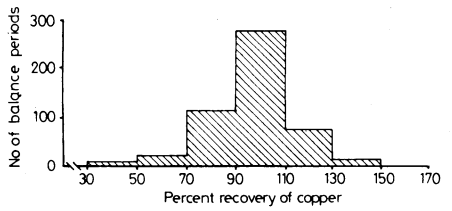

Percentage recovery of faecal copper during 515 four-day balance periods.

very small tendency for balance patients to be selected on the basis of more regular bowel habit, we regard it as highly unlikely that natural variation would cause the twofold to threefold rise above the upper limit of normal in four of our six patients. Furthermore, if one takes as null hypothesis that initial values were due to random anomalies of collection then it may be outside statistical probability that every subsequent one would show a decrease to ultimate normality.

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[1] Dick M. *Gut* 1969;**10**:408-12.

Primidone in essential tremor

SIR,—We read with interest the letter of Dr W R G Gibb (16 October, p 1119) on his experience with primidone in a patient with essential tremor and respiratory disease. Dr Gibb has suggested the possibility that suboptimal control of tremor in our patients was related to dose reduction necessitated by early toxicity of primidone. The reason why we discount this possibility will become clear when a full report of the data is available. In brief, in our first 14 patients with essential tremor studied under double-blind controlled conditions we have not found any correlation between reduction of tremor amplitude and serum concentrations of phenobarbitone or primidone. It seems that the variability between subjects in response observed is not simply due to "suboptimal" drug doses or serum concentrations but to a variation in individual response. A similar phenomenon has been observed in the responses of essential tremors to propranolol.[1] The one patient who failed to respond in our initial study was able to tolerate maximum doses of primidone, and the serum concentrations of phenobarbitone and primidone were at the upper end of the range of concentrations for this group of patients. Incidentally, this patient was unresponsive to propranolol.

We have found that a very slow rate of increment of primidone in patients with essential tremor reduces the dose-related side effects. Four of our patients, however, have shown acute toxic reactions with the first 62·5 mg dose. It may be that pretreatment with another anticonvulsant to induce hepatic enzymes may reduce dose-related side effects[2]; however, the acute toxic effects that may occur with extremely small doses of primidone do so before any appreciable changes in liver metabolism could occur.

As yet there are no controlled studies to establish whether the concurrent use of beta-blocker and primidone is additive or synergistic in the control of essential tremor. We have observed patients anecdotally whose tremor is best controlled when both drugs are used together.

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[1] Sorensen PS, Paulsen OB, Steiness E, Jansen EC. *Ann Neurol* 1981;**9**:53-7.
[2] Feely M. *Br Med J* 1981;**282**:740.

Cyclosporin A as prophylaxis against graft-versus-host disease

SIR,—We read with interest the article by Dr A J Barrett and others on cyclosporin A and bone marrow transplantation (17 July, p 162). The authors emphasised the side effects of cyclosporin A, particularly renal toxicity and hypertension, and found a strong correlation between diastolic blood pressure, blood urea concentration, and serum cyclosporin A concentration. They gave no data about the timing of these phenomena, however, nor about the causes, although they propose that fluid retention was important.

We have been using cyclosporin A since 1978 to prevent graft-versus-host disease after allogenic bone marrow transplantation.[1] In the last 49 patients in whom these data were available we studied diastolic blood pressure, fluid balance, and weight changes after the graft, as well as urea concentration, cyclosporin A values, and cyclosporin A cumulative doses. All patients received bone marrow transplantation for leukaemia after conditioning with total body irradiation and cyclophosphamide. Their ages ranged from three to 46 years (mean 25·2). Cyclosporin A was started the day before the graft and given for the first five days either intramuscularly (12·5 mg twice daily) or orally at 6·25 or 18·5 mg/kg twice daily. It was then continued in a standard oral dose of 6·25 mg/kg twice daily, and later adjusted according to renal function or serum concentrations. Twenty-nine of the 49 patients (aged 7-46 years, mean 28) had a diastolic blood pressure which remained within the normal range during the first 30 days after the graft (< 90 mm Hg for adults, < 70 mm Hg for children under 10). Twenty patients (aged 3-39, mean 22 years) at some time during the 30 days after transplantation had a raised diastolic blood pressure, and these patients showed evidence of fluid retention which correlated with a rise in blood urea concentration (table). We could not find a direct correlation between blood pressure and cyclosporin A concentration, but the group of patients with hypertension had higher cumulative doses of cyclosporin A during the first 30 days after transplantation than the patients with normal blood pressure. We have previously described a correlation between cyclosporin A cumulative doses and urea concentrations.[2]

Nephrotoxicity is a major side effect of cyclosporin A, and renal impairment may well cause fluid retention and hypertension. This is probably not, however, the only factor in producing hypertension. In our study patients who received HLA/MLR mismatched grafts tended to have higher blood pressures than recipients of matched grafts, and they also had higher urea concentrations, although cyclosporin A cumulative doses were the same. Age may also be a factor in that patients with hypertension were younger (mean 22·1 ± 2·6 years) than patients without hypertension (28 ± 2·1 years).

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[1] Powles RL, Clink HM, Spence D, *et al. Lancet* 1980;i:327-9.
[2] Hedley D, Powles RL, Morgenstern GR. In: White D, Powles RL, McMasters P, *et al*, eds. *The proceedings of an international symposium on cyclosporin A.* Amsterdam: Elsevier, 1982.

Changes in diastolic blood pressure, urea concentration, fluid balance, and cumulative dose of cyclosporin A in 49 patients before and after renal transplantation (29 without hypertension, 20 with)

Days after transplantation		−3	10	25
Diastolic blood pressure (mm Hg) (mean ± SE)	Group 1	66 ± 1	71 ± 1	75 ± 2
	Group 2	65 ± 1	77 ± 2	91 ± 1
Urea concentration (mmol/l) (mean ± SE)	Group 1	3·2 ± 0·3	8·9 ± 1·7	7·8 ± 1·4
	Group 2	3·4 ± 0·2	9·4 ± 2·0	13·8 ± 3·0
Cumulative fluid balance (l) (mean ± SE)	Group 1	0	2·9 ± 0·6	6·3 ± 0·7
	Group 2	0	3·8 ± 0·5	9·1 ± 1·1
Cumulative dose cyclosporin A (mg/kg)	Group 1	0	223 ± 17	482 ± 35
	Group 2	0	277 ± 18	605 ± 49

Group 1: 29 patients without hypertension; Group 2: 20 patients with hypertension.
Conversion: SI to traditional units—Blood urea: 1 mmol/l ≈ 6 mg/100 ml.

Attendance at a breast screening clinic

SIR,—I was interested in the paper by Mr K French and others on the problems associated with attendance at a breast screening clinic (28 August, p 617). In a study of patients with breast cancer referred to this department we found that about half of all patients had consciously delayed seeking treatment. This agrees closely with similar findings in a Canadian study (Elwood M, personal communication). If patients with manifest disease delay seeking medical help perhaps it is hardly surprising that women without symptoms may sometimes be reluctant to visit a screening clinic. Moreover, since health is a positive concept rather than merely the absence of symptoms or disease vigorous healthy active individuals may be even less likely to dwell on the prospect of developing cancer.

In a separate study we have also noted that patient delay is not related to the level of education (doctors are notorious patients). This being so, educational measures are unlikely to make a substantial difference to the rate of attendance. Alternatively, we must redefine education in a broader context to include, for example, salesmanship or persuasion. But again, as your authors noted, we must first establish with certainty that we have a product to sell because cancer educators in the United States, who were previously enthusiastic, are now increasingly sceptical about the value of early diagnosis.[1] Until we are able to detect breast cancer in the very early microscopic stage current so-called early diagnosis may not necessarily be associated with increased survival. In such circumstances we may merely be extending