Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 15 (3—4), pp 301 – 321 (1974)

Metabolic and hormonal effects of alternate infusion of hypertonic glucose and Aminosol-glucose in premature infants

By

I. RUBECZ, J. MESTYÁN, GY. SOLTÉSZ and M. HORVÁTH

Department of Paediatrics, University Medical School, Pécs

Received June 12, 1974

The metabolic and hormonal effects of a short term (24–36 hrs), alternating intravenous administration of hypertonic (16%) glucose and Aminosol-glucose were investigated in premature infants. The majority of the infants under 1 500 g showed pathological signs and did not tolerate oral feeding. The purpose of the study was to explore an intravenous alimentation program capable of ensuring an improved amino acid utilization in terms of nitrogen balance, and to prevent some of the adverse effects of the amino acid mixture. It was thought that the hormonal state created by 16% glucose might increase the capacity of the tissues to utilize the amino acids.

The relevant findings were as follows.

1. Plasma free fatty acids and amino acids decreased, plasma insulin and growth hormone increased markedly in response to 16% glucose. The plasma aminogram indicated a profound redistribution of amino acids.

2. Aminosol-glucose infusion after the 16% glucose, increased the concentration of amino acids, but only to the starting level. Thus the previously decreased α-amino nitrogen content allowed to avoid a hyperaminoacidaemia and a marked distortion of the plasma amino acid pattern. Administration of the amino acid–glucose mixture usually failed to maintain the previously stimulated insulin and growth hormone secretion.

3. The hormonal and metabolic responses to the intermittent infusion of hypertonic glucose and Aminosol-glucose were not associated with an improved nitrogen utilization. More than 50% of the administered amino acid nitrogen was excreted.

4. The metabolic acidosis observed under these condition was found to be variable, and practically compensated.

In previous studies [24, 32] dealing with the metabolic pattern of parenterally fed premature infants receiving Aminosol-glucose infusion, a marked shift occurred in substrate utilization: the participation of protein and carbohydrate oxidation increased, while fat metabolism became the smallest energy component. This unphysiological pattern of metalbolism not only involves an inefficient utilization of intravenously administered amino acids, but is also associated with a number of harmful metabolic, biochemical effects such as a quantitative and qualitative distortion of the free amino acid pattern [10, 15, 35], metabolic acidosis [5, 6, 33], hyperammonaemia [18], hyperosmolarity and increased blood urea level [17]. Most of these biochemical consequences are due

to the increased amino acid catabolism which may account for a sizable portion of the energy metabolism [24, 32].

In an attempt to avoid the deleterious effects of an amino acid mixture, and to achieve a satisfactory anabolic amino acid utilization, the alternate administration of hypertonic glucose and Aminosol-glucose was thought to be a useful technique for creating a metabolic and hormonal internal environment in order to prevent hyperaminoacidaemia and to promote protein synthesis. It is well-known that dietary carbohydrate and intravenous glucose have a specific action on protein metabolism, resulting in a decrease of urinary nitrogen output [8, 14, 26]. This nitrogen sparing effect is the resultant of stimulated insulin secretion which increases the transport of amino acids into the tissues [11, 22, 27, 28]. It has also been demonstrated that intravenous glucose, in contrast to the adult, elicits growth hormone release in the early neonatal period [7, 25, 30], which might favourably influence the balance between catabolic and anabolic utilization of amino acids. It appears justified to assume that infusion of an amino acid–glucose mixture would maintain the stimulated insulin and growth hormone secretion induced by hypertonic glucose, since similar hormonal changes are elicited by amino acids [19].

The purpose of the present study was to show whether the ability to conserve amino acids could be increased by such a design of parenteral administration of nutritive mixtures. This report summarizes the metabolic and hormonal data obtained in premature infants undergoing parenteral nutrition for a limited period of time.

Material and Methods

Infants. Nine premature and three full-term infants after unsuccessful attempts at early oral feeding were given glucose and Aminosol-glucose alternately for 24–36 hours. Table I shows the clinical data of the infants as well as the volume and the amount of calories infused. The majority of the infants weighing less than 1500 g were depressed and without clinical and radiological evidence of respiratory distress syndrome. In these infants pH and pCO_2 values obtained prior to intravenous alimentation were not lower than 7.20 and not higher than 50 mm Hg, respectively. Four infants died at a postnatal age ranging from 3 to 6 days. The major autopsy findings are also indicated in Table I. One infant weighing 1890 g had oesophageal atresia and intravenous feeding was started after operation. In a full term infant aged 33 days, secondary malabsorption caused by severe enteritis was the indication for giving intravenous nutrients.

Infusates. 16% glucose and 3.3% Aminosol-glucose mixture (Vitrum, Stockholm) were given intermittently by an infusion pump into a scalp vein. The design of the short-term parenteral feeding was as follows. First, 16% glucose was given at a rate from 0.06 to 0.12 ml/kg/min for 8 hours; this was followed by a 4-hour period of Aminosol-glucose infusion at the same rate; thereafter the alternating infusion of the two solutions was repeated once more over the same periods of time. Thus the 24 hr observation period consisted of two glucose (8 hours each) and two Aminosol-glucose (4 hours each) periods. This intermittent infusion of the two solutions represented a daily input ranging from 45.6 to 95.2 kcal/kg.

Chemical monitoring. Except one infant aged 33 days, blood samples were drawn from the umbilical vein prior to intravenous nutrition and at the end of each infusion period, thus at 8, 12, 20, 24 hours. The following determinations were made: glucose [29], FFA [9, 21], lactate [3], α-amino-nitrogen [34], plasma amino acid ratio (38), urea [4] and individual amino acids using a Beckman Automatic Amino Acid Analyser. Arterial blood samples

Table I.
Clinical data of infants, volume of fluid and amount of calories infused

No. of infant and sex	Gestational age, weeks	Birth weight, g and percentile	Postnatal age	History and perinatal pathology	Autopsy finding	Volume infused		Total calorie input, kcal/kg/day	Amount of nutrients		Amount of calories	
						ml/kg/day	ml/kg/min		Glucose, g/kg/day	Amino acids, g/kg/day	Glucose, kcal/kg day	Amino acids
1♂	29	780 <P_{10}	9 hrs	Hypothermia	Subarachnoidal haemorrhage	107.69	0.0747	59.80	13.84	1.01	56.74	3.06
2♂	29	1060 P_{10-25}	24 hrs	Threatening abortion	Pulmonary atelectasis	101.88	0.0707	55.18	12.56	1.12	51.49	3.69
3♂	27	1000	23 hrs	Threatening abortion	Pulmonary atelectasis	144.00	0.1000	78.02	17.76	1.58	72.81	5.21
4♂	29	1370 P_{25-50}	19 hrs	Internal version and extraction	--------	105.10	0.0729	56.92	12.96	1.15	58.13	3.79
5♂	38	1700 <P_{10}	6 hrs	Intrauterine malnutrition. Hypoglycaemia	--------	84.70	0.0588	45.61	10.44	0.93	42.80	2.81
6♂	37	2870 P_{25-50}	33 days	A–O incomp. Perinatal infection. Hyperbilirubinaemia. Enteritis. Malabsorption.	--------	171.43	0.1190	95.17	21.82	1.88	89.46	5.71
7♀	34	1440 <P_{10}	24 hrs	Toxaemia. Breech delivery. Intrauterine malnutrition. Asphyxia.	--------	100.00	0.0694	48.63	11.05	1.10	45.30	3.33
8♀	29	1430 P_{50-75}	8 hrs	Twin pregnancy. Foeto-foetol transfusion. Anaemia.	--------	100.69	0.0699	54.21	12.41	1.10	50.88	3.33
9♀	29	1500 P_{50-75}	8 hrs	Twin pregnancy. Foeto-foetal transfusion. Plethora.	--------	96.00	0.0666	52.00	11.84	1.05	48.54	3.46
10♀	36	1890 <P_{10}	14 hrs	Toxaemia. Hydramnios. Oesophageal atresia. Aspiration pneumonia.	--------	152.38	0.1058	82.78	18.79	1.67	77.04	5.74
11♀	28	1030 P_{10-25}	6 hrs	Threatening abortion. Bleeding during pregnancy.	--------	104.85	0.0729	56.80	12.93	1.15	53.01	3.79
12♀	27	850	6 hrs	Threatening abortion. Hypothermia	Intraventricular haemorrhage	84.70	0.0588	45.57	10.43	0.93	42.76	2.81

were taken for determination of acid-base status by the equilibration method of ASTRUP et al. [2].

Urine was collected fractionally under toluene and the fractions were frozen separately until analyzed. Urinary titratable acid was measured by the method of GYÖRI et al. [16], ammonium excretion according to MCCULLOUGH [23], and bicarbonate by determining the carbon dioxide content of the urine using a micromethod [31].

Net acid excretion was given by the sum of urinary titratable acid (TA) plus ammonium (NH_4^+) minus bicarbonate (HCO_3). Endogenous acid production was approximated at 2 mEq per kg per day, as assumed by ALBERT and WINTER [1] and confirmed recently in premature infants by CHAN [5]. Exogenous acid input was calculated from the volume of Aminosol-glucose infused, using the value of 14 mEq/l titratable acidity given by WRETLIND [39]. Urinary net acid excretion and the net acid balance calculated for two 12 hr periods (each consisting of 4 hr Aminosol-glucose infusion and 8 hour 16% glucose infusion) was only determined in five premature infants (Nos. 1–5).

In the latter five infants, the amount of nitrogen infused and excreted as urea and α-amino nitrogen was also determined. Nitrogen balance was calculated for two 12 hr intervals as well as for the whole observation period. In these balance studies the excretion rates obtained during a 4 hr preinfusion + the first 16% glucose were used for comparison. For statistical analysis the means and standard errors were calculated; when it seemed necessary, significance was estimated by Student's *t* test.

RESULTS

Metabolic Responses

Blood glucose. The infusion of 16% glucose-solution caused an increase in blood glucose level (Fig. 1). In some instances it exceeded 200 mg per 100 ml when glucose appeared in the urine. During the subsequent period when the amino acid–glucose mixture was given, glucose concentration fell below 100 mg per 100 ml. The mean value obtained at the end of this period was not significantly higher than the fasting glucose concentration.

Plasma FFA. As expected (Fig. 1), plasma FFA declined gradually from a mean fasting concentration of 0.6 mEq/l to 0.1 mEq/l which was a highly significant response in plasma free fatty acids. From Fig. 1 it can be seen that the decline continued during Aminosol-glucose infusion representing a considerably lower glucose load.

Blood lactate. Fig. 1 shows that the lactate level decreased slightly during the consecutive periods of parenteral nutrition resulting in a fall of 8 mg per 100 ml at the end of the observation period. In five instances, however, a rise in lactate was observed during the first infusion period of hypertonic glucose.

α-amino nitrogen. From Fig. 2 it is obvious that 16% glucose administration caused a marked and significant fall in mean total plasma amino acid content. During the Aminosol-glucose infusion it returned to the fasting level and in neither instance was hyperaminoacidaemia observed. In three infants exhibiting a low fasting α-amino nitrogen concentration (3 mg per 100 ml) the amino acid–glucose mixture caused a rise above the starting level which, however, did not exceed 5 mg per 100 ml.

Urea nitrogen. The mean changes in blood urea during the consecutive periods of parenteral feeding are shown in Fig. 2. A definite tendency to increase was observed, but owing to the wide variation of the individual values, the highest mean urea obtained at the end of the second Aminosol-glucose infusion period did not significantly differ from the fasting concentration.

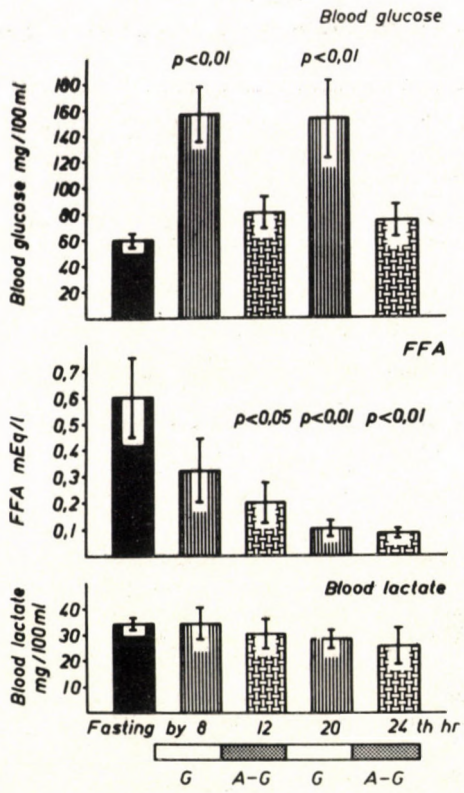

FIG. 1. Responses of blood glucose, lactate and FFA to the alternate infusion of hypertonic glucose and Aminosol-glucose. G = glucose; A–G = Aminosol-glucose

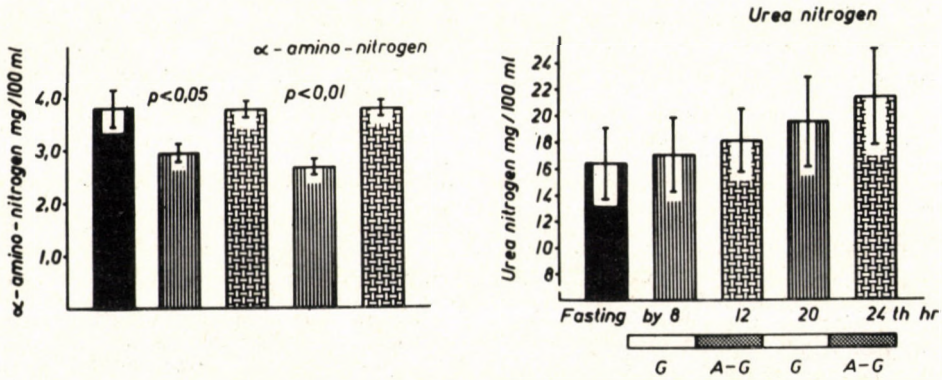

FIG. 2. α-amino nitrogen and urea content of plasma during hypertonic glucose and Aminosol-glucose infusion. G = glucose; A-G = Aminosol-glucose

Table II.

Plasma amino acid concentrations / mean and range / in five premature infants

Amino acid	Fasting, μmol/l	By 8th hr during first glucose period, μmol/l	By 4th hr during first Aminosol-glucose period, μmol/l
Taurine	**196.48** 46.12–359.13	**127.29** 29.17 – 242.90	**103.57** 42.41 – 198.57
Aspartic acid	**31.64** 28,18 – 45.55	**36.92** 26.21 – 42.70	**68.49** 40.56 – 89.67
Threonine	**173.19** 110.16 – 252.37	**124.24** 110.04 – 134.84	**169.93** 127.95 – 214.46
Serine	**62.96** 31.47 – 124.27	**38.97** 17.11 – 64.51	**54.20** 34.02 – 103.60
Glutamic acid	**479.79** 222.51 – 764.04	**317.08** 183.60 – 529.05	**293.99** 219.62 – 401.02
Citrulline	**35.09** 19.79 – 71.01	**17.57** 8.56 – 21.95	**18.44** 12.27 – 24.11
Proline	**243.80** 95.44 – 370.24	**212.62** 76.33 – 510.17	**264.74** 116.30 – 371.70
Glycine	**292.56** 212.50 – 369.43	**229.75** 126.28 – 351.02	**190.88** 144.24 – 250.35
Alanine	**268.02** 212.82 – 308.62	**264.39** 144.25 – 470.46	**277.91** 137.24 – 301.80
Cystine	**64.53** 26.06 – 94.63	**44.23** 28.51 – 65.30	**51.93** 29.41 – 85.16
Valine	**145.56** 71.68 – 203.41	**78.01** 60.88 – 94.56	**140.04** 98.05 – 181.91
Methionine	**38.12** 9.75 – 64.06	**17.60** 3.75 – 37.84	**31.90** 18.26 – 41.35
Isoleucine	**61.71** 31.11 – 79.63	**32.09** 22.31 – 44.44	**60.28** 33.19 – 85.22
Leucine	**86.23** 49.10 – 103.56	**45.02** 34.00 – 52.90	**104.83** 67.15 – 150.07
Tyrosine	**302.90** 185.58 – 467.64	**251.79** 88.55 – 463.07	**249.28** 116.93 – 430.14
Phenylalanine	**141.59** 87.31 – 190.10	**86.90** 49.16 – 122.56	**120.78** 111.92 – 139.20
Histidine	**54.77** 50.21 – 59.90	**83.38** 45.73 – 141.42	**98.01** 44.34 – 207.57
Arginine	**60.36** 23.81 – 78.47	**33.55** 11.02 – 62.64	**52.48** 23.22 – 72.95

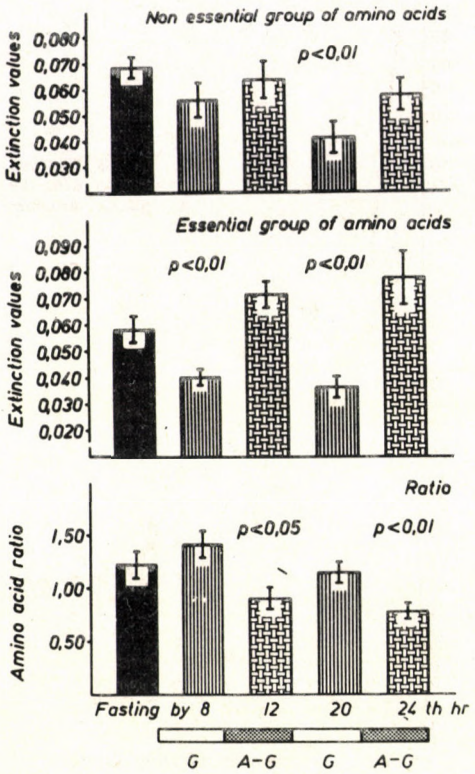

FIG. 3. Responses to hypertonic glucose and Aminosol-glucose of the combined plasma concentration of nonessential (glycine + serine + glutamine + taurine) and essential (leucine + isoleucine + valine + methionine) amino acids. The ratio of these two groups of amino acids is also shown. G = glucose; A-G = Aminosol-glucose

Plasma aminogram. The extinction values indicating the combined plasma concentration of the non-essential (glycine + serine + glutamine + taurine) and essential (leucine + isoleucine + valine + methionine) group of amino acids are shown in Fig. 3. It can be seen that the plasma concentration of both groups of amino acids was depressed by glucose administration. This decline was, however, more pronounced in the level of essential leucine + isoleucine + valine + methionine causing a slight increase in the ratio. Infusion of the amino acid mixture was accompanied by a disproportionate increase in the two groups of amino acids which resulted in a marked fall in their ratio. The more pronounced rise in the concentration of leucine + isoleucine + valine + methionine reflected the higher concentration of these amino acids in the mixture. By the end of the following glucose period the plasma levels of both groups of amino acids were again significantly lower than the starting level. This period was again followed by Aminosol-glucose infusion with similar changes in the plasma content of

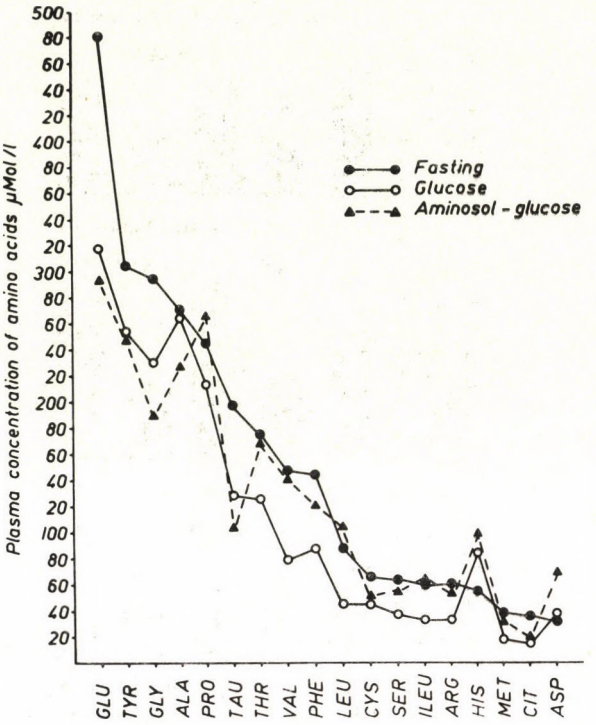

FIG. 4. Plasma concentration of individual amino acids during fasting and the alternate infusion of glucose and Aminosol-glucose

the two groups of amino acids as previously.

In five infants the plasma concentration of 18 amino acids was determined using an automatic amino acid analyser. The fasting values (means and ranges) and those obtained by the end of the first glucose and Aminosol-glucose period are shown in Table II as well as in Fig. 4. Owing to the small number of infants, statistical analysis was not performed. The changes observed were in accordance with those obtained by Whitehead's amino acid ratio test.

From Fig. 4 it is apparent that, except alanine, histidine and aspartic acid, the plasma concentration of the amino acids decreased in response to the infusion of glucose. Administration of the amino acid mixture partly restored the plasma aminogram; the concentration of some of the amino acids was, however, still below the fasting level, and only four (proline, leucine, histidine, and aspartic acid) showed a higher concentration.

Insulin and Growth Hormone

Plasma insulin concentration was followed in eight intermittently fed premature infants (Fig. 5). In one infant no change was observed, in another the high fasting insulin concentration fell in re-

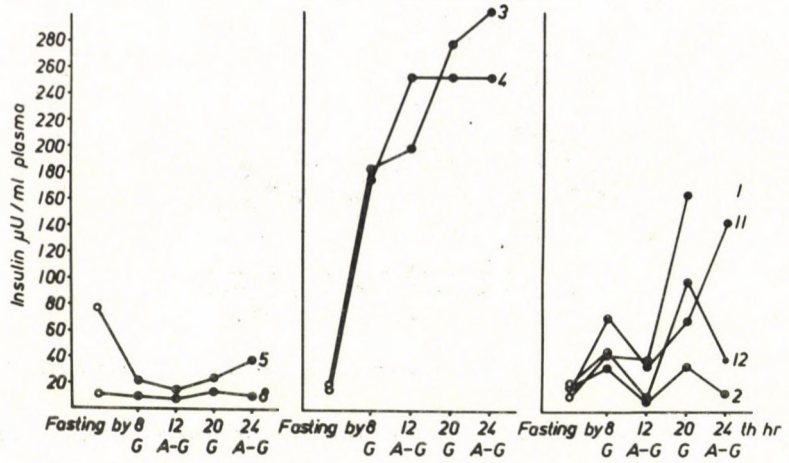

FIG. 5. Response of plasma insulin to the alternate infusion of hypertonic glucose and Aminosol-glucose. The figures correspond to the identification numbers of the infants scheduled in Table I

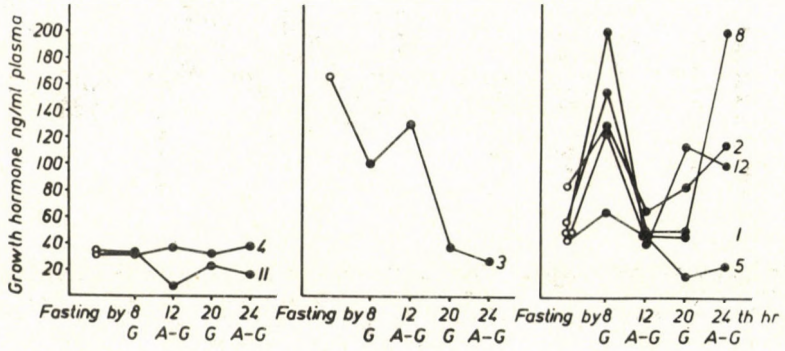

FIG. 6. Response of plasma growth hormone to hypertonic glucose and Aminosol-glucose infusion. The figures correspond to the identification numbers of the infants scheduled in Table I

sponse to parenteral feeding. Two infants responded by a marked increase in plasma insulin content by the end of the first 8 hr interval of 16% glucose, and a further considerable increase occurred during the rest of the observation period. In four premature infants the moderately increased plasma insulin concentration in response to the first glucose infusion fell when Aminosol-glucose was administered, and rose again by the end of the second 8 hr period of glucose.

As it can be seen in Fig. 6, in two infants plasma growth hormone concentration remained practically unchanged and in one the high fasting level declined during intermittent intravenous nutrition. In five infants, however, 16% glucose caused an increase in the plasma growth hormone content. By the end of

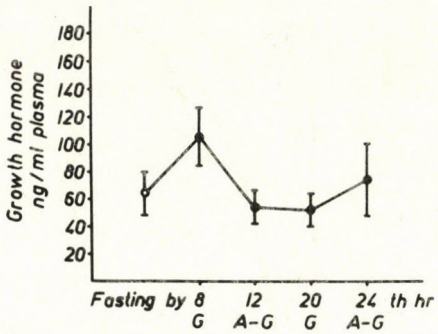

FIG. 7. Mean plasma growth hormone level during glucose and Aminosol-glucose infusion

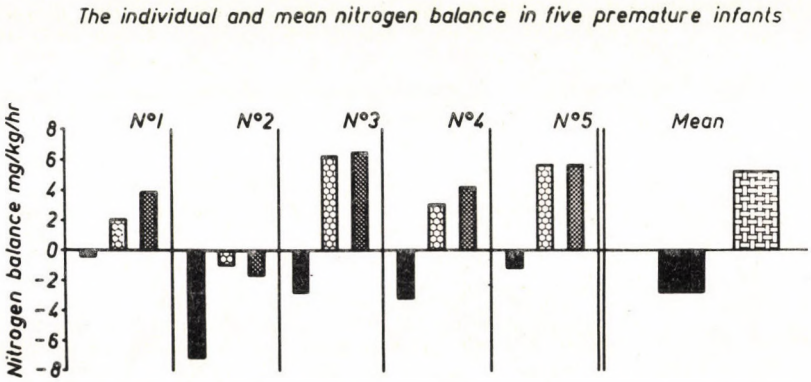

FIG. 8. Individual and mean nitrogen balance in five premature infants receiving hypertonic glucose and Aminosol-glucose alternately. ■ 4 hr fasting + 8 hr glucose infusion; ▨ 4 hr Aminosol-glucose + 8 hr glucose infusion; □ 4 hr Aminosol-glucose + 8 hr glucose infusion; ▥ mean of the two 4 hr Aminosol-glucose + 8 hr glucose periods

Aminosol-glucose infusion, it fell to the fasting level and in three infants it rose again during the further course of parenteral feeding. Mean growth hormone response is demonstrated in Fig. 7.

Nitrogen Balance

In Table III, the amount of nitrogen infused and excreted as urea in the urine during two consecutive 12 hour intervals as well as in the course of the total observation period (24 hours) is demonstrated. The proportion of the nitrogen input excreted with urine varied greatly in the individual infants. While, e.g. in infant No. 5 only about 15% was excreted, in infant No. 2 the loss exceed the amount infused. On the average, somewhat more than 50% of the nitrogen input was excreted as urea nitrogen.

Nitrogen balance in terms of mg/kg/hr is shown in Fig. 8, which visualizes well the individual differences among the five

Table III.

Amount of nitrogen infused and excreted as urea during alternate infusion of hypertonic glucose and Aminosol-glucose

Infant No.	Urea nitrogen excreted during 4 hr preinfusion + 8 hr glucose period, mg	12 hr periods: 4 hr Aminosol-glucose + 8 hr glucose			12 hr periods: 4 hr Aminosol-glucose + 8 hr glucose			Total observation period / 24 hours /		
		Amount of nitrogen infused, mg	Amount of nitrogen excreted, mg	Proportion excreted, per cent	Amount of nitrogen infused, mg	Amount of nitrogen excreted, mg	Proportion excreted, per cent	Amount of nitrogen infused, mg	Amount of nitrogen excreted, mg	Proportion excreted, per cent
1	3.57	63.36	46.78	73.83	68.64	29.86	43.50	132.00	76.64	58.06
2	29.70	89.76	101.39	112.84	95.04	116.48	122.55	184.80	217.87	117.89
3	32.79	126.72	52.35	41.31	126.72	37.43	29.53	253.44	89.78	35.42
4	17.34	126.72	77.86	61.44	126.72	60.65	47.86	253.44	138.51	54.64
5	22.53	126.72	18.49	14.59	126.72	14.71	11.60	253.44	33.20	13.09
Mean	21.18	106.65	59.37	60.80	108.76	51.82	53.00	215.42	111.20	55.82
Range	3.57 - 32.79	63.36 - 126.72	18.49 - 101.39	14.59 - 112.84	68.64 - 126.72	14.71 - 116.48	11.60 - 122.55	132.00 - 253.44	33,20 - 217.87	13.09 - 117.89

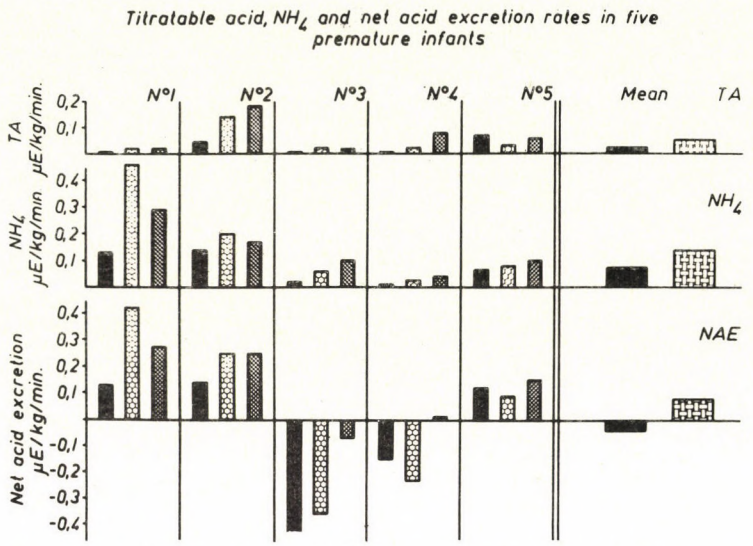

FIG. 9. Titratable acid, NH_4 and net acid excretion in five premature infants. □ 4 hr fasting + 8 hr glucose infusion; □ 4 hr Aminosol-glucose + 8 hr glucose infusion; □ 4 hr Aminosol-glucose + 8 hr glucose infusion; ❑ mean of the two 4 hr Aminosol-glucose + 8 hr glucose periods

premature infants examined. The negative nitrogen balance of the period used as control (4 hr preinfusion period + 8 hr period of 16% glucose) showed a marked individual variation. The positive balance obtained during the combined fractional periods Aminosol-glucose + glucose varied between 2 and 6.2 mg/kg/hr. In infant No. 2, whose urinary nitrogen excretion rate was very high when only glucose was given, a positive balance could not be achieved during the further course of alternate infusion of Aminosol-glucose and glucose solution. The negative balance decreased markedly, but urea-nitrogen excretion rate still exceeded the rate of amino acid nitrogen infusion.

Mean total balance in the five very low birth weight infants is seen in Fig. 8.

In Table IV, urinary α-amino nitrogen excreted during the two 12 hr-intervals (Aminosol-glucose + glucose) and in the total (24 hrs) observation period is shown. For comparison, the excretion rate obtained during the 4 hr preinfusion period + 8 hr 16% glucose period is given. It is seen that in three infants (Nos. 1, 2, 3) α-amino nitrogen excretion increased, in the remainder two it decreased. The mean rise during the total observation period (24 hrs) amounted to about 3 mg/kg.

Net Acid Balance and Acid–Base Status

In Fig. 9, titratable acid, NH_4 and net acid excretion during the 4 hr preinfusion period + 8 hr glucose period and in the course of two consecutive 12 hr infusions of Aminosol-glucose + glucose as well as that for the total parenteral feeding period (24 hrs) is shown. There were great individual differences in renal TA and NH_4 output which did not al-

Table IV.

Urinary amino acid nitrogen excretion during intermittent parenteral feeding

Infant No.	Amino acid nitrogen excreted during 4 hr preinfusion + 8 hr glucose period, mg/kg/12 hrs	12 hour periods				Total observation period / 24 hours /	
		4 hr Aminosol-glucose + 8 hr glucose		4 hr Aminosol-glucose + 8 hr glucose			
		Amino acid N infused, mg/kg/12 hrs	Amino acid N excreted, mg/kg/12 hrs	Amino acid N infused, mg/kg/12 hrs	Amino acid N excreted, mg/kg/12 hrs	Amino acid N infused, mg/kg/12 hrs	Amino acid N excreted, mg/kg/12 hrs
1	1.78	81.20	17.29	88.00	3.05	84.60	10.17
2	6.34	84.68	8.13	89.64	12.27	87.16	10.20
3	3.28	126.72	11.95	126.72	13.73	126.72	12.84
4	18.05	92.48	16.26	92.48	9.53	92.48	12.89
5	7.94	74.52	7.08	74.52	6.06	74.52	6.57
Mean	7.47	91.92	12.14	94.27	8.92	93.09	10.53
Range	1.78 - 18.05	74.52 - 126.72	7.08 - 17.29	74.52 - 126.72	3.05 - 13.73	74.52 - 126.72	6.57 - 12.89

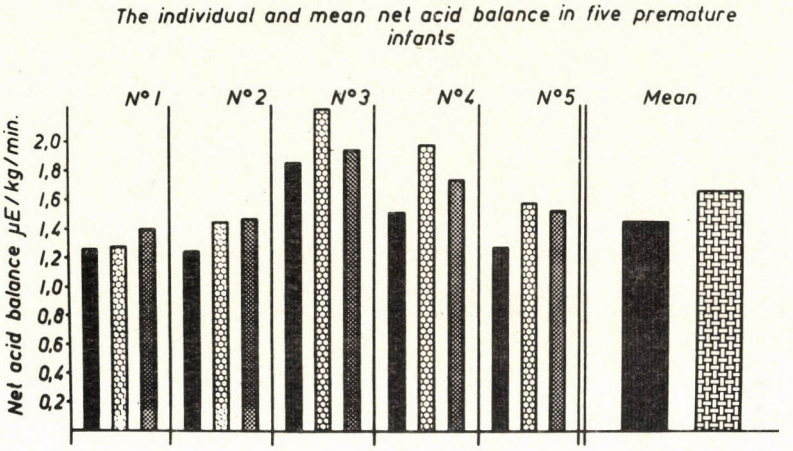

FIG. 10. Individual and mean net acid balance in five premature infants. □ 4 hr fasting + 8 hr glucose infusion; □ 4 hr Aminosol-glucose + 8 hr glucose infusion; □ 4 hr Aminosol-glucose + 8 hr glucose infusion; □ mean of the two 4 hr Aminosol-glucose + 8 hr glucose periods

ways change parallel. For example, in infant No. 1, the response in NH_4 excretion was marked, whereas TA excretion increased slightly. The reverse was observed in infant No. 2: the pronounced rise in urinary TA output was unaccompanied by a response in NH_4 excretion. According to the mean excretion rates, titratable acid constituted about one third, and NH_4 excretion two thirds, of the total net acid output. Two infants (Nos. 3 and 4) excreted large amounts of bicarbonate due to bicarbonate infusion. In the remainder, bicarbonate excretion was low.

Net acid balance in the five premature infants before and during the two 12 hour periods of intravenous alimentation is demonstrated in Fig. 10. In every instance, the positive net acid balance increased in response to intermittent intravenous feeding, indicating H^+ retention. Mean net acid balance of the five infants is also shown.

Fig. 11 shows the pH and BE obtained in the prematures whose net acid balance was calculated. In three infants exhibiting moderate metabolic acidosis the complete acid–base status, and in one infant, who was alkalotic for unknown reasons, only the pH was followed before and during parenteral feeding. In the acidotic infants, BE values fell to levels between –10 and –15 mEq/l by the end of the 24-hour intravenous feeding period. However, the pH showed minor variations, and was more or less maintained at the starting level. Mean pH and BE ± SE for the whole group of infants including those in whom acid balance studies were performed, are demonstrated in Fig. 12. It is seen that the mean pH was maintained throughout the observation period.

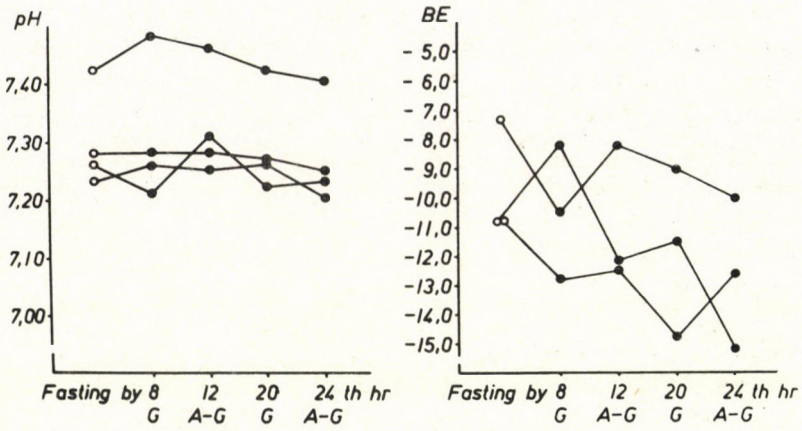

FIG. 11. pH and BE in premature infants whose net acid balance was calculated

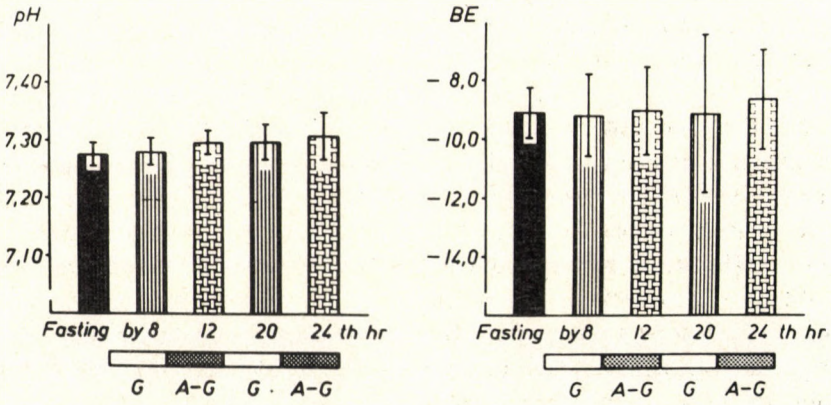

FIG. 12. Mean ± SE pH and BE of the whole group of infants including those in whom acid balance studies were performed

DISCUSSION

The purposes of the alternate administration of hypertonic glucose and Aminosol-glucose were to explore an intravenous alimentation program in order to achieve a more efficient amino acid utilization in terms of nitrogen balance, and to eliminate some of the adverse effects of an amino acid mixture such as hyperaminoacidaemia, metabolic acidosis, and increased urea production. The short-term program followed was not entirely sequentional as far as glucose and amino acid administration are concerned. Only the amino acid mixture was given intermittently for a period of 4 hours; glucose as the basic caloric source was, in fact, infused throughout the observation period.

Glucose concentration of the solutions differed, however, markedly: 16% glucose in water alternated with 5% glucose in the amino acid mixture (Aminosol-glucose).

In order to increase the caloric input, 16% glucose was chosen instead of a 10% solution. The rate of infusion was approximately 0.06–0.12 ml/kg/min, which in the majority of infants was not accompanied by a rise in blood glucose over 200 mg per 100 ml. Although 16% glucose was administered into a scalp vein, no signs of phlebitis were observed. Besides the increase in caloric input, a further aim of giving 16% glucose was to create a metabolic state favourable for transport of amino acids into cells, and thus for improving amino acid utilization.

It is a well-established fact that dietary or intravenous carbohydrate does not only serve as an energy source but has also an important action on protein metabolism [8, 14]. Intravenous glucose is capable of decreasing urinary nitrogen output of the fasting subject [26]. This sparing effect on protein catabolism is probably the result of an increased insulin secretion which is known to promote protein synthesis [22, 27, 28]. Thus our aim with 16% glucose was to induce a hyperinsulinaemic state which might increase the capacity of the tissues to utilize amino acids. At first sight it might seem unreasonable to provide glucose and amino acid alternately, but it should be kept in mind that the amino acid mixture was given together with 5% glucose which, although at a lower rate, was expected to ensure a continuous insulin release. Furthermore, it was assumed that the simultaneously administered amino acid mixture could also contribute to the maintenance of stimulated insulin secretion.

Plasma Metabolites, Insulin, Growth Hormone

FFA and α-amino nitrogen responded with a marked fall to the hyperglycaemia caused by the infusion of hypertonic glucose. Both responses were in all probability due to a common cause, to the stimulation of insulin secretion. The insulin response was variable, in two instances an excessive rise was observed. It is common knowledge that insulin inhibits the release of FFA and enhances amino acid uptake by the tissue, particularly by the muscles. To explain the metabolic consequences of glucose infusion, besides insulin, the release of growth hormone observed in the majority of infants should also be taken into consideration.

As regards the latter effect it appears reasonable to suppose that the stimulation of growth hormone secretion by hyperglycaemia, which is a well-known paradoxical hormonal reaction in the newborn, contributes to the removal of amino acids from the plasma. The simultaneous release of the two hormones might act synergistically as far as the capacity for protein synthesis is concerned. According to the observations of MUNRO and THOMSON [26] made in adults, all the essential amino acids and the majority of the non-essential ones respond by a rapid fall to carbohydrate administration. SWENDSEID et al. [37]

reported similar findings after glucose ingestion by adult subjects. In these studies, while the total amount of essential amino acids was significantly decreased, no change occurred in non-essential amino acids. Some individual dispensable amino acids responded, however, by a fall or rise in their plasma concentration. The qualitative changes in the plasma aminogram obtained in the present studies by using the plasma amino acid ratio test [38] also pointed to a profound redistribution of amino acids. The combined concentration of amino acids comprising the two groups included in Whitehead's quotient were affected, but only that of the essential leucine + isoleucine + valine + methionine fell significantly below the initial level. This was in accordance with the findings of SWENDSEID et al. [37] in adults that the removal of branched chain amino acids from the plasma was particularly pronounced after glucose loading. The greatest decrease was observed in leucine.

The metabolic removal of amino acids from the plasma was evident also from the changes in the concentration of 18 individual amino acids observed in five infants. In view of the small number of examinations, statistical analysis of the differences in the means was not performed. However, except alanine, histidine and aspartic acid, both non-essential and essential amino acids decreased markedly during the 8 hr glucose period.

Experimental evidence suggests that the changes in plasma amino acid concentration brought about by glucose infusion reflect an enhanced protein synthesis in muscle. MUNRO and THOMSON [26] as well as SWENDSEID et al. [37] concluded that the pattern of amino acid removal from plasma resembled the composition of muscle protein. But the increased amino acid transport to tissues caused by insulin secretion in response to glucose might not necessarily indicate an enhanced protein synthesis. The organs can probably take up and accumulate amino acids in the free amino acid pool without immediately metabolizing them or using them for anabolic processes. Since muscle constitutes a large proportion of body weight, it is quantitatively the major site of free amino acid deposition during glucose or amino acid infusion.

The infusion of Aminosol-glucose at a rate of 0.06–0.12 ml/kg/min increased the concentration of the circulating free amino acids, but only to the starting level. Thus, the previously depressed α-amino nitrogen content allowed to avoid a hyperaminoacidaemia, one of the undesirable consequences of infusing amino acid mixtures.

The alterations in the individual amino acids were both qualitatively and quantitatively similar to those included in the plasma amino acid ratio. While the plasma levels of the essential amino acids approached or attained the fasting value, some of the non-essential amino acids remained at lower levels.

The interrelation between plasma insulin and amino acid levels is well-known. On the one hand, insulin reduces the amount of amino acids, which in the present studies was indirectly achieved by glucose administration. On the other hand, many amino acids, particularly the

branched chain ones, induce a prompt and considerable increase in the plasma insulin levels [12, 13]. Thus one would expect a stimulation of insulin secretion in response to the amino acid mixture, which might be potentiated by the simultaneously administered 5% glucose (Aminosol-glucose).

As seen in Fig. 5, a persistently and excessively high insulin level was observed in two infants only. In four others the insulin concentration, which was previously increased by 16% glucose, fell during Aminosol-glucose infusion, and rose again in the course of the following glucose period. Thus, except two instances, the amino acid mixture failed to maintain stimulated insulin secretion, although a variety of amino acids are capable of causing insulin release. An explanation of this lacking insulin response might be that the Aminosol-glucose infusion was not accompanied by hyperaminoacidaemia, it only normalized the amino nitrogen content which had previously been decreased by hypertonic glucose. Therefore, it appears reasonable to assume that an increased plasma amino acid content represents an intensive stimulus on insulin release, such as it is the case when a marked rise in blood glucose occurs in response to a hypertonic solution. The normalization of the suppressed aminoacidaemia was probably insufficient for ensuring a marked rise of the plasma insulin level. Neither the alteration in the plasma amino acid pattern, characterized by an increase in the proportion of branched chain amino acids, appeared to be capable to release insulin. This is interesting in the light of recent observations of FELIG et al. [11], that in obese adults branched chain amino acids may have an important role on the feed-back regulation of insulin secretion.

Besides insulin, growth hormone might also have a role in the reduction of plasma amino acids caused by glucose administration in the newborn infant. Growth hormone is known to augment amino acid uptake, and to increase protein synthesis. As it was expected [7, 25, 30] hypertonic glucose increased the growth hormone level, but this was not maintained by the infusion of the amino acid–glucose mixture. This indicated that the amino acids given under our experimental conditions did not elicit a release of growth hormone although certain amino acids such as arginine, may act as a potent stimulus of growth hormone secretion even in the full term newborn infant [20, 36]. The lack of response in the present investigations might have been due to the infants' immaturity or to the absence of hyperaminoacidaemia during Aminosol-glucose infusion.

Nitrogen Balance

The present design of parenteral nutrition in premature infants was not associated with a nitrogen utilization better than in our previous examinations [24]. More than 50% of the administered amino acid nitrogen was excreted as urea by the kidney. There was, however, a great individual variation which reflected the difference in the anabolic utilization of amino acids. The mean increase in renal amino acid excretion in

terms of α-amino nitrogen was negligible.

The hormonal and metabolic responses to the short-term intermittent administration of hypertonic glucose and Aminosol-glucose was not associated with an increased amino acid sparing action, although hypoaminoacidaemia was induced by the former and hyperaminoacidaemia had been avoided by means of the latter.

A large amount of amino acid removed from the plasma was probably rapidly oxidized, resulting in a low utilization of amino acids for protein synthesis. This was reflected by the gradually increasing blood urea concentration. Since the amino acid mixture was not given in an excessive amount, which is known to stimulate amino acid degradation, imbalance, and the catabolic state of the newborns' insufficient calorie supply might have been the major factor responsible for the failure of achieving a better nitrogen retention. All these factors increase the likelihood of amino acids becoming degraded instead of being incorporated into protein.

The increased uptake of amino acids by the organs during intravenous feeding was probably temporary, and a large part of it seems to have been released on cessation of the stimulated hormonal secretion participating in the control of distribution and utilization of the administered amino acids. A smaller part of the increased tissue amino acid pool may be used for protein synthesis which, however, does not imply net protein formation. An unphysiological route of administration, imbalanced mixture, excessive amount, grossly changed internal amino acid environment, multiple metabolic and hormonal response are the factors which in the early postnatal period hinder to achieve the main goal of parenteral feeding: to influence favourably the balance between synthesis and breakdown.

Acid–Base Balance

The metabolic acidosis observed was variable and practically compensated. Hydrogen ion input exceeded hydrogen ion excretion with a drop in base excess. The acidifying effect was, however, less pronounced than that associated with Aminosol-glucose administered continuously, and at a higher rate in our previous studies [33]. This can simply be explained by the less excessive acid load represented by the parenteral feeding design.

The pattern of hydrogen ion excretion showed individual variations. Mean ammonia ion excretion amounted approximately to two thirds of the total net acid excretion. As regards the renal responses, the majority of premature infants studied was immature and sick, and thus less capable of adequately responding to an acidogenic amino acid mixture.

ACKNOWLEDGEMENT

We are indebted to Dr. R. D. G. MILNER (Dept. of Child Health, Manchester University) for growth hormone and insulin estimations.

References

1. Albert, M. S., Winters, R. W.: Acid-base equilibrium of blood in normal infants. Pediatrics **37**, 728 (1966).
2. Astrup, P., Jorgensen, K., Siggaard-Andersen, A.: The acid-base metabolism: A new approach. Lancet **1**, 1035 (1960).
3. Barker, S. B., Summerson, W. H.: The colorimetric determination of lactic acid in biological material. J. biol. Chem. **138**, 535 (1941).
4. Ceriotti, G.: Ultramicro determination of plasma urea by reaction with diacetylmonoxide antipyrine without deproteinization. Clin. Chem. **17**, 400 (1971).
5. Chan, J.C.M.: The influence of synthetic amino acid and casein hydrolysate on the endogenous production and urinary excretion of acid in total intravenous alimentation. Pediat. Res. **6**, 789 (1972).
6. Chan, J.C.M., Ash, M.J., Lin, St., Hays, D.M.: Hyperalimentation with amino acid and casein hydrolysate solutions. Mechanisms of acidosis. J. Amer. med. Ass. **220**, 1700 (1972).
7. Cornblath, M., Parker, M.L., Reisner, S.H., Forbes, A.E., Daughady, W.H.: Secretion and metabolism of growth hormone in premature and full-term infants. J. clin. Endocr. **25**, 209 (1965).
8. Cuthbertson, D.P., Munro, H.N.: The relationship of carbohydrate metabolism to protein metabolism. Biochem. J. **33**, 128 (1939).
9. Dalton, C., Kcwalski, C.: Automated colorimetric determination of free fatty acids in biologic fluids. Clin. Chem. **13**, 744 (1967).
10. Das, J. B., Filler, R.M., Rubin, V.G., Eraklis, A.J.: Intravenous dextrose-amino acid feeding: the metabolic response in the surgical neonate. J. pediat. Surg. **5**, 127 (1970).
11. Felig, P., Marliss, E., Cahill, G.F.: Plasma amino acid levels and insulin secretion in obesity. New Engl. J. Med. **28**, 811 (1969).
12. Floyd, J.C., Fajans, S.S., Conn, J.W., Knopf, R.F., Rull, J.: Stimulation of insulin secretion by amino acids. J. clin. Invest. **45**, 1486 (1966).
13. Floyd, J.C., Fajans, S.S., Knopf, R.F., Rull, J., Conn, J.W.: Postprandial aminoacidemia and insulin secretion: Physiologic relationship. J. Lab. clin. Med. **64**, 858 (1964).
14. Gamble, J.L.: Chemical anatomy. Physiology and pathology of extracellular fluid: A lecture syllabus. 5th ed. Harvard University Press, Cambridge 1947.
15. Ghadimi, H., Abaci, F., Kumar, S., Rathi, M.: Biochemical aspects of intravenous alimentation. Pediatrics **48**, 955 (1971).
16. Győri, A.Z., Nergin, A., Edwards, K.D.: Urinary excretion of titratable acid and its relationship to urinary pH and inorganic phosphorus excretion. Aust. Ann. Med. **17**, 236 (1968).
17. Helmuth, W.V., Adam, P.A.J., Sweet, A.Y.: The effects of protein hydrolysate-monosaccharide infusion on low-birth-weight infants. J. Pediat. **81**, 129 (1972).
18. Johnson, J.D., Albritton, W.L.: Hyperammonemia accompanying parenteral nutrition in newborn infants. J. Pediat. **81**, 154 (1972).
19. Kipnis, D.M., Noall, M.W.: Stimulation of amino acid transport by insulin in the isolated rat diaphragm. Biochim. biophys. Acta. (Amst.) **28**, 226 (1958).
20. Knopf, R.F., Conn, J.W., Floyd, J.C., Fajans, S.S., Rull, J.A., Guntsche, E.M., Thiffault, C.A.: Plasma growth hormone response to intravenous administration of amino acids. J. clin. Endocr. **25**, 1140 (1965).
21. Laurell, S., Tibbling, G.: Colorimetric microdetermination of free fatty acids in plasma. Clin. chim. Acta **16**, 57 (1967).
22. Manchester, K.L., Young, F.G.: Insulin and protein metabolism. Vitam. and Horm. **19**, 95 (1961).
23. McCullough, H.: A simple microtechnique for the determination of blood ammonia and a note to the effect of exercise. Clin. chim. Acta **19**, 101 (1968).
24. Mestyán, J., Rubecz, I.: The metabolic pattern of premature infants receiving Aminosol-glucose infusion. Acta paediat. Acad. Sci. hung. **14**, 319 (1974).
25. Milner, R.D.G., Wright, A.D.: Blood glucose, plasma insulin and growth hormone response to hyperglycaemia in the newborn. Clin. Sci. **31**, 309 (1966).
26. Munro, H. N., Thomson, S.W.T.: Influence of glucose on amino acid metabolism. Metabolism **2**, 354 (1953).
27. Munro, H.N.: The role of insulin in the regulation of protein metabolism. Scot. med. J. **1**, 285 (1956).
28. Munro, H.N., Black, J.G., Thomson, S.W.T.: The mode of action of dietary carbohydrate on protein metabolism. Brit. J. Nutr. **13**, 475 (1959).
29. Pryce, J.D.: A simple rapid method for determining glucose in blood or plasma. Analyst **92**, 198 (1967).
30. Roth, J., Click, S.M., Yalow, R.S., Berson, S.A.: The influence of blood glucose on the plasma concentration of growth hormone. Diabetes **13**, 395 (1964).
31. Roughton, F.J.W., Scholander, P.J.: Microgasometric estimation of the blood gases. J. biol. Chem. **148**, 541 (1943).
32. Rubecz, I., Mestyán, J.: Energy metabolism and intravenous nutrition of premature infants. Biol. Neonate **23**, 45 (1973).
33. Rubecz, I., Mestyán J.: The effect of infusion of Aminosol-glucose on the acid-base balance

of low birth weight infants. Acta paediat. Acad. Sci hung. **14**, 309 (1974).
34. RUBINSTEIN, H.M., PRYCE, J.D.: The colorimetric estimation of amino nitrogen in tissue fluids. J. clin. Path. **12**, 80 (1959).
35. STEGINK, L.D., BAKER, G.L.: Infusion of protein hydrolysate in the newborn infants: Plasma amino acid concentrations. J. Pediat. **78**, 595 (1971).
36. STUBBE, P., WOLF H.: Glucosebelastungen und Arginin-Infusionen bei Neugeborenen. Einfluß auf Wachstumshormon, Blutzucker, Fettsäuren und Glycerin. Klin. Wschr. **48**, 919 (1970).
37. SWENDSEID, M.E., TUTTLE, S.G., DRENICK, D.J., JOVEN, C.B., MASSEY, F.J.: Plasma amino acid response to glucose administration in various nutritive states. Amer. J. clin. Nutr. **20**, 243 (1967).
38. WHITEHEAD, R.G.: Rapid determination of some plasma amino acids in subclinical kwashiorkor. Lancet **1**, 250 (1964).
39. WRETLIND, A.: Complete intravenous nutrition: theoretical and experimental background. Nutrition (Lond.) **14**, Suppl. 1 (1972).

DR. I. RUBECZ
Gyermekklinika
7623 Pécs, Hungary