Cyclone over Cyclamates

SIR,—In your leading article (1 November, p. 251) you point out that the decision to ban the manufacture of cyclamates has been taken without evidence that they cause disease in man, whereas the production of cigarettes, which are known to be highly dangerous, is less severely censored.

A curtailed consumption of cyclamates might well lead to a compensatory increase in the consumption of sugar, for which they are a substitute. Whereas cyclamates have produced no proved ill-effects in man, excessive sugar consumption is believed by many to be a major factor in the causation of much disease, including diabetes,¹⁻³ coronary disease,³⁻⁵ dental caries,⁶ and obesity.

Almost anything taken in gross excess is harmful.

Would the replacement of cyclamates by sugar not be tantamount to recommending a therapeutic procedure carrying a 10% mortality to treat a disease having a 1% mortality?—I am, etc.,

DENIS P. BURKITT.

Medical Research Council,
External Staff,
London W.1.

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Tests for Cancer

SIR,—Your leading article "Diagnostic Tests for Advanced Cancer" (11 October, p. 63) prompts us to make the following report.

The presence of an abnormal serum alkaline phosphatase band on starch gel electrophoresis in non-jaundiced patients with hepatic metastases was noted by Newton.¹ He thought this might prove a useful simple test in predicting hepatic malignancy and avoidance of unnecessary surgery. We have recently had three patients with secondary carcinoma of liver, all correctly predicted on the basis of the serum alkaline phosphatase starch gel isoenzyme pattern. None of these patients was jaundiced, and in two of them the total alkaline phosphatase activity was only slightly raised above normal.

Case 1.—A man aged 33 years presented with a history of intermittent epigastric pain for seven weeks, and acute persistent pain radiating to the right shoulder for three days. On examination he was tender in the right hypochondrium with muscle guarding and rebound tenderness. All the investigations were normal with the exception of a raised E.S.R. (52 mm./1 hour Wintrobe) and serum alkaline phosphatase 28.5 King-Armstrong units/100 ml.). A provisional clinical diagnosis of acute cholecystitis was made and a laparotomy was performed. A carcinoma of the recto-sigmoid junction of the colon with multiple secondaries in both liver lobes was present and confirmed by biopsy.

Case 2.—A woman of 63 years presented with a history of sudden acute pain in the right hypochondrium. On examination she was tender in the right hypochondrium with rebound tender-

ness. All the investigations were normal with the exception of a slightly raised serum alkaline phosphatase (33 King-Armstrong units/100 ml.). A provisional clinical diagnosis of acute cholecystitis was made and laparotomy was performed. This showed large carcinomatous deposits in the liver with no obvious primary. A biopsy suggested a primary of the ovary.

Case 3.—A woman aged 33 years originally presented with mild abdominal pain, constipation, and occasional rectal bleeding for two years. This was investigated by sigmoidoscopy and barium enema, with negative results. One year later the patient returned with acute right-sided abdominal pain radiating to the right shoulder for three days. On examination a large, hard, and slightly tender mass was felt in the right hypochondrium. All the investigations were normal with the exception of a raised E.S.R. (53 mm./1 hour Wintrobe) and serum alkaline phosphatase (73.5 King-Armstrong units/100 ml.). A provisional clinical diagnosis of empyema of the gall bladder was made and a laparotomy decided. This showed large metastatic carcinomatous deposits in both liver lobes with no obvious primary. The history was suggestive of a primary carcinoma of the bowel.

In these three patients a slow-moving origin band of alkaline phosphatase activity was present in conjunction with a liver band (see

Fig.). The origin band is not found in normal people, but it may be present in patients with obstructive jaundice, of both intra- and extra-hepatic type.² In view of its position on the gel, it is presumably a high molecular weight alkaline phosphatase, and possibly a lipoprotein complex.¹ Dunne *et al.*,³ using Sephadex filtration methods, have found approximately 30% of alkaline phosphatase activity in the 19S protein peak in the serum of patients with metastatic hepatic malignancy. The remainder of the alkaline phosphatase activity was in the 7S fraction, whereas in normal controls approximately 98% was in the 7S fraction with only 2% in the 19S peak. It seems possible that some, or all, of this 19S fraction may be identical with the origin band present in the above cases.

The origin of this 19S enzyme fraction is debatable. Several hypotheses have been suggested,³ and it is possible that a different mechanism may operate in different clinical conditions. In malignant cases it may represent a constituent of tumour tissue, which when present in a large amount is detectable in the serum by a simple spill-over mechanism. Fennelly *et al.*⁴ have shown that

up to 100% 19S alkaline phosphatase activity is present in extracts of malignant tumour tissue. The unique case described by Fishman *et al.*⁵ is of interest in this connexion. These workers found marked placental type alkaline phosphatase activity in the serum of a patient suffering from bronchogenic carcinoma, and tissue extracts of the tumour tissue showed a similar enzyme to be present. Further large-scale studies of serum activity in malignant cases with appropriate tissue extraction procedures⁶ on fresh tumour tissue would seem necessary to determine whether there is a relationship between serum alkaline phosphatase enzyme patterns and proliferating neoplastic tissue.—We are, etc.,

R. C. JENNINGS.
D. BROCKLEHURST.
M. HIRST.
A. ZIROS.

General Hospital,
Altrincham, Cheshire.

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Rhesus Sensitization and Abortion

SIR,—We would disagree with the comment in your leading article (11 October, therapeutic and spontaneous abortion that because of the scarcity of Rh-immunoglobulin and the very small risk entailed in therapeutic and spontaneous abortion "there is certainly no indication to give Rh-immunoglobulin. . . ."

The importance of abortion in relation to rhesus iso-immunization was emphasized by Clarke,¹ because of the possibility of a Rh-negative woman immunized by an Rh-positive abortus having her future pregnancies affected by haemolytic disease. Therapeutic abortion carries a higher risk of transplacental foeto-maternal haemorrhage than spontaneous abortion (Matthews²). Krebs³ demonstrated that the risk of transplacental haemorrhage is increased if therapeutic abortion is carried out late in pregnancy.

In our own series of 110 cases of therapeutic abortions, in which maternal blood was taken before and after abortion for fetal cell count, the incidence of transplacental haemorrhage was much higher in the cases terminated by abdominal hysterotomy or Utus paste, as opposed to vaginal evacuation (Table). Since induction of abortion with Utus paste and abdominal hysterotomy was carried out in cases past 12 weeks' gestation the Table shows that the important factor with regard to the incidence of transplacental haemorrhage in cases of therapeutic abortion

Fetal Cells in Maternal Blood Following
Therapeutic Abortion

Method of Termination	No. of Cases	% Positive
Dilatation and evacuation	77	22.7
Utus paste	11	45
Hysterotomy	12	41.5

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-