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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Anaemia in Pregnancy

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; $P > 0.05$.