is the gestation age of the fetus, and not the route by which termination is effected, as was also shown by Matthews.²

There is a national shortage of anti-D immunoglobulin, and while the risk may be small we cannot agree that there is no indication to give immunoglobulin in cases of therapeutic and spontaneous abortion. If rhesus sensitization is to be considered a preventable disease³ Rh-negative women having a termination of pregnancy should be afforded protection as soon as sufficient anti-D immunoglobulin is available. This is particularly true in primigravidae, where the postoperative fetal cell count is high and the termination is carried out late in pregnancy. There is no reason to condemn Rh-negative women to affected infants in a later marriage because they had a therapeutic abortion earlier.—We are, etc.,

E. A. M. NORMINGTON.

R. F. JENNISON.

St. Mary's Hospitals,
Manchester.

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SIR,—Your leading article on rhesus sensitization and abortion (11 October, p. 61) invites comment. It is stated, "Passage of fetal red cells is mainly associated with delivery, but smaller haemorrhages occasionally occur during pregnancy" (my italics). There is ample evidence in the literature that foeto-maternal bleeding occurs frequently during pregnancy.¹⁻³ Indeed, Cohen and her colleagues⁴ suggested that the intermittent entry of fetal cells into the maternal blood during pregnancy is so common as to be considered a physiological event.

I would also question the statement that "large haemorrhages through the placenta are common after its manual removal, after caesarean section, and in prolonged labour." In reviewing the literature on foeto-maternal bleeding it becomes clear that the natural tendency to report positive rather than negative associations may have resulted in the impression that all procedures likely to disturb the placenta result in significant foeto-maternal haemorrhage. There is evidence that this is not always the case. Montague and Krevans⁵ considered that foeto-maternal bleeding was the result of the indication for a section rather than because of the operation itself. In a recent prospective study of 200 primiparae 11 of our patients were delivered by caesarean section, and in these the incidence of fetal bleeding was not changed by the operation. Brown⁶ and Cohen *et al.*⁴ found no relationship between prolonged labour and foeto-maternal bleeding, and we confirmed this for the majority of cases in our study. We also found that in only one out of nine patients treated by manual removal of the placenta did a fetal bleed of more than 0.2 ml. occur in association with the procedure.

Although it is generally agreed that fetal bleeds associated with delivery may lead to sensitization, the evidence that they "usually initiate" the process is inconclusive. The Liverpool group⁷ have demonstrated an association between the size of transplacental haemorrhage and Rh iso-immunization, but

cases of immunization did occur in patients where few or no fetal cells were found in the maternal blood after delivery. Zipursky and his colleagues,⁸ and Cohen and Zuelzer¹⁰ believe that perhaps 50% of those women who become immunized are sensitized by small bleeds during their pregnancies. Subsequent to the early experiments quoted by your author, Zipursky and his colleagues⁹ have shown that intermittent fetal bleeds of only 0.1 ml. can result in sensitization. Thus the argument that abortion with curettage is unlikely to be a significant factor in Rh iso-immunization because fetal bleeds of 0.5 ml. or more are uncommon during the procedure is probably fallacious.—I am, etc.,

PETER JONES.

Royal Victoria Infirmary,
Newcastle upon Tyne.

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Delayed Phenytoin Idiosyncrasy

SIR,—Phenytoin (diphenylhydantoin) intoxication can be correlated with the concentration of the drug in the blood. Nystagmus develops when the blood level is 20 µg./ml. and ataxia when the level approaches 30 µg./ml.¹ Those who have a congenital enzymatic deficiency, and are thus unable to metabolize the drug, show a low tolerance and a high blood level as soon as treatment with phenytoin is inaugurated. Individuals who are able to metabolize the drug normally maintain their tolerance indefinitely. Idiosyncrasy may, however, appear with corresponding rise in the blood level of the drug following liver damage² or exposure to certain drugs, which include anticoagulants,³ chlorpromazine,⁴ and aminosalicilate and isoniazid.⁵

I wish to report that I have recently encountered several patients who, after many years of regular phenytoin treatment for epilepsy, developed signs of intoxication without any of these known provocative factors. Replacement of phenytoin by sulthiame abolished the ataxic gait and nystagmus. Three of the patients were seen in psychiatric and one in general hospitals.—I am, etc.,

SIMON BEHRMAN.

London W.1.

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Glyceryl Trinitrate and Angina

SIR,—It seems likely that glyceryl trinitrate relieves angina by a generalized peripheral vasodilatation with a resultant reduced load on the heart, as suggested in your leading article (1 November, p. 252). Forty-one years ago Merklen¹ suggested that the underlying cause of anginal pain was due to "sudden left ventricular distension." Bradycardiac angina occurs within one to two beats when the heart rate is halved.² The abrupt onset suggests that the pain is due to the sudden stretching of the ventricular wall. This theory of the causation of the pain is supported by the observation that the Valsalva manoeuvre will relieve angina at the same time that the heart shrinks.³

Today there is much study of the underlying mechanisms of disease which is praiseworthy. At the same time there is a prevailing but erroneous belief that all that can be found by simple bedside observation has already been discovered. It is an observed but little-known fact that occasionally angina may be aggravated or even precipitated by glyceryl trinitrate. This occurs when the angina is due to anaemia,⁴ and in some cases to bradycardiac angina.⁵—We are, etc.,

P. B. S. FOWLER.

HAMID IKRAM.

Charing Cross Hospital,
London W.C.2.

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Sudden Death after Exertion

SIR,—I should like to suggest that the primary cause of the defect described by Dr. R. C. R. Connor (4 October, p. 30) was a physiological failure of the cardiorespiratory reflex. In the normal subject severe exertion is literally brought to a standstill by the hyperventilation developed as a result of the build-up of carbon dioxide in the tissues. Until the oxygen debt has been paid off and the ventilation rate reduced no further demands can be made on the already over-stretched heart. Generally, the cut-out phase of human exertion is well within the limits of the heart, which is in consequence able to cope with the extra demands made on it during times of severe exertion.

In the case in question it is possible that the gradually increasing oxygen debt failed to effect the normal physiological response, and in the absence of hyperventilation a tremendous build-up of carbon dioxide and other metabolites occurred in the myocardium. This may or may not have been due primarily to the failure of the respiratory centre to respond to the normal stimulus of carbon dioxide. Eventually this was such as to give rise to acute cardiac failure and death from syncope.

I would venture to suggest that if beforehand this boy had been subjected to a full-scale lung function analysis a defect might have been found. Unfortunately there is often no evidence beforehand to suggest that such a catastrophe is in the bounds of pos-