

## 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.<sup>1</sup> 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%.<sup>2</sup> 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.<sup>1</sup> 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.<sup>2-4</sup> 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,<sup>2</sup> 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.

4 Lindner W, Seidel M, Versmold HT, Döhlemann, Riegel KP. Stroke volume and left ventricular output in preterm infants with patent ductus arteriosus. *Pediatr Res* 1990;27: 278-81.

### 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.<sup>1</sup> The authors suggested that the low glucose concentration in the subgroup without overt evidence of hyperinsulinism might be explained by a transient deficiency in glucagon secretion.<sup>2</sup> 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 carboxykinase) would be inoperative and it has recently been shown that glucose-6-phosphatase also requires glucagon for catalytic activity.<sup>3</sup>

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,<sup>2</sup> 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