

LETTERS TO THE EDITOR

Unusual course of neonatal hyperinsulinaemic hypoglycaemia (nesidioblastosis)

EDITOR.—Neonatal hyperinsulinaemic hypoglycaemia (NHH) is characterised by hypoglycaemia, inadequate hyperinsulinism, a lack of urinary ketones, and requires instant and effective treatment to prevent cerebral damage. This consists of diazoxide, glucagon, and octreotide, a somatostatin analogue. None the less, most patients require subtotal pancreatectomy.

We report the second child of a healthy family, who was delivered at 37 weeks after an uneventful pregnancy (birthweight 3430 g). Initially, hypoglycaemia (blood glucose of 80 mg/l) was noted. Table 1 summarises the most important laboratory values. The glucose:insulin ratio was decreased in controlled hypoglycaemia (days 3 and 15) whereas a glucagon test yielded a normal response. An oral glucose tolerance test was performed in the mother with normal results. The glucose supplementation exceeded 16 mg/kg/min to achieve normoglycaemia. It could be tapered to 11.8 mg/kg/min without inducing hypoglycaemia.

Treatment with octreotide (4 × 30 µg subcutaneously from day 18) achieved normoglycaemia despite reduced glucose supplementation (5.6 mg/kg/min on the second treatment day). This was maintained even when the octreotide regimen was completed (day 52). No adverse effects of octreotide treatment were noted. On day 59 the patient was discharged. His diet consisted of four formula meals supplemented by 3g maltodextrin/kg/day. There were no further episodes of hypoglycaemia.

At 12 months of age, the patient was healthy with no neurological deficits, age related nutrition, and normal laboratory tests (table 1).

Treatment with diazoxide (15–20 mg/kg/day) is often used to inhibit insulin secretion and increase gluconeogenesis, but it produces a wide range of side effects.¹ Surgery had to be carried out in a further six patients we treated.^{2–4} However, pancreatectomy with partial resection carries a risk of continued hypoglycaemia, and total pancreatectomy carries a risk of life long insulin dependent diabetes mellitus and exocrine pancreatic insufficiency.^{2–3} Even if the immediate postoperative result is normoglycaemia, the risk of insulin dependent diabetes mellitus is increased.⁶

Based on a report of somatostatin deficiency in pancreatic tissue and effective supplementation,³ we started a course of

octreotide. Normoglycaemia was maintained despite reduced glucose supplementation and we stopped the treatment after only 34 days. Because length of treatment was significantly shorter than that reported previously and the glucose requirement decreased just before octreotide treatment, we suspect that maturation of the endocrine pancreas occurred. A similar conclusion was reached by Horev *et al* for three of four patients who became normoglycaemic.⁷ Therefore, we suggest a trial of stepwise reduction of glucose supplementation in combination with octreotide in NHH before subtotal pancreatectomy.

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Informed consent for randomised controlled trials in neonates

EDITOR.—We read with some concern the Annotation by Mason *et al* in which she seems to endorse a major paradigm shift in the informed consent process for neonatal randomised trials. But she does not provide sufficient evidence (as opposed to opinions) that such a shift is really needed. Although reference has been made to an ongoing European study which will “determine the validity of...parents of babies requested to provide proxy consent,” Dr Mason has already concluded that “the existing position with regard to informed consent for neonatal research is problematic.” She questions the rational basis of the consent process, especially for “those who are poorly educated and emotionally

stressed.” She also states that voluntariness may be undermined because of the complexity of the medical arguments, feelings of parental powerlessness, and inadequate time for information transfer.

We recently published the first study to correlate the determinants of parental authorisation for the involvement of newborn infants in clinical trials with the direction of the consent decision.²

It should be reassuring to your readers that we found no association between the consent decision and the sociodemographic characteristics of the parents, or the severity of the infant's illness. Moreover, we showed that parents assessed the probability and magnitude of risks and benefits. Importantly, those parents who did not feel free to decide or who felt that the consent process was too complex, were, in fact, least likely to authorise their infant's participation in a trial.

Our study results call into question many of Dr Mason's assumptions, and we eagerly await the results of the European study to see whether European parents differ in attitude from those in our Canadian sample. We would also like to differentiate the process from the substance of the consent process. Issues of complexity or coercion are process problems which may be resolved with more conscientious attention to the demands of the current format, or if necessary, with new ways of approaching parents for authorisation.

One final point: Dr Mason observes that the need for equipoise in a randomised trial “involves the need to admit uncertainty,” and she asserts that this may lead patients to doubt the doctor's ability. Equipoise will be an issue in any controlled trial, regardless of who makes the decision, and should not be an argument for an overhaul of the system. As for the necessity to admit uncertainty, many parents would argue that this is long overdue, both in the context of informed consent for research and in daily clinical practice.^{3–4} Where is the evidence that honesty may lead patients to doubt the doctor's ability?

Ethicists, too, should take heed of the rules of evidence, and in considering action should recall Claude Bernard's admonition: “True science teaches us to doubt and, in ignorance, to refrain.”

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Dr Mason responds:

Contrary to the supposition of Zupancic *et al*, I do not “endorse a major paradigm shift in the informed consent process for neonatal randomised trials.” Indeed, I have rejected alternative approaches as neither providing

Table 1 Values of blood glucose, insulin, C peptide and glucose:insulin ratio (normal range in parenthesis); controlled hypoglycaemia on days 3 and 15

Age (days)	Glucose (mg/dl; newborn 40–60, child 50–90)	Insulin (mU/l; <30)	C peptide (mcg/l; 5–30)	Glucose:insulin ratio (4,1–11)
3	12	107	4,6	0,11
15	12	8	1,9	1,5
64	87	19,7	2,6	4,4
365	72	1	0,6	72

Normal values were found for free fatty acids, lactate, cortisol and somatostatin in the blood (day 2), thyroxine free, thyroid-stimulating hormone (day 365); ketones or organic acids in the urine were not detectable (day 2).

adequate protection nor conforming to the central ethical principle of respect for autonomy of the individual.⁵

I do entirely concur with the point made that the admission of uncertainty in medical practice is desirable. I pointed out that education about randomised controlled trials would be helpful as a long term approach to increasing their general acceptability. This would thus include discussion of uncertainty of treatment options as being a part of this process.

Where I disagree with Zupancic *et al* is in their suggestion that informed consent in neonatal research is not problematic. Evidence suggests that parents do not always fully understand the randomisation process.⁶ Indeed, the Euricon project arose initially out of concerns in this area, expressed by neonatologists at the European Neonatal Brain Club at their meeting in October 1994 in Leeds, UK.

In Zupancic *et al*'s Canadian study² 32% of all parents of neonates (103 who consented to research and 37 who declined) agreed with the statement "I would prefer to have the doctors advise me whether my baby should be in the study, rather than asking me to decide." To me, this implies the reluctance of "a significant minority of parents" to shift entirely from a more paternalistic approach, and it is a factor to take into consideration when aiming for emphasis on patient autonomy in research.

To ignore inconsistencies and concerns in the area of informed consent would be to do a disservice to parents and neonates. To debate and explore the problems, to raise awareness and improve the situation is to act ethically, in the best interests of the patient, and with respect for individual autonomy.

- 5 Mason SA. Obtaining informed consent for neonatal randomised controlled trials - an "elaborate ritual"? *Arch Dis Child* 1997;76:F143-F5.
6 Snowdon C, Garcia J, Elbourne D. Making sense of randomization: responses of parents of critically ill babies to random allocation of treatment in a clinical trial. *Social Sci Med* 1997; 45:1337-55.

Timing of surfactant treatment

EDITOR.—We enjoyed reading Morley's systematic review of the timing of surfactant treatment.¹ His overall conclusion that "the data from this systematic review show a 39% reduction in the neonatal mortality if the babies are treated with surfactant at birth compared with a few hours later" is valid only if a number of provisos are taken into account:

The surfactant should be natural or derived from mammalian lungs. The overview contained studies using bovine or porcine surfactants. It cannot be assumed that similar findings apply to the synthetic, protein free surfactants which, both animal studies² and clinical trials,³ have shown, are not as good as natural surfactants. Exosurf has been studied and early and late treatment compared,⁴ but not as prophylaxis, and there are no comparative data for ALEC.

Prophylaxis is really treatment given before 15 minutes has elapsed. Prophylactic treatment defined by Morley as "surfactant given down an endotracheal tube at initial resuscitation" did not apply in at least four of the studies where treatment was within 5 to 15 minutes of birth.⁴

The babies must be between 24 and 31 weeks of gestation.

Follow up data from these studies are scanty. Follow up to school age showed improved pulmonary outcome in children

who had been treated with a bovine surfactant.⁵ In another trial using human surfactant, not included in Morley's review, babies treated prophylactically had lower Bayley scores at 12 months adjusted age.⁶

Morley suggests that "prophylactic treatment saves about seven extra lives for every 100 treated," but this is based on "total mortality" which analyses just four trials. If all seven trials of prophylaxis and rescue treatment are included,⁴ and neonatal mortality is used as the endpoint, 33 babies (95% CI 20–100) would need to be treated to save an extra life. If these figures are used the cost analysis is considerably different. About 17 (not 7) extra doses of surfactant would be needed for every extra life saved, but the confidence interval on this figure is extremely wide (about 10–50 extra doses).

A major problem is that we have no trials comparing true prophylaxis, as defined by Morley, with early treatment, say within the first 30–60 minutes of life. We cannot therefore advise neonatologists which babies should be intubated at birth solely for the purpose of giving surfactant. Morley is probably correct in saying that for babies of less than 32 weeks' gestation treatment with surfactant is warranted as soon as they are intubated for the treatment of RDS.

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- 1 Morley CJ. Systematic review of prophylactic vs rescue surfactant. *Arch Dis Child* 1997;77:F70-F4.
- 2 Corcoran JD, Berggren P, Sun B, *et al*. Comparison of surface properties and physiological effects of a synthetic and a natural surfactant in preterm rabbits. *Arch Dis Child* 1994;71:F165-F9.
- 3 Halliday HL. Natural vs synthetic surfactant in neonatal respiratory distress syndrome. *Drugs* 1996;51:226-37.
- 4 Halliday HL. Prophylactic surfactant for preterm infants - the case against. In: Cockburn F, ed. *Advances in Perinatal Medicine*. Lancaster: Parthenon Press, 1997.
- 5 Kramer BM, Sinkin RA, Merzbach JL, *et al*. Improved pulmonary outcome at school age with prophylactic surfactant administration. *Pediatr Res* 1995;37:263A.
- 6 Vaucher YE, Harker L, Merritt TA, *et al*. Outcome at twelve months of adjusted age in very low birth weight infants with lung immaturity: a randomized, placebo-controlled trial of human surfactant. *J Pediatr* 1993;122:126-32.
- 7 Soll RF. Appropriate surfactant usage in 1996. *Eur J Pediatr* 1996;155 (Suppl 2):S8-S13.

Dr Morley responds:

I am pleased Professors Halliday and Soll enjoyed my article and have opened the debate. They are right that the only randomised trials of prophylaxis vs rescue surfactant treatment were with animal derived surfactants—I dislike the term "natural" surfactants because they are highly derived and far from natural.

Surprisingly, they persist in perpetuating the myth that synthetic surfactants are inferior to "natural" surfactants. Firstly, there has been no head to head trial of ALEC against a "natural" surfactant so we do not know about ALEC. Secondly, there has been no head to head trial of Curosurf against a synthetic surfactant so we do not know about Curosurf. These are the main surfactants in use in the UK. Thirdly, in the largest head to head trials

of Exosurf against Survanta^{8,9} one showed a difference in air leak and both showed a slight difference in oxygenation and mean airway pressure, but only in the first three days. There was no difference in death, chronic lung disease, and other major outcomes.

Professors Halliday and Soll are overly pedantic in saying that four trials did not have true prophylaxis because the surfactant was given "within 15 minutes of birth."

I agree that the meta-analysis clearly shows that prophylactic surfactant should be given to intubated infants from 25 to 31 weeks of gestation. The incidence of worrying respiratory distress syndrome after 31 weeks is so low that it would be wasteful to treat them prophylactically unless they were very ill.

The comments on follow up are well taken, but the review was not about follow up. The references Professors Halliday and Soll cite do not compare outcome in the prophylactic vs rescue trials.

The analysis does show that prophylactic treatment saves seven extra lives for every 100 infants treated at less than 32 weeks of gestation. But I do not understand why they want to use neonatal mortality as their outcome when total mortality is much more important. One of the reasons that there seems to be such a difference between the effect on total mortality and neonatal mortality in the meta-analysis is that data on total mortality were not available for the trial which enrolled babies from 29 to 32 weeks of gestation and had a 1% mortality rate. As prophylaxis will mainly be used on the smaller babies, I think the data without this trial are more realistic.

My opinion is that premature babies should be intubated only for the treatment of respiratory failure and not electively for surfactant treatment.

- 8 Vermont-Oxford Neonatal Network. A multicentre, randomized trial comparing synthetic surfactant with modified bovine surfactant extract in the treatment of neonatal respiratory distress syndrome. *Pediatrics* 1996;97:1-6.
- 9 Horbar JD, Wright LL, Soll RF, *et al*. A multicentre randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. *J Pediatr* 1993;123:757-66.

Nasal deformities arising from flow driver continuous positive airway pressure

EDITOR.—As the manufacturer of the device featured in the paper by Robertson *et al*,¹ we would like to make several points. Although we understand that the article was written in good faith, and that St George's is committed to the use of the Infant Flow device, we remain concerned about the effect of the study on practitioners not yet familiar with the unique benefits of the device.

We do not in any way consider that the prong is wrongly designed. In any event, the design was not the cause of the problems identified by Robertson *et al*.

We do not understand the basis for the allegation that the prong is wrongly designed, and we are not aware of any research that could justify this conclusion.

It is incorrect to state that "we are working together to modify the design of the prong," and we are surprised that this was written without any reference to us.¹

The cause of the difficulties at St George's was the manner of the fixation of the device.

We confirmed on our visits to the hospital that babies will sustain injury if an inappropriate (small) size prong is used. If the device is

fitted too tightly, in a misguided attempt to prevent leaks, the subsequent pressure may cause tissue damage. This can be avoided if a larger prong is used. The choice of correct hat/bonnet size will also determine pressures on the nose.

We have provided guidelines and comprehensive training on the use of our device since its release: we have always emphasised the need for proper fixation and the proper choice of prong size.

The Infant Flow has been used for several years in the Karolinska University Hospital in Sweden for several years, and in the County Hospital in Östersund, Sweden, and has not resulted in any of the difficulties reported in Robertson *et al.*'s article.

Our anecdotal monitoring in the UK has indicated that the device is regularly used without incurring the damage described at St George's. With proper training and understanding, the Infant Flow can be used with confidence.

We regret that the study by Robertson *et al.* may have deterred some practitioners from using the Infant Flow, meaning that some babies who would otherwise have safely been able to benefit from the device will not have done so.

All at EME are very much concerned about the damage caused to patients for whatever reason. We will always endeavour to improve the design and performance of our equipment whenever the opportunity presents itself.

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- 1 Robertson N J, McCarthy L S, Hamilton PA, *et al.* Nasal deformities resulting from continuous positive airway pressure. *Arch Dis Child* 1996;75:209-12.

Nasal deformities at a UK hospital

EDITOR.—The neonatal unit at St George's hospital, London, recently reported their findings of nasal trauma associated with nasally applied treatment using continuous positive airway pressure (NCPAP).¹ They reported that 20 per cent of the very low birthweight infants treated in this way developed nasal injury. The equipment used was the Infant Flow system.

These figures are shocking and inconceivable. For many years NCPAP has been used extensively with this technique at the neonatal units in our hospitals, the Karolinska Institute, Stockholm, Sweden, and the county hospital in Östersund, Sweden. NCPAP has been given to infants weighing upwards of 430 g at birth. The duration of treatment has varied from a few hours, up to two or three months, in a few cases. One patient has been receiving NCPAP for six months. A total of about 750 infants have been treated (Stockholm 500, Östersund 250), and as yet, we have not experienced any kind of nasal injury. Only very occasionally have we seen minor nasal trauma (< 1%), and this has healed without complications. In fact, one patient (a boy weighing 577 g at birth) transferred from another hospital with a severely swollen mucosal nasal lining that had been caused by a conventional NCPAP device (Argyle cannula). This injury healed completely, even during continued NCPAP treatment, during which the patient was treated using the Infant Flow device.

From our experience, we are convinced that nursing is critical to the handling of NCPAP. No matter how well the equipment is designed, if it is applied with sufficient pressure to the skin to impair the circulation of the underlying tissues, trauma is the inevitable risk. The silastic prongs in the Infant Flow have therefore been designed to seal without applying any major pressure to the nose, provided the right size is chosen—that is, the largest size to fit into the nostrils. However, a varying gas leak through the patient's mouth and at the nasal attachment is an unavoidable consequence of the method of nasal administration itself. The efficacy of a treatment therefore depends on the capacity of the pressure generator to maintain the CPAP level, even when there is a clinically significant leakage of breathing gas.

The Infant Flow device has been designed to cope with moderate air leaks without significantly altering the level of CPAP.² The positive upper airway pressure can be monitored directly through the device, a fall in pressure due to a major persisting leak can be compensated for by increasing the gas flow in case the nasal attachment cannot be sufficiently sealed with careful adjustment.

NCPAP allowed us to reduce the requirement for mechanical ventilation and so reduce the risk of baro/volutrauma and bronchopulmonary dysplasia.³ In the Stockholm area only about 40% of the very low birthweight infants are mechanically ventilated compared with 70 to 80% in the US and the UK, thanks to NCPAP.

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- 1 Robertson N J, McCarthy L S, Hamilton P A, Moss H L S. Nasal deformities resulting from flow driver continuous positive airway pressure. *Arch Dis Child* 1996;75:F209-12.
2 Moa G, Nillsson K, Zetterström H, Jonsson L O. A new device for administration of nasal continuous positive airway pressure in the newborn: an experimental study. *Crit Care Med* 1988;16:1238-42.
3 Avery M E. Is chronic lung disease in low birthweight infants preventable? A survey of eight centers. *Pediatrics* 1987;79:26-30.

Treatment of hypotension in very low birthweight infants

EDITOR.—We note with interest the paper by Bouchier and Weston.¹ Their study concluded that both hydrocortisone and dopamine were effective treatments for hypotension in very low birthweight (VLBW) infants. The use of steroids in the management of hypotension in very low birthweight infants has already been shown to be effective anecdotally or in small uncontrolled studies.^{2,3}

In our experience with a similar group of VLBW infants and even in those with a mean gestation less than in the study group, we have used hydrocortisone as a prophylactic measure. Infants less than 27 weeks of gestation were routinely administered bolus doses of hydrocortisone for the first 2 to 3 days which was then tapered off. If inotropes were needed in addition, then the hydrocortisone was given for an extended period of time, well after discontinuation of inotropes.

Our results so far, albeit in a small sample size (n = 20) and with a mean gestation of 25 weeks, have shown that the number of infants who required inotropic support to treat hypotension in this group has been small. Furthermore, since the introduction of prophylactic hydrocortisone, we have not had any cases of refractory hypotension. We have also failed to show any increase in the incidence of infections (bacterial or candidal)⁴ or intraventricular haemorrhage.

We note that the maintenance dose of hydrocortisone used in Bouchier and Weston's study was 2.5 mg/kg every 6 hours. We have used smaller doses of 1.5 mg/kg every 6 hours and given over 20–30 minutes. This regimen has given us similar treatment outcomes outlined in their study.

In those infants who have required more prolonged courses of hydrocortisone we have encountered problems with hyperglycaemia and occasionally ventricular and septal hypertrophy.

We believe that a prospective randomised controlled trial comparing prophylactic hydrocortisone to placebo treatment is required.

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- 1 Bouchier D, Weston PJ. Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birthweight infants. *Arch Dis Child* 1997;76:F174-8.
2 Helbeck HJ, Insoft RM, Conte FA. Glucocorticoid-responsive hypotension in extremely low birth-weight newborn. *Pediatrics* 1993;92:715-17.
3 Moise AA, Wearden MF, *et al.* Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. *Pediatrics* 1995;95:845-50.
4 Botas C, Kurlat I, Young S M, Sola A. Disseminated candidal infections and intravenous hydrocortisone in pre-term infants. *Pediatrics* 1995;95:883-7.

Alcohol, pregnancy and the Holy Bible

EDITOR.—In an interesting article Dunn presented some insights on perinatal practice mentioned in the Holy Bible.¹ One of his examples is about alcohol use and pregnancy. Dunn refers to Judges 13:3–4. This passage deals with the saga of Samson. An angel appears to the hero's mother before she is pregnant and cautions:

Behold now, thou art barren, and bearest not: but thou shalt conceive, and bear a son. Now therefore beware, I pray thee, and drink not wine nor strong drink, and eat not any unclean thing.

According to Dunn, this passage indicates that barren women were warned not to drink alcohol if they wished to conceive. However, in an excellent review on the various epochs of the history of the fetal alcohol syndrome, Abel points out what the real meaning of this excerpt is.² The angel is not warning Samson's mother for the teratogenic effects of alcohol, but makes it clear that Samson is predetermined to live the ascetic life of a Nazirite. In the next verse (Judges 13:5) it is stated: "...for the child shall be, a Nazirite unto God from the womb..." The pledge of the Nazirites prohibited those who took it, from the use of intoxicants, from cutting their hair, and from

touching dead bodies. Samson was predestined to become a Nazirite from the moment of his conception ("from the womb").

There are more passages in the ancient and medieval world where there seems to be a pre-recognition of the deleterious effects of alcohol on the fetus. According to Abel, in all these passages the drinking habits of the father are considered to be harmful for the developing child. An awareness that drinking by the mother during pregnancy could be related to birth defects did not come into being until the end of the 19th century. But the evidence at that time was not considered very convincing. It was not the drinking habits of the parents, but rather the way in which their social and constitutional factors differed from those of non-alcoholic parents that were regarded as the real culprits. The first detailed description that offspring may be harmed by excessive drinking appeared as late as 1968.³

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- 1 Dunn PM. The Holy Bible: insights into perinatal practice in ancient times. *Arch Dis Child* 1996;75:F219-F20.
- 2 Abel EL. *Fetal alcohol syndrome and fetal alcohol effects*. 3d edn. New York: Plenum Press, 1993.
- 3 Lemoine P, Harousseau H, Borteyru JP, Menuet JC. Les enfants de parents alcooliques: anomalies observées à propos de 127 cas. *Quest Med* 1968;21:476-82.

Tracheobronchomalacia in preterm infants

EDITOR.—We read with interest the paper by Doull *et al* regarding tracheobronchomalacia in preterm infants with chronic lung disease.¹ We have also recently investigated several infants with severe chronic lung disease who have become ventilator dependent. As part of our investigation, we assessed the large airways for evidence of tracheobronchomalacia using a flexible bronchoscope (Olympus BFN20 2.2 mm). We detected clinically significant airway collapse in a proportion of these infants and, like Doull *et al*, have found that a high opening pressure of up to 20 cm of water was required to improve this. We accept that the report by Doull *et al* suggests that a tracheobronchogram may detect tracheobronchomalacia, but we do not agree that this is superior to flexible bronchoscopy, and that the latter should be precluded, as implied by Doull and colleagues, for technical reasons. Flexible fibre optic bronchoscopy can be performed in infants using an adapted endotracheal tube connector which permits good airway control with the ability to ventilate the patient when necessary. The extent and severity of tracheobronchomalacia can be assessed directly and the airway pressure required to ablate airway collapse can be determined during the examination. More information regarding the distal airways and the presence of any focal structural lesions can be obtained by bronchoscopy than from tracheobronchography. We suggest that flexible fibre optic bronchoscopy should be the investigation of choice for suspected tracheobronchomalacia.

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1 Doull J M, Mok Q, Tasker R C. Tracheobronchomalacia in preterm infants with chronic lung disease. *Arch Dis Child* 1997;76:F203-F5.

Dr Doull *et al* respond:

We welcome Shaw and Smyth's observations on the use of flexible bronchoscopy to diagnose tracheobronchomalacia, but feel that they have misconstrued our conclusions. In our discussion we make the point that tracheobronchography is more sensitive than rigid endoscopy for diagnosing tracheobronchomalacia. We have also used flexible bronchoscopy in the diagnosis and assessment of tracheomalacia, and found it very useful. We agree with Smyth and Shaw that flexible bronchoscopy may offer superior information on distal focal structural lesions. However, in the chronically ventilated infant, with an endotracheal tube in situ, proximal focal structural lesions are almost certainly better visualised using rigid endoscopy. Combined upper and lower airways assessment is therefore essential, although clearly the optimal regimen has yet to be determined.

Estimating total body water in neonates

EDITOR.—The body weight of the preterm babies in the study by Tang *et al* predicted the total body water better than any other single anthropomorphic measure, and that it accounted for 99% of the variations seen in body water measurements.¹

The authors then used a variety of other measurements and anthropomorphic characteristics and combined them in a number of equations and picked the best (involving a constant, body weight, body weight squared, and the length of the foot squared divided by electrical impedance taken under very specific conditions). They claim that by doing this they have produced a potentially useful clinical tool because the equation in their particular group of babies was able to predict not 99%, but 99.5% of the variations in measured body water. This prediction equation has not, so far, been tested in an independent group of babies.

There must be a wide variety of other anthropomorphic characteristics and clinical features—for example, the length of the left eyebrow cubed, divided by the ratio of the lengths of the right palm and index finger—that are both inconvenient to measure and make no effective difference to the total body water prediction based on weight alone. In my view, Tang's paper suggests that we should assume babies' total body water to be 0.8 of their body weight, and forget about impedance measurements.

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- 1 Tang W, Ridout D, Modi N. Assessment of total body water using electrical impedance analysis in neonates receiving intensive care. *Arch Dis Child* 1997;77:F123-6.

Dr Modi *et al* respond:

We enjoyed reading Dr Coulthard's amusing letter but fear that his wit might have obscured his understanding. The proportion of body weight that is body water is very variable in newborn infants and changes rapidly after preterm birth, from about 85% at birth in an infant below 32 weeks of gestation, to about 80% at one week, 75% at one month, and 65% at three months.² Dr Coulthard's suggestion that one simply assumes total body water to be 0.8 of body weight would clearly be unhelpful

and indeed nonsensical. He is also mistaken in his belief that the basis of our claim that we have a potentially useful clinical tool is because our regression equation accounts for 99.5% of the variation in measured total body water. Our model incorporating resistance measurements is significantly better than the model using body weight alone ($p < 0.001$) and has a 95% prediction interval of ± 82.5 ml. Although it is self evident that body weight is closely correlated with body water and therefore acceptable as an index of percentage body water in large cross sectional population studies, bioelectrical impedance analysis offers a small but significant improvement to estimates of absolute body water content. This may be of particular clinical value in the assessment of fluctuations in total body water on a day to day basis when body solid mass is also altering rapidly, as in the newborn infant.³

2 Friis Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics* 1961;28:169-81.

3 Tang W, Ridout D, Modi N. The influence of respiratory distress syndrome on body composition during the first week after birth. *Arch Dis Child* 1997;77:F28-F31.

BOOK REVIEWS

Fetal and early environment: Long term health implications. Editors Michael E Marmot, Michael E J Wadsworth. (Pp 227; £45 hardback.) Royal Society of Medicine Press, 1997. ISBN 1-85315-316-8.

For the first half of this century the fetus and newborn infant received scant attention from the medical profession after the conversion of the physician-accoucheurs into surgeon-gynaecologists. Rescued from obscurity and neglect by physiologists, paediatricians, and more recently, by obstetric specialists in fetal medicine during the past 30 to 40 years, perinatal medicine has become recognised as the most critically important period of early development, with long term implications for health throughout the rest of life.

The editors of this book, with the assistance of David Barker and Chris Power, have brought together review papers from many specialities concerned with the study of fetal and infant origins of adult health. The book contains contributions from the disciplines of epidemiology, public health, nutrition, psychiatry, paediatrics, physical medicine, psychology, comparative ethnology and the social sciences.

The 17 chapters by some 20 well known authors and scientists cover a wide range of subjects, including the influence of early environmental factors on adult growth, nutrition, infectious disease, respiratory disorders, and cardiovascular, neurological, and mental or psychosocial disease. The last four chapters discuss comparative animal studies, critical periods in childhood learning, the implications of changing social factors and the pathways linking early life and adult disease.

The authors are to be congratulated. This book is likely to be the first of many publications focusing on the important of the perinatal period to the rest of life. It should be read by every paediatrician, and indeed by all doctors and other s interested in shaping the health of our society. Perhaps the adage: "The child is the father to the man" should be

changed to “the fetus and newborn infant is the father to the man.”

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Fetal therapy. Invasive and transplacental. Edited by Nicholas Fisk and Kenneth Moise. (Pp 369; £70 hardback). CUP, 1997. ISBN 0-531-46133-2

This book brings together several expert “reviews” from the field of fetal therapy, mostly drawn from those who lecture on the advance course in fetal medicine at Queen Charlotte’s Hospital, London. The book’s editors are both leading figures in fetal medicine.

The text deals with this rapidly expanding area, which, despite an exponential increase in knowledge over the past 10 to 15 years, is still a relatively new specialty.

The book is divided into five sections which makes it easy to digest. I enjoyed the chapters on multifetal pregnancy reduction, fetal infec-

tion, and feto–fetal transfusion. The chapter on open fetal surgery, although describing data which are still revolutionary, was presented in a rather tired way. Indeed, this section has changed little over the past few years, and is similar to chapters in other books.

As well as established invasive and transplacental methods of fetal therapy, which are comprehensively and meticulously covered, discussions on open and endoscopic fetal surgery are also provided within chapters. Generally, these are balanced and the authors’ enthusiasm tempered by caution and a call for a better understanding of pathogenesis and registers to monitor fetal and maternal outcome. The chapter on fetal goitre and thyroid function is interesting and I cannot recall a similar review in other texts.

The section on future developments is of general interest, embracing both stem cell transplantation and gene therapy. Data are presented in terms of applied basic science research and anecdotal treatment in humans.

Again, balanced views are put forward and possible potential problems of such treatment discussed.

Refreshingly, and importantly, Frank Chervanek’s review of the ethics of fetal therapy is comprehensive. Such a review should be mandatory reading for any subspecialist involved in this field.

This book will be of interest to trained fetal medicine physicians, those in training posts, and will appeal to such individuals on both sides of the Atlantic. It will also be of general interest to those professions that interface with fetal medicine, such as neonatal paediatrics, paediatric surgery, and genetics. Despite the relatively small number of fetal medicine specialists and trainees in the UK, the appeal of such a text is universal.

The rapid and continued expansion of fetal medicine will perhaps give this text a limited shelf life.

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