LETTERS TO THE EDITOR

Tests for growth hormone secretion

SIR,—Professor Brook and Dr Hindmarsh claim that children growing at a less than 3rd centile velocity carry a 97% chance of showing an abnormality on investigation.¹ In a leading article in the *British Medical Journal* in 1986 they wrote 'If a third centile velocity is chosen for immediate action the chances of investigating a normally growing child are only 3%.² The latter statement is capable of two interpretations. It could mean that 3% of normal children would be investigated, which is true. It could also be taken to mean that 3% of investigated children would be normal, which is not true, unless by chance. Only this second interpretation, however, fits with the assertion that 97% of investigated children would be abnormal.

The percentage of children below the third centile who are abnormal is:

$$\frac{\text{Number of abnormal children in the group (<3rd centile)}}{\text{Total number of abnormal + normal children in the group}} \times 100$$

Growth chart centiles concern only normal children. They cannot tell us about the number, or even the existence, of abnormal children and therefore cannot provide the figures necessary for the calculation.

The chances of finding an abnormality on investigation depend on the sensitivity of the methods of investigation, and on what proportion of those perceived as having the problem have a pathological cause for it and what proportion represent simply the extremes of biological variability. Brook and Hindmarsh give no indication that they have taken these factors into account in arriving at their figure of 97%.

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1 Brook CGD, Hindmarsh PC. Tests for growth hormone secretion. *Arch Dis Child* 1991;66: 85-7.

2 Brook CGD, Hindmarsh PC, Healy MJR. A better way to detect growth failure. *BMJ* 1986; 293:1186.

Professor Brook and Dr Hindmarsh comment
We thank Dr Addy for his interest and we accept his point.

In practical terms it makes not the slightest difference because the total number of abnormal children will so greatly outweigh the number of normal children that the fraction he gives will approach unity or 100%, which is the point we were trying to make.

Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin

SIR,—The paper by Coombs *et al* claims to show indomethacin has direct effects on the

splanchnic circulation that are independent of its desired effect, that is, closure of the duct.¹ Indomethacin is such a widely used and important drug that such a claim must be carefully evaluated.

The observed effects of drug administration were a decrease in systolic gut flow velocity with a change to antegrade diastolic flow by one hour. In the group given a rapid bolus the systolic velocity fell further and more rapidly; it is claimed that this is due to splanchnic vasoconstriction. The evidence provided does not support this. The conclusions are presumably based on the assumption that left ventricular stroke volume does not change after indomethacin administration. In fact several papers have shown that left ventricular stroke volume falls dramatically, with a fall in systolic aortic velocity, if the duct closes.²⁻⁴ An abnormally raised cardiac output returns to normal. The decrease in systolic mesenteric flow velocities observed in this study could therefore merely reflect aortic flow changes secondary to rapid ductal constriction. The observed velocity changes could have occurred in the descending aorta, the renal arteries, and even the femoral arteries,² in fact in any systemic artery. Indomethacin normally closes the duct; therefore, to study its generalised effects, the haemodynamic consequences of ductal constriction must be taken into consideration. The observation that the fall in gut flow velocities decreases with second and third doses could be explained by the duct becoming progressively smaller and therefore the haemodynamic consequences of ductal constriction becoming less marked.

The suggestion that rapid administration of indomethacin causes an undesirable fall in splanchnic circulation is probably a misinterpretation of the observations presented in this paper. We note that none of the 19 infants given indomethacin suffered serious side effects and that, in every case, retrograde or absent diastolic flow changed to normal antegrade flow.

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1 Coombs RC, Morgan MEI, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. *Arch Dis Child* 1990;65:1067-71.

2 Alverson DC, Eldridge MW, Johnson JD, *et al*. Effect of patent ductus arteriosus on left ventricular output in premature infants. *J Pediatr* 1983;102:754-7.

3 Hirsimaki H, Kero P, Wanne O, *et al*. Doppler-derived cardiac output in healthy newborn infants in relation to physiological patency of the ductus arteriosus. *Pediatr Cardiol* 1988;9: 79-83.

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Hyperinsulinaemic hypoglycaemia in small for dates babies

SIR,—The paper by Collins *et al* on hypoglycaemia in the small for dates infant raises two important issues about the pathogenesis

and hence management of such infants.¹ The authors suggested that the low glucose concentration in the subgroup without overt evidence of hyperinsulinaemia might be explained by a transient deficiency in glucagon secretion.² This implies that they believe that the remaining infants had normal plasma glucagon concentrations. However is it not equally likely that a proportion of their 'hyperinsulinaemic' group were also relatively deficient in this vital gluconeogenic hormone? Thus could not the persistence of the fetal insulin effect be due to a failure of the normal postnatal surge in glucagon release? In the absence of glucagon, the key enzymes of the gluconeogenic pathway (for example, phosphoenol pyruvate carboxy-kinase) would be inoperative and it has recently been shown that glucose-6-phosphatase also requires glucagon for catalytic activity.³

The second and related issue is that given the wealth of theoretical evidence of the potential importance of this hormone, why is the glycaemic response so poor after an intramuscular injection? In pilot studies before the original paper on transient glucagon deficiency,² I observed that infants who failed to respond to intramuscular glucagon nevertheless showed a brisk, sustained rise in peripheral plasma glucose concentration after an intravenous bolus (200 µg/kg). The most likely explanation is that the sustained peak plasma concentrations of this hormone after intravenous injection might be sufficient to raise the concentration in the portal vein above the local insulin concentrations and thereby reverse the direction of net hepatic glucose flux. Thus the early use of intravenous glucagon in all hypoglycaemic infants is likely to shorten their dependence on intravenous glucose supplementation and in addition prevent rebound hypoglycaemia when oral feeding is introduced.

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1 Collins JE, Leonard JV, Teale D, *et al*. Hyperinsulinaemic hypoglycaemia in small for dates babies. *Arch Dis Child* 1990;65:1118-20.

2 Mehta A, Wootton R, Cheng KN, Penfold P, Halliday D, Stacey TE. Effect of diazoxide or glucagon on hepatic glucose production rate during extreme neonatal hypoglycaemia. *Arch Dis Child* 1987;62:924-30.

3 Burchell A. The molecular pathology of glucose 6 phosphatase. *FASEB J* 1990;4:2978-88.

Drs Collins, Leonard, Teale, and Marks comment:

We thank Dr Mehta for his letter. In the original protocol it was planned to measure plasma glucagon concentrations in all the babies, but there was insufficient blood in all but a few samples for us to do this. In two patients who were hyperinsulinaemic (cases 6 and 9) glucagon was not detectable in plasma at the time of hypoglycaemia (limit of detection 25 pmol/l). These results are consistent with the hypothesis that the hyperinsulinaemic babies were relatively glucagon deficient as well.

Development of intestinal motility

SIR,—In Dr Bisset's article on development of intestinal motility he notes that little is known of the development of colonic motility in humans and that most infants pass their first

bowel motion during either labour or the ensuing 48 hours.¹ While this is true there is a very noticeable gestational age effect on the passing of meconium by a fetus during labour which gives some idea of the maturation of this aspect of gut function. Increasing gestational age is by far the strongest predictor of the presence of meconium in amniotic fluid at delivery with 10% of infants at 35 weeks' gestation, 17% at 40 weeks' gestation, and 25% at 42 weeks' gestation having passed meconium before delivery.² The presence of meconium in labour before 34 weeks' gestation is uncommon and infections such as listeria need to be excluded. The mechanism resulting in the passage of meconium is unknown but has been said to depend on hypoxia or acidosis,³ with vasoconstriction of the fetal intestinal blood supply, hyperperistalsis, and anal sphincter relaxation.⁴ However it seems highly likely that the passage of meconium is generally a normal physiological event reflecting increasing fetal maturity.

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- 1 Bisset WM. Development of intestinal motility. *Arch Dis Child* 1991;66:3-5.
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- 4 Saling E. *Fetal and neonatal hypoxia in relation to clinical obstetrical practice*. London: Arnold 1968:117.

Gastro-oesophageal reflux in apparent life threatening events

SIR,—Your editorial on surgery for gastro-oesophageal reflux stated that apparent life threatening events (ALTE or 'near miss' SIDS episodes) associated with confirmed gastro-oesophageal reflux was 'probably an absolute' indication for surgery.¹ While having some difficulty with the concept of probable absolutes the following points should be noted.

Gastro-oesophageal reflux is a common event in infants and the application of techniques such as continuous lower oesophageal pH measurement has resulted in its association with a variety of conditions from asthma, recurrent bronchitis, pneumonia, apnoeic periods in the newborn, cyanotic attacks, ALTE, rumination, torticollis, abnormal movements of the head and neck, and neuropsychiatric disorders.² However as Carré previously noted none of these disorders, with the exception of pulmonary infections, occurred with increased frequency in a 35 year prospective study of 710 children with partial thoracic stomach (hiatal hernia) and gastro-oesophageal incompetence.²

The presence of gastro-oesophageal reflux in infants who have suffered an ALTE does not establish a causal relationship. Before embarking on surgical treatment of a common, and usually harmless, condition it is imperative that a clear association be established between the two events—that is, it has to be shown that gastro-oesophageal reflux causes the ALTE in a particular child. Previous studies do not support surgical intervention with no clear causal relationship established and no benefit from fundoplication.³

Even if gastro-oesophageal reflux is shown to cause an ALTE in an infant we should perhaps ponder on why this infant reacts so differently from the majority of infants with gastro-oesophageal reflux.

At present the role of gastro-oesophageal reflux in ALTE is still unclear and needs to be firmly established before the various management options (including medical and conservative) can be prospectively evaluated.

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- 1 Kiely EM. Surgery for gastro-oesophageal reflux. *Arch Dis Child* 1990;65:1291-2.
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Nutrition and bronchopulmonary dysplasia

SIR,—We read the article by Wilson *et al* on nutrition and bronchopulmonary dysplasia¹ with interest and should like to report some of our own data for comparison. Between January 1980 and December 1989, 4389 infants under 72 hours of age have been admitted to the neonatal intensive care unit at Liverpool Maternity Hospital. Two hundred and forty two of these developed bronchopulmonary dysplasia, which was defined as being present if an infant had received ventilatory support for over 24 hours in the first 72 hours of life and had a persistent requirement for supplementary oxygen together with an abnormal chest radiograph on day 28. We performed a multiple logistic regression analysis of these data with bronchopulmonary dysplasia as the dependent variable and sex, birth weight, gestation, survival to discharge, and year of birth as independent variables. This showed an inverse correlation between the occurrence of bronchopulmonary dysplasia and birth weight which was independent of gestational age (odds ratio for a rise of 250 g in birth weight above 500 g=0.83; 95% confidence interval=0.77 to 0.90).

We have also investigated in detail the growth of nine infants with severe bronchopulmonary dysplasia who have recently been discharged from hospital receiving supplementary oxygen. Of the six that had been born at more than 28 weeks' gestation only two were below the 3rd centile for weight at birth, three were between the 10th and 50th, and one was above the 90th. At term all nine infants were below the 3rd centile for weight and at discharge from hospital eight were still below the 3rd centile.

The above findings are in agreement with those of Wilson *et al* and lend strong support to the hypothesis that infants who develop bronchopulmonary dysplasia fail to achieve optimal growth postnatally as well as antenatally.

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- 1 Wilson DC, McClure G, Halliday HL, Reid M, McC, Dodge JA. Nutrition and bronchopulmonary dysplasia. *Arch Dis Child* 1991;66:37-8.

Continued need for pneumococcal prophylaxis after splenectomy

SIR,—In a recent issue of this journal Drs Murdoch and Dos Anjos reported two children who died of overwhelming pneumococcal infection, five and eight years after splenectomy.¹ They might have included in their report a patient at Guy's Hospital who died last summer 30 years after splenectomy performed at the age of 2 years at the Evelina Children's Hospital.

The girl was admitted to the Evelina Children's Hospital in 1959 when I was paediatric registrar. She had idiopathic hypoglycaemia—at that time labelled McQuarrie's syndrome. Heavy doses of steroid controlled her symptoms but rendered her grossly cushingoid. A single insulin estimation (30 ml blood from a femoral vein that was incubated on a rat's diaphragm) showed high circulating insulin concentrations and a subtotal pancreatectomy was carried out. To achieve this it was necessary to remove her spleen. The operation cured her hypoglycaemia and did not cause diabetes mellitus. The child thrived well physically and intellectually.

Some 20 years later, when I met a case of nesidioblastosis, I asked for the original blocks of her pancreas to be brought out, appropriately stained, and confirmed the diagnosis that she also had nesidioblastosis. At a meeting on hypoglycaemia at Guy's Hospital I presented the case history and the 'patient' attended; she was healthy and holding down a good job. The fact of splenectomy was noted but since she was now in her early 20s and very well, no prophylactic penicillin was suggested.

She married, bore two children successfully, and never had any obvious problem with infection. On the summer of her death she became unwell with a high fever and joint pains in the knee. She was seen in Guy's Hospital casualty department where the abdominal scar was attributed to pancreatectomy, and the casualty officer was unaware of the splenectomy. Radiographs were taken and tests were initiated but she was not admitted. In the small hours of that night she was brought in dead to King's College Hospital. Necropsy showed overwhelming infection with *Streptococcus pneumoniae*.

This tragic story, together with other cases encountered in my 30 years as a paediatrician, leads me to endorse Drs Murdoch and Dos Anjos' recommendations on prophylaxis, though they would not have saved the woman described here. (Pneumovax II was not available in 1959 and the infection occurred long after she had passed 'increased epidemiological risk of pneumococcal infection such as school, university, or the armed forces'.) Therefore, prophylactic penicillin should be continued for life. As this will inevitably lead to problems with compliance, an alternative is that the patient should carry a card and always have a large dose of amoxycillin capsules to be taken at once in any sudden feverish systemic illness, and seek medical advice promptly. I would also add that wherever the circumstances allow, Pneumovax II should be given before splenectomy.

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- 1 Murdoch IA, Dos Anjos R. Continued need for pneumococcal prophylaxis after splenectomy. *Arch Dis Child* 1990;65:1268-9.