SIR,—It gives confidence to read in the article by Dr P Curtis (27 December, p 747) that patients on long-term digoxin medication in general practice remained fairly well despite the apparent inadequacy of monitoring of most patients by the doctors. Although "the correct use of digitalis is a clinical art which can only be learned at the bedside," I do not agree with the conclusion "that estimating serum digoxin in general practice is of little value as a measure of the quality of care." The measurement of serum digoxin levels in cases of obesity, leanness, and renal failure, for example, after a fortnight of the best estimated digoxin maintenance dose will prevent long-term under- or over-digitalisation. Generally a serum digoxin level of 1·3-2·6 nmol/l (1-2 ng/ml) will do. Only in the case of severe congestive heart failure, superventricular tachycardia, etc, will higher levels be necessary.

With regard to the poor correlation between toxic levels of digoxin and clinical symptoms of toxicity (two out of 12 patients with levels higher than 2·6 nmol/l (2 ng/ml)), which is in contrast to observations by others,[1] three remarks should be made. Firstly, blood samples were obtained about five hours after the morning dose of digoxin. This is rather early. Generally it is assumed that only after at least six hours does the distribution phase of digoxin come to an end[2]; recently even 16 hours has been mentioned.[3] Secondly, Dr Curtis does not mention which radioimmunoassay method or kit was used. Systematic errors between radioimmunoassays have been documented.[4] Thirdly, a higher digoxin level increases only the *risk* of toxic symptoms.

In short, I feel that digoxin levels should be measured in doubtful cases in conformation to pharmacokinetic principles.

W J F VAN DER VIJGH

Department of Clinical Pharmacology,
Free University,
Amsterdam

[1] Smith, T W, *Circulation*, 1972, **46**, 188.
[2] Zeegers, J J W, *et al*, *Clinica Chimica Acta*, 1973, **44**, 109.
[3] Kramer, W G, *et al*, *Journal of Pharmacokinetics and Biopharmacology*, 1974, **2**, 299.
[4] Boink, A B T J, *Pharmaceutisch Weekblad*, 1974, **109**, 674.

Trental and peripheral vascular disease

SIR,—I read with interest the full-page colour advertisement for Trental (oxpentifylline) tablets which has been included in a number of recent editions of the *BMJ*. Hoechst claim that "Trental offers a totally different action from any other treatment in this field"—that is, peripheral vascular disease. This drug apparently increases blood flow by lowering blood viscosity and is also claimed to restore red cell flexibility and inhibit platelet aggregation.

The evidence for the beneficial action of oxpentifylline is scanty and merits further attention. Two publications demonstrate that this drug lowers blood viscosity, but only when given intravenously.[1 2] The evidence that it restores red cell flexibility is based solely on one investigation in which blood was filtered through 8-μm pores.[3] As erythrocytes have a mean diameter of 7 μm one would not expect this system to measure erythrocyte flexibility. Only two clinical double-blind studies, both using very small numbers of patients, seem to have been carried out. The first, which remains unpublished since 1972, suggested that oral oxpentifylline increases blood flow.[4] The second showed an improvement in claudication distance.[5]

It is encouraging to see that drug companies are looking for a new approach to the problem of vascular disease. However, the launching of powerful sales drives for compounds for whose effectiveness and mode of action there is very limited and incomplete evidence may bring these possibly valuable new approaches into disrepute.

A J BARNES

Department of Endocrinology,
Royal Postgraduate Medical School,
Hammersmith Hospital,
London W12

[1] Hess, H, Franke, I, and Jauch, M, *Fortschritte der Medizin*, 1973, **91**, 743.
[2] Heidrich, H, and Ott, M, *Herz Kreislauf*, 1974, **6**, 542.
[3] Ehrly, A M, *IRCS Medical Science*. In press.
[4] Baitsch, R, unpublished observations, 1972.
[5] Bollinger, A, in press.

Aetiology of anencephaly and spina bifida

SIR,—We are interested in the comments Dr J H Elwood (24 January, p 218) made about our paper (27 December, p 743) in which we suggested that previous miscarriage was a possible cause for anencephaly and spina bifida (ASB). He points out that an argument against this hypothesis is that ASB is common in first pregnancies. We agree, but the recall of a miscarriage by a woman will vary for several reasons. It may represent an accurate history, it may be biased because the child *has* ASB, or it may have occurred so early that it has passed unnoticed. Dr Elwood's figures show a non-significant reduction in the incidence of para-0 ASB mothers—he found only 25% of total ASB births, whereas, taking all births, about 30% are primiparae. This small difference, if not due to chance, is consistent with either biased reporting or a real effect, since if there is a history of miscarriage the woman will move from the category of para 0 to para 1.

Two other relevant aspects of the problem have become known to us since we published our paper. Firstly, Stevenson (personal communication) and Stevenson and McClarin[1] have pointed out that they have detected living villi in curettage material as long as 10 weeks after a miscarriage, confirming the persistence of rests. Secondly, Smith[2] suggests that α-fetoprotein (AFP) plays a role in the normal structural development of the organism and that lack of it causes various types of congenital abnormality in man. Furthermore, his experiments on rats demonstrated that similar effects can be produced by injecting them with anti-AFP.

More recently Mizejewski and Grimley[3] have demonstrated that anti-AFP has abortogenic activity in mice. They did not obtain congenital malformations, but the antibody was given late in pregnancy. Since Leek *et al*[4] have shown that trophoblastic material can produce AFP, it is just possible that a rest could initiate anti-AFP (though the antibody is apparently not known in normal pregnancies[5] which could damage the next baby. The difficulty with this hypothesis is that one would expect subsequent children also to be affected unless the antibody production normally falls off and is not always restimulated sufficiently rapidly by the next pregnancy. Furthermore, if does not explain the non-concordance in the twin data in ASB. The fact that there are high mean values of AFP in the mothers of affected children[6] does not necessarily contradict the anti-AFP hypothesis since the damage to the fetus will have been done early and the anti-AFP may not be sufficient to neutralise the AFP resulting from fetal leakage.

Whatever may be the truth of the matter, as a prospective investigation it seems worth testing maternal blood for fetal proteins, including AFP, and their corresponding antibodies after miscarriages, moles and normal births.

CYRIL A CLARKE
DEREK HOBSON
O M MCKENDRICK
P M SHEPPARD

Liverpool

S C ROGERS

Rugby

[1] Stevenson, A C, and McClarin, R H, *Nature*, 1957, **180**, 198.
[2] Smith, J A, *Lancet*, 1972, **1**, 581.
[3] Mizejewski, G E, and Grimley, P M, *Nature*, 1976, **259**, 222.
[4] Leek, A E, Kitau, M J, and Chard, T, *Lancet*, 1974, **2**, 1088.
[5] Adinolfi, A, Adinolfi, M, and Lessof, M H, *Journal of Medical Genetics*, 1975, **12**, 138.
[6] Leighton, P C, *et al*, *Lancet*, 1975, **2**, 1012.

SIR,—Sir Cyril Clarke and his colleagues (27 December, p 743), reporting on the results of an inquiry into the aetiology of anencephaly and spina bifida, conclude that the hypothesis which best accords with the facts is that residual trophoblastic material from a former pregnancy or a co-twin may react unfavourably with a subsequent fetus to produce these malformations. The debate has been continued by Dr J H Elwood (24 January, p 218), who discusses the possible role of genetic and post-conceptional factors and points out that 25% of children with these malformations recorded in Ireland were born to women pregnant for the first time.

This discussion has prompted a look at the data of an unpublished series of 164 anencephalic births recorded personally over some 30 years. It does not include instances of uncomplicated spina bifida, for indeed it is open to question whether anencephaly and spina bifida are causally identical conditions. If they were one would expect the minor lesion to be a more constant concomitant of the major than it is. In this series 64 (40%) of the anencephalics were born to primiparae of an average age of 23 years. Of these women, 52 had had no previous abortion; of the remaining 12, eight had had one or more early abortions and four had had late abortions previously. Of the 100 multigravidae, 86 had had no previous abortions and of the remaining 14, eight had had early abortions and six late abortions. The distinction is significant because late abortion is usually due to a fetal malformation rather than the random causes of early abortion. In the series there were seven instances of recognised recurrent anencephaly.

A genetic cause for anencephaly was first suggested by Penrose[1] by analogy with the work of Snell and Picken on anencephaly in the rat and perhaps receives support from the high incidence of the condition of young primiparae. That postconceptional factors may be responsible in addition is suggested by the abortion history of some of the mothers, though some of these may have been also due to malformations. It receives some support too from the 13 cases in the series in which anencephaly followed a sequence of at least five normal births.