mother with no personal or family history of thyroid or related autoimmune disease. The parents were first cousins.

We thank Mr. R. Cudmore for surgical help, and Dr. S. M. Dirmikis, of the University of Sheffield, for the LATS protector measurement.

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Neonatal brain growth during prolonged intravenous feeding

Total intravenous feeding may occasionally be a life-saving procedure for the seriously ill low birthweight infant. The technical and metabolic complications associated with total intravenous nutrition have been well reviewed (Harries, 1971; Harries, 1972; Heird *et al.*, 1972; Heird and Winters, 1975; Baum and Aynsley-Green, 1975). However, little is known about the effects of prolonged intravenous feeding on tissue growth and development in the newborn. In particular it would be important to know the effects of long-term intravenous nutrition on the brain, since in the neonatal period when the brain is growing rapidly it may be susceptible to nutritional deprivation (Dobbing, 1974).

Dobbing and Sands (1973) have provided standards for the biochemical development of the neonatal brain by analysing brains ranging in age from 10 weeks' gestation to 7 postnatal years. Using these standards for comparison, we have attempted to assess the effects of long-term

intravenous nutrition on the growth and development of the brain from an infant who was born at 32 weeks' gestation and who died after 10 weeks of continuous intravenous feeding.

Case report

A male infant weighing 1270 g was born at 32 weeks of gestation. He required assisted ventilation from birth and for the next 7 weeks, initially on intermittent positive pressure ventilation and subsequently on continuous distending airways pressure. During the first few days the infant had delayed emptying of the stomach. On day 5 he was started on total intravenous feeding using a regimen of Vamin (fructose) and Intralipid (Baum *et al.*, 1975). During the second week of life there was abdominal distension and clinical evidence of intestinal obstruction. X-ray of the upper gastrointestinal tract, using gastrografin contrast material, showed obstruction at the level of the jejunum and at the ileocaecal valve. Intravenous feeding was continued. Over the next 7 weeks there was evidence of persistent intestinal obstruction but the infant was too ill for a laparotomy to be performed. At 9 weeks' postnatal age a gastrografin enema showed the presence of a jejunocolic fistula. His respiratory status had improved sufficiently for an exploratory operation to be performed which showed multiple fistulae and perforations throughout the jejunum, ileum, and caecum. 10 cm of jejunum were resected and a colostomy constructed. Postoperatively the colostomy did not function and there was further evidence of fistula formation; at a postnatal age of 10 weeks (gestational age 42 weeks) he died of faecal peritonitis.

Details of the intravenous feeds which this infant received are given in Table I. For most of his life he received 100 cal/kg per 24 hours, 4 g of fat as intralipid/kg per 24 hours, and 3 g amino acids/kg per 24 hours. In addition, attempts were made to maintain homeostasis for electrolytes, vitamins, and trace minerals. The most serious metabolic problem documented was hypophosphataemia, which was corrected by the addition of increased phosphate supplements and has been reported elsewhere (Woods *et al.*, 1974).

Growth on intravenous feeding. The infant received continuous intravenous feeding from day 5 after birth until death 10 weeks later, during which time there was a strong clinical impression of increase in length and, to a limited extent, in muscle bulk. Unfortunately no clinical measurements of length nor of limb girth were made. Birthweight was 1270 g, which is on the 10th centile for 32 weeks, and at necropsy weight was 1680 g, below the 3rd centile for 42 weeks' gestation. The occipitofrontal head circumference at birth was 29 cm, on the 50th centile for 32 weeks, whereas the post-mortem head circumference was 33 cm, 10th centile for 42 weeks' gestation (standards from Davies *et al.*, 1972).

Measurement of brain growth. A post-mortem examination was performed on the day the infant died.

TABLE I

Outline of total intravenous feeding regimen used (/kg per 24 h)

Solution	Concentration	Volume (ml)	Calories	Fructose (g)	Glucose (g)	Fat (g)	Amino acids (g)	Sodium (mEq)	Potassium (mEq)	Chloride (mEq)	Calcium (mEq)	Magnesium (mEq)	Phosphate (mg)
Vamin (fructose)	—	45	30	4.5			3.0	2.25	0.9	2.4			
Intralipid	20%	20	36			4.0							
Dextrose	10%	85	34		8.5								
Calcium gluconate	0.5mEq/ml	4									2.0		
Magnesium sulphate	2 mEq/ml	0.5										1.0	
Potassium phosphate	1 mEq/ml	1.5							1.5				22.5
Multi-vitamin mixture		3											
Total		159	100	4.5	8.5	4.0	3.0	2.25	2.4	2.4	2.0	1.0	22.5

The brain including cerebellum and brain stem was removed intact, deep frozen immediately, and subsequently transferred in a frozen state for analysis. Measurements were made of whole brain weight, forebrain weight, and cerebellum weight; DNA concentration, cholesterol concentration, and percentage water content, according to the methods of Dobbing and Sands (1973). The results are shown in Table II, and when compared with normal values from Dobbing and Sands (1973), the weights of the whole brain, forebrain, and cerebellum are very low. The brain weight : body weight ratio was above normal, however, reflecting the very low body weight for 42 weeks' gestation.

DNA concentration, as a measure of cellularity, was normal. Total DNA, as a measure of total cell number, was low for the whole brain, forebrain, and cerebellum each. Cholesterol concentration was low in the whole brain, forebrain, cerebellum, and brain stem, while percentage of water was high.

Discussion

In man the brain normally grows very quickly between 32 and 42 weeks of gestation (Dobbing, 1974). For this reason we considered it important to collect information on the composition of the brain of this infant who was born early in gestation and required total intravenous feeding throughout this period of time. The centiles on which the weight and head circumference lay at birth and 10 weeks later at necropsy suggested 'brain sparing': the weight had fallen from the 10th centile to well below the 3rd centile during the 10 weeks (and the post-mortem weight was deceptively high because of peritonitis and free abdominal fluid), and head circumference had fallen from the 50th centile to the 10th centile. This suggestion of 'brain sparing' was further borne out by the brain

TABLE II
Post-mortem analysis of the brain after 10 weeks of intravenous feeding

	Observed values	Normal values at 42 weeks*	Comment
Brain weight (g)			
whole brain	283	350-530	Very low
forebrain	253	320-450	"
cerebellum	11.8	18-33	"
Cerebellum weight/brain weight	4.26%	4%-6.5%	"
Brain weight : body weight			
for age	16.85	9.1-15.6	+2 SD
for body weight	16.85	10-16.1	+2 SD
DNA concentration (μmol/g fresh weight)			
whole brain	2.24	2.0-3.3	Normal
forebrain	1.90	1.5-3.0	"
cerebellum	9.57	8.0-12.0	"
Total DNA (μmol)			
whole brain	619	775-1400	Low
forebrain	482	460-940	"
cerebellum	113	170-420	"
Cholesterol concentration (mg/g fresh weight)			
whole brain	6.5	6.2-10.0	Low
forebrain	6.5	6.4-9.4	"
cerebellum	5.2	5.0-8.5	"
stem	7.8	9.0-15.0	Very low
% Water			
whole brain	89.6	87.0-89.6	High
forebrain	89.7	87.2-89.7	"
cerebellum	88.2	85.5-89.3	"
stem	88.3	84.0-89.6	"

*From Dobbing and Sands (1973).

weight : body weight ratio obtained after death, which was 2 SD above the mean for 42 weeks' gestation. It thus appeared that there had been an increase in brain size while somatic growth had been restricted.

Nevertheless, the brain weight was very low for 42 weeks of gestation as was the cerebellar weight. In addition, the cerebellar weight : brain weight ratio was at the lower range of normal. A low cerebellar weight : brain weight ratio has also been found in animals whose growth is restricted at the time of rapid brain growth, indicating a more pronounced effect upon the cerebellum than upon the forebrain at this stage in development (Dobbing and Sands, 1973).

The cellularity of the brain measured by DNA concentration per unit weight was appropriate for age, but the total number of cells was reduced, reflecting the smaller overall size of the brain. It is likely that this represents a glial rather than a neuronal deficit as far as the forebrain is concerned, since forebrain neuronal multiplication occurs between 10 and 18 weeks of gestation (Dobbing, 1974). Cerebellar neuronal multiplication occurs later than in the forebrain and the reduction in cerebellar cellularity in this case may have been neuronal in addition to glial.

The cholesterol concentration (a good, though crude, index of myelination), and the water content (which is usually the reciprocal of the cholesterol concentration), are both considered good indices of brain maturation. The low cholesterol concentration (especially in the brain stem) and the rather high percentage of water found in this infant suggests immaturity in addition to smallness for a brain of 42 weeks of gestational age.

The human brain normally grows very quickly between 32 and 42 weeks of gestation (Dobbing, 1974), and by the phenomenon of 'brain sparing' may continue to grow comparatively well in adversity. This infant suffered serious cardio-respiratory and gastrointestinal complications which resulted in somatic growth restriction. In spite of these complications this infant on total intravenous feeding showed some postnatal brain growth over this 10-week period. Nevertheless, the brain as measured after death did show features of restriction in its growth and maturation by standards for 42 weeks' gestational age.

The 10-week period between 32 and 42 weeks of gestation is comparatively short in relation to the total period of the brain growth-spurt in man, which probably continues until about 2 years of postnatal age. It seems reasonable to assume that this infant would have had a good chance of normal brain growth and development if he had survived.

Summary

Little is known about the affects of long-term intravenous nutrition on brain growth and develop-

ment in low birthweight infants. We report the post-mortem analysis of the brain of an infant born at 32 weeks of gestation who died after 10 weeks of continuous intravenous feeding. During this time there was evidence of brain growth while somatic growth was severely restricted. Compared with normal data for brain biochemistry for 42 weeks of gestational age, measurements showed that the brain was small and biochemically immature with the cerebellum and brain stem being particularly affected.

We acknowledge the enormous amount of time and effort given to the care of this infant by all the resident medical staff, and in particular Sister P. Townsend and staff on the Special Care Baby Unit. We acknowledge also the surgical expertise and support of Mr. M. Gough, Consultant Paediatric Surgeon.

J.D. gratefully acknowledges the support of the National Fund for Research into Crippling Diseases and of the Medical Research Council, both of Great Britain.

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