of five patients who while meeting our entry criterion subsequently had much lower pressures than the rest. We think that this may have been due to the use of inappropriate cuff size when measuring blood pressure in obese arms (contrary to our recommended practice for routine measurements in the health centre) because these five patients were much heavier than the others (mean weight 95 kg *v* 71 kg). It is interesting that four of these five patients were unable to reduce their sodium intake below 120 mmol a day because it means that our principal finding of no difference in blood pressure (140/87 mm Hg *v* 140/86 mm Hg) despite a substantial difference in sodium excretion (59 mmol *v* 139 mmol) applies to patients of normal adult weight and with the highest pressures in our study. Their initial pressures were 144/93 mm Hg based on six casual readings and 152/94 mm Hg based on two standard measurements at the start of the study. Irrespective of the pressures that were recorded during the trial these initial pressures cannot be described as a "normal level of blood pressure."

Dr MacGregor and others point out that at this pressure moderate sodium restriction might be expected to reduce pressure by only 3-5 mm Hg; they further suggest that this reduction would be obscured by the large background fall in pressure observed during the study. We designed the study to have a 90% chance of detecting a fall of 3 mm Hg due to sodium restriction, however, and the very purpose of the crossover design was to estimate the effect of sodium restriction independently of any overall change between the first and second four week periods. In any case most of the background fall occurred between the baseline and first trial period, not between the two trial periods.

Dr MacGregor and others ask for further information on the two patients whose blood pressure was 9 mm Hg higher during the period on placebo. They were a 52 year old miner and a 62 year old housewife, who both started the trial on placebo. Their 24 h urinary sodium excretions were 40 mmol and 38 mmol respectively while taking placebo and 110 mmol and 118 mmol respectively while taking slow sodium. There were no significant changes in potassium excretion.

We note that Dr MacGregor and others do not dispute our opinion that initial pressures in their study must have been higher than the published figures of 156/98 mm Hg supine, 155/108 mm Hg standing. In summary,

the two studies provide opposite findings but in patients with different levels of blood pressure. It is not good enough for Dr MacGregor and others to recommend that a reduction in sodium intake and a range of other non-pharmacological approaches "may well be worth trying." More evidence is required.

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¹ MacGregor GA, Markandu NDD, Best FE, *et al*. Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. *Lancet* 1982;i:351-4.

² Management committee of Australian therapeutic trial in mild hypertension. Untreated mild hypertension. *Lancet* 1982;i:185-91.

Ampicillin and alternatives

SIR,—We agree with Dr A Dyas and Dr R Wise (19 February, p 583) that agents which achieve higher serum and therefore higher sputum concentrations might have an advantage over ampicillin in the treatment of chest infections. This was the logic behind our open pilot study of 3 g oral amoxycillin twice daily, which was safe and improved (symptoms and lung function) 11 out of 17 chronic sputum producers who were "highly selected" for severity of bronchiectasis refractory to previous treatment.¹ In this particular condition the logic lies in the clinical observation that treatment with conventional doses fails and parenteral treatment is often required and in the hypothesis that chronic lung scarring impedes access of antibiotic to the luminal site of persistent microbial flora uneliminated by impaired host clearance mechanisms. The same approach cannot be advocated in mild chronic bronchitis related to tobacco smoke, which we consider to be a different condition in which clinical resolution of infective exacerbations usually occurs with most antibiotics. Nor do we think that antibiotic concentration in bronchial secretions is necessarily relevant to treatment of acute infections of the normal respiratory tree.

In contrast with the finding by Leigh *et al*² that 17.5% of patients with urinary tract infections had diarrhoea after a single 3 g oral dose of amoxycillin we have seen only two such cases in more than 100 patients with bronchiectasis treated twice daily for 48 hours or longer. Patients prefer this regimen to previous hospital admission, often for parenteral treatment.

We disagree with the conclusions regarding the cost of amoxycillin. When chronic bronchial sepsis is considered patients studied two hours after 3 g oral amoxycillin achieved a mean serum concentration one and a half times that achieved by a subsequent equal dose of ampicillin. More importantly, the mean sputum concentration was five times greater. Although we need to determine exactly how high the concentration must be in the bronchial secretions of these patients to achieve the "gold standard" of clinical response, it must exceed at least the minimum inhibitory concentration for the organisms—and in a number of patients who lack normal respiratory defences it should exceed the minimum bactericidal concentration. Since laboratory minimum inhibitory concentrations probably underestimate the *in vivo* minimum

inhibitory concentration,² to achieve this goal with ampicillin (were it possible at all) would require such a massive oral dose as to cause side effects or incur equal or greater cost.

With respect to comparison of the regimen of 3 g oral amoxycillin twice daily with conventional dosage our retrospective study³ of the cost incurred by 58 patients responding to the former for infective exacerbations during one year indicated a saving both in the cost of drugs and beds when compared with the cost of treatment with conventional dosage during the previous two years—due to longer remissions, shorter milder episodes, and shorter less frequent hospital admissions. The real cost of treatment must, therefore, be more carefully considered than by a cursory glance at the cost of molar drug equivalents or of empirical courses, the duration of which seems more often plucked from the sky than based on logic. As Dr D Young wrote (5 March, p 799): "Good medicine is cheaper than bad."

May we respectfully suggest that the last sentence of Dr Dyas's and Dr Wise's leading article might be amended in the instance of severe chronic bronchial sepsis to read: "And if cost is a consideration amoxycillin in appropriate dose is probably the one to choose."

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¹ Cole PJ, Roberts DE, Davies SF, Knight RK. A simple oral antimicrobial regimen effective in severe chronic bronchial suppuration associated with culturable *Haemophilus influenzae*. *J Antimicrob Chemother* 1983;11:109-13.

² Leigh DA, Marriner J, Fabb S. Treatment of domiciliary urinary tract infections with a single dose of amoxycillin. *J Antimicrob Chemother* 1980;6:403-5.

³ Cole PJ, Roberts DE. High dose antibiotic is logical, effective and economical in treatment of severe bronchial sepsis. *Lancet* 1983;i:248-9.

Pneumocystis pneumonia

SIR,—We read with interest your leading article on pneumocystis pneumonia (12 February, p 499). We have measured sulphamethoxazole concentrations in the plasma of 14 patients receiving high dose co-trimoxazole (mean dose of sulphamethoxazole (SD)=85(13.9) mg/kg/day) for presumed pneumocystis pneumonia. Mean age was 16.05 (14.5) years. Eleven patients had acute lymphoblastic leukaemia, two were undergoing haemodialysis, and one had undergone renal transplantation.

Treatment was given for 11.2(4.4) days. Mean steady state free sulphamethoxazole concentrations of 212(66) mg/l were recorded. These concentrations are considerably higher than the 100 mg/l of free sulphamethoxazole reported by Winston *et al*¹ to be the optimal concentration for treatment. They are also at variance with the data sheet recommendation that treatment should be interrupted if the concentration of total sulphamethoxazole (drug and metabolite) exceeds 150 mg/l. One of the patients reported by McKenna *et al*² responded only to very high doses of co-trimoxazole.

As might be expected there was a higher incidence of side effects. Nausea and vomiting occurred in five patients, and bone marrow toxicity in three, though the latter could not be definitely attributed to the co-trimoxazole

as other drugs potentially toxic to the bone marrow were being taken.

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²McKenna F, Davison AM, Giles GR. Response of pneumocystis carinii pneumonia only after high-dose Co-trimoxazole. *Lancet* 1982;i:174.

Failure patterns after total hip arthroplasty

SIR,—Although we share Dr J E Charlton's enthusiasm for local anaesthesia during major hip surgery (5 February, p 476) and also advocate the use of intrathecal narcotics for postoperative pain relief,¹ we consider that the note of caution sounded by Dr D P Cartwright (26 February, p 721) is justified. Apart from the study by McLaren *et al*² no other workers have been able to show such unfavourable results when general anaesthesia is compared with spinal anaesthesia. Indeed, Wickström *et al*³ were unable to find any difference in mortality after surgery for hip fracture in women geriatric patients when five anaesthetic methods were compared.

We should recognise that elderly patients with hip fractures do not constitute a population that can be compared with patients having total hip replacement for osteoarthritis. Reduction in the incidence and extent of deep vein thrombosis may not automatically reduce the frequency of fatal pulmonary embolism. In the past year of about 300 patients having hip arthroplasty in our service five have died in the first three postoperative months. Three of these patients had spinal and two general anaesthesia. Although there may be some selection of poorer risk patients for spinal anaesthesia, these are still in the minority and the figures do not support moves toward a radical change in anaesthetic practice as suggested in the last paragraph of Dr Charlton's letter.

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²McLaren AD, Stockwell MC, Reid VT. Anaesthetic techniques for surgical correction of fractured neck of femur. A comparative study of spinal and general anaesthesia in the elderly. *Anaesthesia* 1978;33:10-4.

³Wickström I, Holmberg I, Stefansson T. Survival of female geriatric patients after hip fracture surgery. A comparison of five anaesthetic methods. *Acta Anaesthesiol Scand* 1982;26:607-14.

Is serum γ -glutamyltransferase a misleading test?

SIR,—The recent review of serum γ -glutamyltransferase (12 February, p 531) is to be applauded but for one notable omission which would add to Mr R Penn's and Dr D J Worthington's conclusion that measurement of this enzyme is of limited diagnostic value. I refer to the observation that serum γ -glutamyltransferase activity is raised in some

patients with active rheumatoid arthritis. Reports on the incidence and cause of raised serum γ -glutamyltransferase activity in rheumatoid arthritis are conflicting, but they are agreed in so far as concentrations can be raised independently of drug treatment.

Mr Penn and Dr Worthington referred to the problems of defining normal serum ranges for γ -glutamyltransferase, and this has probably contributed to the discrepancies in results relating to rheumatoid arthritis. Lowe *et al*¹ used 6-28 units/l for men and 4-18 units/l for women and showed raised serum γ -glutamyltransferase activity in 77% of patients. A later report² using the same normal range limits indicated that 62% of patients with seropositive rheumatoid arthritis had raised serum γ -glutamyltransferase values compared with 43% with seronegative rheumatoid arthritis and 38% with ankylosing spondylitis. Spooner *et al*,³ however, used 1-35 units/l as their normal range for both sexes and found that 23% of their patients with rheumatoid arthritis had raised serum γ -glutamyltransferase values.

In addition, the patients reported by Spooner *et al* may have had less active disease (mean erythrocyte sedimentation rate 32 mm in the first hour) than those reported by Lowe *et al* (mean erythrocyte sedimentation rate 47 mm in the first hour). This may also contribute to the different figures since there may be some correlation between serum γ -glutamyltransferase values and disease activity.¹ Furthermore, liver involvement in some patients with rheumatoid arthritis is well recognised, but raised serum γ -glutamyltransferase is not necessarily a reflection of this.³

Serum γ -glutamyltransferase values are undoubtedly raised in some patients with active rheumatoid arthritis but the origin and significance of this remains unclear.

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¹Lowe JR, Pickup ME, Dixon JS, *et al*. Gamma glutamyl transpeptidase levels in arthritis: a correlation with clinical and laboratory indices of disease activity. *Ann Rheum Dis* 1978;37:428-31.

²Dixon JS, Bird HA, Wright V. A comparison of serum biochemistry in ankylosing spondylitis, seronegative, and seropositive rheumatoid arthritis. *Ann Rheum Dis* 1981;40:404-8.

³Spooer RJ, Smith DH, Bedford D, Beck PR. Serum gamma-glutamyltransferase and alkaline phosphatase in rheumatoid arthritis. *J Clin Path* 1982;35:638-41.

Sun beds

SIR,—Dr J L M Hawk (29 January, p 329) mentioned that skin cancers may develop in mice after continuous exposure to high doses of ultraviolet A. This statement was based on a study by Urbach *et al*¹ showing that ultraviolet A and ultraviolet B induced tumours more rapidly than ultraviolet B alone. But the authors later attributed this tumour enhancing effect of ultraviolet A to differences in dose delivery rather than to differences in the ultraviolet spectrum.² Until recently it has been assumed that ultraviolet A given intermittently in doses equivalent to those occurring in nature is not carcinogenic,³ and one study has shown that small doses of ultraviolet A might inhibit ultraviolet B induced skin tumours in mice.³ Based on these findings it has been stated that the use of potent artificial radiant sources of

ultraviolet A for cosmetic purposes does not carry any risk for the human skin.⁴

We have studied the carcinogenic effect on hairless mice of ultraviolet A irradiation in doses used in human solariums.⁵ Nine months of ultraviolet A irradiation alone induced no tumours. The combination of artificial ultraviolet sunlight (ultraviolet A and ultraviolet B) and subsequent ultraviolet A irradiation for 2-6 months, however, increased the tumour incidence about threefold as compared with artificial ultraviolet sunlight alone. This tumour enhancing effect of the radiation from the ultraviolet tubes with emission spectra similar to those used in human ultraviolet A solariums might, however, be partly or totally due to the small ultraviolet B component (below 320 nm) emitted by the ultraviolet A bulbs. In a recent study, however, we have shown a tumour enhancing effect (at a reduced level) when the ultraviolet A radiation was filtered through window glass to eliminate the radiation below 320 nm.

People using ultraviolet A solariums for tanning purposes have probably been exposed previously to a great deal of natural sunlight and, therefore, it may be that ultraviolet A irradiation in large "solarium like doses" is not as innocuous to the human skin as previously believed.⁴

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²Parish JA, Anderson RR, Urbach F, Pitts D. *UV-A: biological effects of ultraviolet radiation with emphasis on human responses to long-wave ultraviolet*. New York: Plenum Press 1978:165-8.

³Forbes PD, Davies RE, Urbach F. Experimental ultraviolet photocarcinogenesis: Wavelength interactions and time-dose relationships. *Natl Cancer Inst Monogr* 1978;50:31-8.

⁴Raab W. Die Wirkungen von langwelligem Ultraviolettlicht (UV-A) und von mittelwelliger Ultraviolettstrahlung (UV-B) auf die menschliche Haut. Ein kritischer Vergleich. *Z Hautkr* 1980;55:497-513.

⁵Staberg B, Wolf HC, Poulsen T, Klemp P, Brodthagen H. The carcinogenic effect of sequential artificial sunlight + UVA irradiation. Consequences for solarium "therapy"? *Arch Dermatol* (in press).

Double indemnity in oesophageal carcinoma?

SIR,—While the results of all forms of management of oesophageal carcinoma are depressing Mr R M Kirk (19 February, p 582) gives a gloomy representation of the role of resection. There could be no disagreement that an operative mortality of 30% is far too high, but it must be appreciated that this figure emerges from a comprehensive review of the published work over the last 30 years, including some patients treated in the 1940s.¹ In attempting to relate operative mortality of resection to alternative forms of management results currently obtained in Britain must be considered.

The last two decades have seen important advances in preoperative nutritional support, in operative techniques to minimise anastomotic leakage, and in postoperative management of such patients in intensive therapy units, with early elective ventilatory support, epidural analgesia, and thromboembolism prophylaxis. The application of these factors, accompanied by appropriate selection of those patients most likely to withstand and benefit from resection by virtue