Beta-blockade and Myocardial Infarction

SIR,—Dr. K. M. Fox and his colleagues (18 January, p. 117) suggest that established beta-blockade may protect some patients from the development of myocardial infarction and that these drugs in no way prejudice the outcome in patients admitted to hospital with prolonged ischaemic myocardial pain. We suggest that the data presented are not sufficient to warrant their reaching these conclusions.

For the study to be accurately called "prospective," patient matching and follow-up should have started before the initiation of beta-blockade. Insufficient evidence is provided concerning the comparability of the treatment and control groups. It is quite possible that the prognostic composition of the two groups was different because it is not stated why the beta-blocked group was prescribed these drugs. Assuming that conventional indications, such as persistent angina or acute coronary insufficiency, were the reasons for treatment, the excess of "coronary insufficiency" in the beta-blocked patients might merely represent a continuation of the symptoms for which they were treated in the first place. Also, it is known that severity of previous infarction and perhaps cigarette smoking, hypertension, and other risk factors may be important determinants of prognosis, yet these factors were not mentioned in establishing comparability. Furthermore, without prospective follow-up we cannot even be certain that those on beta-blockers were not the survivors of a larger group of whom a significant number may have died before admission to hospital.

The authors have failed to guarantee the representativeness of the matched controls. Selecting the first consecutive 90 "matches" instead of a randomly selected subset from the total population of matching controls in the 251 remaining patients immediately prejudices the results of the study.

We wonder why the unconventional diagnoses "myocardial necrosis" and "coronary insufficiency" were used. Coronary insufficiency as defined by the authors is merely a symptom without objective confirmation and we feel that, as such, it is too "soft" an end-point to be acceptable in their study. If, as we contend, "coronary insufficiency" is not an acceptable end-point, their table I becomes meaningless.

The authors' groups do not include patients with the widely accepted diagnosis of acute coronary insufficiency, where typical cardiac pain is associated with serial ST-T changes without enzyme elevation. In our experience such patients make up about 20% of all cases of acute coronary heart disease admitted to the coronary care unit.

We believe that table II has been misinterpreted. The data, as reproduced in our table, do not support the conclusion that there was a significant excess of total late cardiac failure in the control group. A more searching analysis using a log-linear model

approach also failed to support this conclusion.

The mortality data provided by the authors are insufficient for analysis. If, as seems likely from table III, only the patients with myocardial infarction died, then the myocardial infarction mortality for the beta-blocked patients was 9/30 (30%) compared with 10/62 (16.1%) for the control group. This is not compatible with the conclusion that beta-blockers in no way prejudice the outcome in patients with coronary heart disease.

Though we do not deny that established beta-blockade "may protect some patients from . . . myocardial infarction and so enhance their long-term prognosis," more evidence will be needed before we are entitled to recommend the prophylactic use of beta-blockers. It will take a prospective randomized control trial to provide such evidence.—We are, etc.,

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SIR,—In their paper (1 February, p. 259), Dr. Jean M. Scott and her colleagues beg an important question by assuming that the haemoglobin concentration in pregnant women should be maintained by "prophylaxis" with iron at a level characteristic of non-pregnant women. The level itself is important only to the extent that it serves to diagnose anaemia, defined in the *Oxford English Dictionary* as "lack of blood" and characterized in physiological terms as an inadequate capacity for the transport of oxygen by the red cells.

The haemoglobin concentration is determined by two quantities which are physiologically independent. One is the total volume of red cells, which usually increases during pregnancy without the stimulus of extra iron,¹ thereby increasing oxygen transport capacity, and presumably in excess of oxygen consumption because the arteriovenous P_{O_2} difference at the heart is reduced.² The other quantity is the plasma volume, which increases by nearly 50%¹ and provides inter alia for increased renal plasma flow³ and the increased blood flow in skin.⁴ The relatively greater increase of plasma volume causes the concentration of haemoglobin to fall by up to 2 g/dl in venous blood. The difference may be greater in the capillary blood of pregnant women.⁵ It is of interest that in "poor reproducers" the increase of plasma volume and of glomerular filtration rate is less than normal, and that birth weight may be inversely correlated with the lowest haemoglobin concentration reached.⁶ In a non-pregnant population the total circulating haemoglobin is loosely correlated with the haemoglobin concentration, but this association is inevitably weakened during pregnancy by the greater variability of plasma volume. Therefore the haemoglobin concentration becomes less satisfactory during pregnancy as an indicator of "anaemia," and a lower haemoglobin level by no means necessarily implies a reduced capacity for transporting oxygen.

Many haematologists argue that the fall in haemoglobin levels during pregnancy should nevertheless be eliminated, or at least minimized, by universal prophylaxis with iron medication. Such disregard of altered physiology may be bad medicine. The depression of haemoglobin concentration is only one of many physiological adaptations that characterize normal pregnancy and which, in the absence of any evidence to the contrary, may be presumed to create a desirable environment for the product of conception. On this basis it could be harmful to force up the haemoglobin concentration in peripheral blood to levels which are not physiological during pregnancy. To do so is no more logical than, for example, to "correct" the reduced albumin concentration in plasma by giving supplementary protein or, for that matter, to suggest that mothers should protect themselves against lowered P_{CO_2} levels by wearing paper bags over their heads.

That having been said, we accept that the risk of true anaemia, though small in Britain, is increased during pregnancy. Further research is needed to establish reliable diagnostic criteria and efficient screening mechanisms. An Expert Committee of W.H.O.⁷ pointed out that "the indiscriminate issue of iron preparations as a routine to all pregnant women in situations where there is no indication for them is to be deplored. It is not merely wasteful; it also impedes research upon the problem and a more rational approach to the prophylaxis and treatment of anaemia."—We are, etc.,

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Magnesium Depletion and Digoxin Toxicity

SIR,—Your recent leading article (25 January, p. 170) draws attention to magnesium depletion in patients on long-term diuretic therapy and the possible effect such depletion may have in patients concomitantly taking digoxin.

We have measured plasma and erythrocyte levels of magnesium by atomic absorption spectrophotometry¹ in a group of 80 unselected patients aged 23–88 (mean 59) years receiving digoxin maintenance therapy and in 22 healthy controls receiving no medication. Plasma digoxin measurements were made by radioimmunoassay. The results (mean values ± 1 S.D.) are shown in the table.

Among the patients, nine (11.2%) were considered to be showing definite or possible symptoms of digoxin toxicity and the mean plasma digoxin levels in the toxic and non-toxic groups were significantly different ($P < 0.0005$, Student's *t* test). The mean plasma levels of magnesium were not significantly different between the controls and either of the patient groups or between the digoxin-toxic and non-toxic patients ($P > 0.1$). The mean erythrocyte magnesium levels

Re-analysis of Table II of Fox et al. after Collapsing the Diagnosis Dimension in Order to Isolate the Marginal Effect of Type of Heart Failure

Subject	Heart Failure Classification			Total
	Early	Late	None	
Control group . .	19 (21.11)	13 (14.44)	58 (64.44)	90 (100)
Beta-blocker group . .	16 (17.78)	6 (6.67)	68 (75.56)	90 (100)
Total	35 (19.44)	19 (10.56)	126 (70.00)	180 (100)

Figures in parentheses represent percentages. $\chi^2 = 3.63$; D.F. = 2; $P > 0.05$.

	Patients		Controls (n = 22)
	Toxic (n = 9)	Non-toxic (n = 71)	
Plasma digoxin (nmol/l)	2.91 ± 0.90	1.42 ± 0.82	—
Plasma magnesium (mmol/l)	0.885 ± 0.11	0.83 ± 0.11	0.855 ± 0.06
Erythrocyte magnesium (mmol/l)	2.215 ± 0.345	2.32 ± 0.365	2.085 ± 0.225

Conversion: SI to Traditional Units—Plasma digoxin: 1 nmol/l ≈ 0.78 ng/ml.
Plasma and erythrocyte magnesium: 1 mmol/l ≈ 2 mEq/l.

were higher in both patient groups than in the controls but were significantly higher only in the non-toxic group ($P < 0.01$). There was no significant difference in mean erythrocyte magnesium levels between the two patient groups.

Diuretic therapy was documented in 33 of the patients; the mean plasma and erythrocyte magnesium levels in this group were 0.8 ± 0.07 and 2.275 ± 0.27 mmol/l (1.6 ± 0.14 and 4.55 ± 0.54 mEq/l) respectively. Both measurements were significantly different from the control values, the plasma level being lower and the red cell level higher ($P < 0.005$).

Our results suggest that though diuretic therapy does cause a lowering of mean plasma magnesium levels (by 6.4%) the reduction is only slight. This does not necessarily indicate an insignificant depletion of tissue stores, it merely reflects the inadequacy of sampling the plasma compartment. Erythrocyte measurements of magnesium, despite an approximately 3:1 concentration ratio compared with plasma, are not appropriate for the detection of magnesium depletion since digoxin therapy appeared to produce an increase in mean concentration of the ion, possibly by alterations in Na^+/K^+ ATPase activity in red cell membranes.

The absence of any correlation between plasma magnesium concentration and the incidence of digoxin toxicity suggest that the routine measurement of this ion is of little assistance in the detection of digoxin toxicity, the plasma digoxin assay being of much greater value. However, plasma magnesium should be one of the measurements made in cases of equivocal digoxin toxicity complicated by an apparently normal plasma digoxin level. It has even been demonstrated recently² that digitalis-induced ventricular arrhythmias can be abolished by magnesium chloride treatment in the presence of normal plasma magnesium levels.—We are, etc.,

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Dementia Associated with Clonidine Therapy

SIR,—We have noted recently an interesting side effect of clonidine in one of our patients.

A 74-year-old man being treated satisfactorily for hypertension with debrisoquine 80 mg a day, bendrofluthiazide 2.5 mg daily, and clonidine 0.1 mg three times a day, with a past history of depression on methyldopa, developed dementia approximately five months after starting clonidine. This was manifest by loss of memory, unsteadiness

of gait, drowsiness, aggressive behaviour with a change in personality, and urinary incontinence.

He was admitted to hospital for investigation. Routine investigations and an E.E.G. were normal. Approximately one week after clonidine was withdrawn he showed marked improvement. His blood pressure was then controlled on a small dose of debrisoquine, methyldopa, and a diuretic. He was seen two months later in the outpatient department and had made a complete recovery and was back to his usual self.

So far as we know, transient dementia has not before been reported with clonidine.—We are, etc.

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Teaching and the Patient

SIR,—The practical training of medical students inevitably involves some invasion of patients' privacy. The Patients Association is anxious that patients should suffer as little mental distress and physical discomfort as possible and we think that improvements in medical teaching methods could and should be made with this objective in mind.

We believe that the direct involvement of patients should be reduced to the minimum compatible with good teaching by the use of all possible aids and devices, and that when it is necessary for students to see patients ideally this should be on a one-to-one basis. We should be grateful to receive comments from any of your readers who have views on how these objectives could best be achieved.

Following discussions with the Department of Health and Social Security we think it might be possible to obtain a grant for research into this subject and we should be glad to hear from anyone who would be interested in carrying out or co-operating in such a project. The aim would be to investigate and demonstrate the extent to which the ideal can be achieved in practice.—I am, etc.,

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Aetiology of Chronic Renal Failure and Renal Osteodystrophy

SIR,—Dr. J. F. Moorehead and his colleagues (7 December, p. 557) suggested that patients with polycystic disease were less likely to develop erosions of bone than other patients with chronic renal failure during treatment with intermittent haemodialysis. This conclusion is at variance with a previous report¹ and with the findings from our own renal unit,² which suggested that poly-

cystic renal disease was not associated with a lower incidence of renal osteodystrophy.

It is not clear why the patients reported by Dr. Moorehead and his colleagues had such a low overall incidence of erosions when compared to that found in other centres. It seems probable, though details are not supplied, that the overall incidence of erosions of bone was half that found in our own population of dialysis patients in the Oxford area, which is nevertheless lower than that found in many other centres.³ Our own findings² suggested that patients with interstitial nephropathy may have a greater incidence of osteitis fibrosa. While their report suggested that the incidence of erosions was low in the polycystic group of patients, they did not compare these figures with those from the remaining patients when subdivided according to the aetiology of their renal disease. The manner in which this factor biased their control group of patients is therefore unclear.

Their conclusion that erosive bone disease was not progressive in these patients may also be unjustified on the evidence presented. A cohort of 53 patients were studied to demonstrate that the natural history of renal osteodystrophy on dialysis was not biased by a diminishing population of patients with time. However, this tactic was apparently not carried out on the polycystic patients. A further source of bias could be that their patients with polycystic disease were studied for a shorter period of time than their control patients. In the control population a marked increase of erosions occurred principally after the sixth year of dialysis. None of the patients with polycystic disease was studied for a comparable length of time. Furthermore, the finding of differing incidences of erosions with time could also result from changes in their dialysate calcium.⁴ Thus more control patients (treated for longer periods) would have been exposed longer to lower concentrations of calcium in the dialysate fluid.

We therefore feel unable to support the view that polycystic disease protects against the development of erosions.—We are, etc.,

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Abortion Service

SIR,—Mr. D. B. Paintin and Professor R. W. Beard in their review of the remarkable tape recordings in *Babies for Burning* (8 February, p. 340) use the phrase "In concentrating on the 'sanctity' of the life of the fetus they [the authors] disregard the well-documented evidence that the unwanted baby and her mother may be condemned to a way of life that we regard as unacceptable these days." Now, dear reviewers, give us the evidence for this thesis.—I am, etc.,

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