FULL-TERM NORMAL INFANTS

GLUCAGON TOLERANCE TESTS

The rapid fall in liver glycogen during early period of life reflects its quick mobilization and its importance in maintaining the blood glucose concentration. Assessment of the glycogenolytic activity and glycogen reserve have been demonstrated by Cornblath, Levin and Marquetti (1958), Cornblath et al. (1961, 1963) and by Mulligan and Schwartz (1962) after administration of glucagon. In an attempt to evaluate the glycogen stores and hepatic glucose output, both during early neonatal period and after stabilization of blood glucose level, glucagon tolerance tests were carried out on the first day (within two to three hours after birth) and on the eighth day of life in 17 full-term normal infants. A dose of 30 µg./kg. of glucagon was administered intramuscularly on both these days.

RESULTS:

The results of mean plasma glucose, inorganic phosphorus, potassium, urea and total amino acid nitrogen (TAN) concentrations before and after glucagon administration on the first and eighth days are presented in Table 3 and 4 respectively. The net increases in the plasma glucose concentration after glucagon administration are given in Table 5. Fig. 2a shows the behaviour of the above mentioned parameters after glucagon administration. The net increases are presented in Fig. 3a.

First day:

The basal plasma glucose concentration is found to be 42.0 ± 2.46 (mean ± S.E.) mg./100 ml.

After administration of glucagon, the maximum plasma glucose concentration of 88.5 ± 5.80 (mean ± S.E.) mg./100 ml. is attained at 90 minutes with a net increase of 46.5 ± 4.48 (mean ± S.E.) mg./100 ml. above the basal level. Decrease in plasma glucose is then observed and at the end of the glucagon tolerance test, i.e. at 150 minutes, the plasma glucose concentration is found to be 68.5 ± 6.28 (mean ± S.E.) mg./100 ml. with a net increase of 26.5 ± 5.82 (mean ± S.E.) mg./100 ml.

The basal plasma inorganic phosphorus concentration is found to be 5.45 ± 0.86 (mean ± S.D.) mg./100 ml. A gradual fall is seen after glucagon administration. A maximum fall of 0.70 mg./100 ml. is observed in the last sample, i.e. at 150 minutes.

The initial concentration of 5.02 ± 0.84 (mean ± S.D.) mEq/L. is seen in plasma potassium, which also shows a gradual decrease. The maximum fall of 0.64 mEq/L. is observed at 120 minutes after glucagon administration. A negligible increase is seen at 150 minutes.

The basal plasma urea concentration is found to be 21.0 ± 4.53 (mean ± S.D.) mg./100 ml. Maximum level of 26.1 ± 6.38 (mean ± S.D.) mg./100 ml. is attained at 150 minutes, with a significant rise of 5.1 mg./100 ml. ($t = 6.80$; $P < .001$).

The basal plasma total amino acid nitrogen concentration is found to be 5.69 ± 1.79 (mean ± S.D.) mg./100 ml. Significant decrease of 2.28 mg./100 ml. is observed at 60 minutes after glucagon administration ($t = 3.21$; $.001 < P < .01$). This is followed by a slight increase upto 150 minutes.

Eighth day:

The basal plasma glucose concentration on the eighth day is found to be 70.2 ± 3.15 (mean ± S.E.) mg./100 ml. This level is significantly higher than that observed on the first day of life ($t = 7.14$; $P < .001$).

Comparatively rapid rise is observed in plasma glucose concentrations at 20 and at 40 minutes after glucagon administration. The net increases are significantly higher at 20 minutes ($t = 2.79$; $.001 < P < .01$) and 40 minutes ($t = 2.29$; $.02 < P < .05$) as compared to those observed on the first day of life. These results indicate a quicker response to glucagon on the eighth day.

The maximum concentration of 119.2 ± 7.12 (mean ± S.E.) mg./100 ml. in plasma glucose level is observed at 60 minutes with a net rise of 49.0 ± 6.87 (mean ± S.E.) mg./100 ml.

Net increases in plasma glucose concentrations are significantly lower than those observed on the first day at 120 minutes ($t = 3.85$; $P < .001$) and at 150 minutes ($t = 4.56$; $P < .001$). Results of these observations indicate

an increased rate of glucose disappearance on the eighth day as compared to that on the first day of life.

At 150 minutes the plasma glucose attains a level of 63.6 ± 3.05 (mean ± S.E.) mg./100 ml. This level is lower than the initial basal level by -6.6 ± 2.20 (mean ± S.E.) mg./100 ml.

The initial plasma inorganic phosphorus concentration on the eighth day is found to be 5.92 ± 1.03 (mean ± S.D.) mg./100 ml. The maximum fall of 0.97 mg./100 ml. is observed at 60 minutes after glucagon administration. Level of plasma inorganic phosphorus then gradually increases during the rest of the tolerance period except a negligible drift at 120 minutes.

The basal plasma potassium level on the eighth day is found to be 4.61 ± 1.02 (mean ± S.D.) mEq/L., which is then gradually decreased upto 3.91 ± 0.79 (mean ± S.D.) mEq/L. at 40 minutes. A fall of 0.70 mEq/L. is observed. This is followed by a gradual increase during the rest of the tolerance period.

The basal plasma urea concentration is found to be 21.3 ± 10.14 (mean ± S.D.) mg./100 ml. Significant rise of 3.40 mg./100 ml. is observed at 120 minutes ($t = 2.25$; $.02 < P < .05$). Negligible decrease is then observed at 150 minutes.

The basal plasma TAN level of 4.22 ± 1.07 (mean ± S.D.) mg./100 ml. is observed which is followed by a gradual fall

during the rest of the tolerance period. Significant fall of 1.64 mg./100 ml. is observed between the basal level and the lowest level at 150 minutes ($t = 3.91$; $.001 < P < .01$).

Representative data from the literature as regards the changes in blood sugar/glucose concentrations after glucagon administration during the early neonatal period are summarised in Table 6.

The changes in concentrations of sugar in the capillary blood of full-term newborn infants after intramuscular and intravenous (i.v.) administration of glucagon were studied by Cornblath et al. (1958) in infants varying in age from three to 15 hours. Mothers of these infants received various types of anaesthesias during their labour period and the whole blood sugars were estimated by Somogyi-Nelson's method. Maximum increase of 32 mg./100 ml. in the blood sugar level after intramuscular route and 49 mg./100 ml. after intravenous administration were observed at 60 minutes in these groups. Both prolonged and increased hyperglycaemic responses were obtained after intravenous glucagon in their series. In the infants between five and 14 days of age, Cornblath et al. (1958) observed a maximum rise of 47 mg./100 ml. in the blood sugar level at 45 minutes after intravenous administration of glucagon. Increased rate of disappearance of blood sugar was observed in the above infants.

Cornblath et al. (1961) studied full-term newborn infants at a more specific age period of zero to three hours

and found maximum increase of 36 mg./100 ml. in the blood sugar level at 60 minutes after i.v. glucagon. Administration of fluids to the mothers during the labour period did not seem to alter the hyperglycaemic responses of the neonates after glucagon. Although no prolonged hyperglycaemic response was observed during this age period after 30 µg./kg. glucagon dose, an increase in the dose to 300 µg./kg. showed a well marked and sustained hyperglycaemic effect after i.v. glucagon. Furthermore, a prolonged hyperglycaemic response with moderate increase in the net rise of blood sugar concentration was seen after 30 µg./kg., i.v. glucagon administration in the infants of six to 31 hours age group.

Mulligan and Schwartz (1962) carried out intravenous glucagon tolerance tests in the full-term newborn infants between two and a half to five and a half hours after birth. They observed a maximum increase of about 35 mg./100 ml. in the blood sugar level at 45 minutes after i.v. glucagon administration. Combined epinephrine (i.m.) and glucagon (i.v.) tolerance tests showed an increased and a prolonged hyperglycaemic responses. Still higher hyperglycaemic and prolonged responses were observed after 300 µg./kg. (i.v.) glucagon and epinephrine administration.

DISCUSSION:

The response to glucagon administration would depend upon the route of administration, dose of glucagon, age of the infant, glycogen stores of the liver and gluconeogenetic activity during the early neonatal period.

Intravenous route may have the quicker hyperglycaemic response because of its effective glucagon concentration as seen from the results of Cornblath et al. (1958, 1961) and Mulligan and Schwartz (1962). The intramuscular route has a prolonged hyperglycaemic response as evident from the results of present series on the first day. Delayed absorption from the muscles, but not the tissue binding or destruction (Cornblath et al., 1958) could be the factor for prolonged hyperglycaemic response. Relative deficiency of the proteolytic enzyme which destroys glucagon in the liver could be an alternative explanation for the production of prolonged hyperglycaemia (Tomizawa, Tyberghein, Hafsey and Williams, 1966).

Higher hyperglycaemic response is obtained after 300 µg./kg. glucagon with no secondary rise of blood sugar after a repeat dose of 100 µg./kg. glucagon, two hours after the first post-injection period (Cornblath et al., 1961). In the present series, similar higher responses are seen in the infants delivered by Caesarean section who were given 300 µg./kg. glucagon. Cornblath et al. (1961) suggested that this increased hyperglycaemic response after a higher dose of

glucagon could be attributed to either the suppressive action of the glucagon on the inhibitors of phosphorylase activation, or the inactivation of glucagon or the overcoming of the possible effect of 17-hydroxycorticosteroids. Phosphorylase almost certainly plays a key role in the control of the degradation of liver glycogen immediately after birth. A considerable rise in the hepatic phosphorylase activity occurs in rat, sheep and guinea-pig immediately after birth (Walker, 1968). Dawkins (1963) demonstrated in vitro activation of phosphorylase in liver slices of newborn rats by adrenalin and glucagon. The role of glucagon on the production of cyclic adenosine monophosphate (AMP), which in turn stimulates the reactivation of the inactive phosphorylase enzyme has been suggested by Sutherland and Rall (1960). This obviously rules out the possibility of the suppressive action of the glucagon on the inhibitors of phosphorylase activation. Inactivation of glucagon has been considered as a second alternative explanation which emphasises the need of a larger dose of glucagon for a better hyperglycaemic response. This does not seem to be a convincing mechanism as the intramuscular route has shown enough hyperglycaemic response to a lesser dose of glucagon (30 µg./kg.) on the first day in the present series. The third alternative explanation is of overcoming the possible effect of deficient 17-hydroxycorticosteroids on the phosphorylase activation after a larger dose of glucagon. This possibility cannot be ignored in the infants who have

not undergone the normal stress of labour; however, it fails to account for a better hyperglycaemic response after a larger dose of glucagon seen in the infants who have already undergone stress of labour. Probably with a smaller dose of glucagon the threshold for maximal phosphorylase activation is not reached, this being attained by a larger dose. Thus the attainment of the maximal phosphorylase activity through cyclic AMP after a higher dose of glucagon seems to be a convincing explanation for a better hyperglycaemic response.

It is however not known, whether the entire glycogen stores is depleted following 30 µg./kg. glucagon dose. In the premature infants 30 µg./kg. glucagon administration after first week (seven days onwards) showed a better response as compared to that seen within one week (three to seven days) following 300 µg./kg. glucagon (Cornblath et al., 1963). These authors are of the opinion that age is more significant than the dosage as far as hyperglycaemic response to glucagon is concerned.

After glucagon, the maximum increase in plasma glucose is seen at 90 minutes on the first day and at 60 minutes on the eighth day. However, the magnitude of the increases on both these days are nearly equal. Comparatively quicker response is seen on the eighth day. A level less than the initial basal level is observed on the eighth day after 150 minutes, while the basal level is not attained on the first day.

Resultant hyperglycoaemia of nearly equal magnitudes after glucagon administration in the full-term normal infants indicate the adequacy of the carbohydrate reserves on both the days.

Following the intramuscular route of glucagon administration the net increases in plasma glucose are comparatively higher and the responses are more prolonged in the present series than those observed by Cornblath et al. (1958). A more precise age period (within two to three hours of life), absence of anaesthesia to these mothers during labour period and the measurements of true glucose in plasma samples could be the contributory factors leading to better responses observed in the present series.

The quicker hyperglycaemic response on the eighth day as compared to that on the first day is seen in the same infants and after the same glucagon dose. The two key enzymes in the glycogenolytic pathway seem to play an important role in the degradation of glycogen stores. The glycogenolytic action of glucagon on the liver has been shown to be due to activation of the inactive phosphorylase through the mediation of 3 '5' adenosine monophosphate (Sutherland and Rall, 1960). The low phosphorylase activity has been shown in the rat and sheep foetal liver (Dawkins, 1963). Sharp increase of the hepatic phosphorylase activity occurs in these species immediately after birth. Dawkins (1963) demonstrated in vitro activation of phosphorylase in liver slices of the newborn rats by

adrenalin and glucagon. Shelley (1969) reported that the activity of glucose-6-phosphatase usually reaches adult levels before term and is several times more, immediately after birth. She also reported that the activities of phosphopyruvate carboxylase and fructose 1-6 diaphosphatase (two of the gluconeogenetic enzymes) start rising after birth and reach peak levels in two days following birth. Cornblath et al. (1963) demonstrated that in the premature infants under three days of age, the rate of fructose disappearance and conversion to glucose is slower than that in the infants over three days of age. Furthermore, Shelley (1969) reported that the rate of neoglucogenesis is double in the nine day old rat liver as compared to that in the adult. Thus it seems reasonable to conceive that the quicker response to glucagon administration on the eighth day could be due to an increase in the gluconeogenetic activity.

The slow rate of glucose disappearance on the first day and the subsequent improvement seen on the eighth day are supported by similar trends observed in the results of the oral glucose tolerance tests (O.G.T.T.). The mechanisms of this change are explained under O.G.T.T. discussion.

No comparable data are available as regaeds the inorganic phosphorus, potassium, urea and TAN concentrations after glucagon administration particularly during the early neonatal period. It has long been recognised that glucagon produces a decrease in plasma/serum inorganic phosphorus concentration

(Kirtley, Waife, Helmer and Peck, 1953; Kirtley, Waife and Peck, 1953; Bondy and Cardillo, 1956; Natelson, Pincus and Rannazzisi, 1963). Decrease in the plasma inorganic phosphorus level is also observed in the present series after glucagon administration. The resultant hypophosphataemia after glucagon can be taken to reflect glycolysis with attendent phosphorylation. A part of it can also be attributed to dilution of extracellular fluid by transfer of cell water, in response to the changes in osmotic pressure produced by admission of glucose (Danowski, 1957).

A fall in the plasma potassium concentration is observed after glucagon administration. The decrease in plasma potassium is not as pronounced as the change in plasma inorganic phosphorus. Though the definite mechanism of the potassium fall is not clear, the osmotic effect of the glucose is sufficient to produce potassium decrease, as a part of dehydration reaction (Danowski, 1957).

Significant increase in the plasma urea concentration is observed after glucagon administration on both the days in the present group. This could be explained as a sequential effect of glucagon towards gluconeogenesis in the presence of adequate substrate of amino acids undergoing deamination reactions resulting into the formation of urea.

Significant decrease is seen in the plasma TAN concentrations both on the first and eighth days. Decreases in alpha-amino acid nitrogen concentrations after glucagon

administration have been reported by Bondy and Cardillo (1956). These workers have reported a decrease of 13.8 to 30 per cent in TAN concentration after continuous glucagon drip in the adults.

The above changes in the urea and TAN concentrations, after glucagon are suggestive of the inducation of neoglucogenesis. However, the magnitude of glucose production through this pathway can not be ascertained from these results.

TABLE 3.

PLASMA GLUCOSE, INORGANIC PHOSPHORUS, POTASSIUM, UREA AND TOTAL AMINO ACID NITROGEN CONCENTRATIONS (MEAN) OF THE FULL-TERM NORMAL INFANTS ON THE FIRST DAY (within 2 to 3 hours) OF LIFE AFTER GLUCAGON (30 µg./kg., i.m.) ADMINISTRATION. (PRESENT SERIES)

	Basal level	Minutes after glucagon administration					
		20	40	60	90	120	150
Glucose (mg./100 ml.)							
Mean	42.0	60.4	76.5	88.0	88.5	82.5	68.5
S.E.±	2.46	3.48	4.03	4.80	5.80	6.79	6.28
Range	24-64	33-97	54-109	54-124	54-138	54-139	38-127
No.	17	17	17	17	17	17	17
Inorganic phosphorus (mg./100 ml.)							
Mean	5.45	4.99	5.07	4.92	4.95	4.83	4.75
S.D.±	0.86	0.92	0.97	1.01	0.92	0.81	0.88
Range	4.5-7.1	3.9-6.9	4.1-7.1	3.5-7.1	3.5-6.9	3.5-6.3	3.1-6.0
No.	11	11	11	11	11	11	11
Potassium (mEq/L.)							
Mean	5.02	4.73	4.61	4.54	4.53	4.38	4.45
S.D.±	0.84	0.83	0.85	0.84	0.42	0.62	0.64
Range	3.9-6.7	3.6-6.1	3.3-5.9	3.3-5.9	3.5-5.2	3.5-5.3	3.6-5.2
No.	10	10	10	10	10	10	10
Urea (mg./100 ml.)							
Mean	21.0	22.5	23.6	24.2	24.7	25.6	26.1
S.D.±	4.53	4.51	3.97	3.83	5.33	5.49	6.38
Range	14-28	16-29	18-29	16-30	16-35	18-36	18-38
No.	11	11	11	11	11	11	11
Total amino acid nitrogen (mg./100 ml.)							
Mean	5.69	4.41	3.55	3.41	3.43	3.82	3.82
S.D.±	1.79	2.02	1.54	1.51	1.20	1.75	1.73
Range	3.6-8.6	1.2-7.8	0.9-5.7	0.6-5.8	1.5-6.2	2.2-6.6	1.2-6.3
No.	11	11	11	11	11	11	11

TABLE 4.

PLASMA GLUCOSE, INORGANIC PHOSPHORUS, POTASSIUM, UREA AND TOTAL AMINO ACID NITROGEN CONCENTRATIONS (MEAN) OF THE FULL-TERM NORMAL INFANTS ON THE EIGHTH DAY OF LIFE AFTER GLUCAGON (30 µg./kg., i.m.) ADMINISTRATION.

(PRESENT SERIES)

	Basal level	Minutes after glucagon administration					
		20	40	60	90	120	150
Glucose (mg./100 ml.)							
Mean	70.2	101.9	117.3	119.2	105.1	77.9	63.6
S.E.±	3.15	5.88	6.07	7.12	6.78	6.26	3.05
Range	46-81	84-154	89-166	93-181	83-162	54-129	41-79
No.	12	12	12	12	12	12	12
Inorganic phosphorus (mg./100 ml.)							
Mean	5.92	5.19	4.99	4.95	5.10	5.08	5.22
S.D.±	1.03	1.04	0.90	1.18	0.83	0.79	0.89
Range	4.6-7.9	4.3-7.6	3.7-6.5	3.8-7.2	4.1-6.5	4.0-6.5	4.1-7.1
No.	9	9	9	9	9	9	9
Potassium (mEq/L.)							
Mean	4.61	4.00	3.91	4.02	4.05	4.09	4.20
S.D.±	1.02	0.80	0.79	0.94	0.90	0.92	0.96
Range	2.7-5.6	2.5-4.8	2.2-4.8	2.3-5.7	2.6-5.7	2.7-5.8	2.7-6.0
No.	9	9	9	9	9	9	9
Urea (mg./100 ml.)							
Mean	21.3	23.3	23.2	23.8	24.5	24.7	24.5
S.D.±	10.14	10.44	10.86	11.49	9.95	10.15	10.86
Range	8-44	9-46	9-46	8-48	12-47	11-47	10-48
No.	9	9	9	9	9	9	9
Total amino acid nitrogen (mg./100 ml.)							
Mean	4.22	3.43	3.38	3.38	2.71	2.66	2.58
S.D.±	1.07	1.16	0.80	0.80	1.00	0.80	0.68
Range	2.7-5.6	1.7-5.2	2.3-4.8	2.6-4.7	1.1-4.1	1.9-3.6	1.4-3.5
No.	9	9	9	9	9	9	9

TABLE 5.

INCREASE IN THE PLASMA GLUCOSE CONCENTRATIONS (mg./100 ml.) OF THE FULL-TERM NORMAL INFANTS ON THE FIRST (within 2 to 3 hours) AND EIGHTH DAY OF LIFE AFTER GLUCAGON (30 µg./kg., i.m.)ADMINISTRATION. (PRESENT SERIES)

	Basal level	Minutes after glucagon administration					
		20	40	60	90	120	150
First day (within 2 to 3 hours)							
Mean	42.0	18.4	34.5	46.0	46.5	40.5	26.5
S.E.±	2.46	2.38	2.58	3.42	4.48	6.00	5.82
Range	24-46	5-33	18-52	18-66	18-91	11-83	-1 to 74
No.	17	17	17	17	17	17	16
Eighth day							
Mean	70.2	31.7	47.1	49.0	34.9	7.7	-6.6
S.E.±	3.15	4.53	5.58	6.87	5.90	5.55	2.20
Range	46-81	14-71	25-86	15-101	4-82	-14 to 49	-21 to 4
No.	12	12	12	12	12	12	12

TABLE 6.

INCREASE IN THE BLOOD SUGAR CONCENTRATIONS (mg./100 ml.) AFTER GLUCAGON ADMINISTRATION IN THE FULL-TERM NORMAL INFANTS. (REPRESENTATIVE DATE FROM LITERATURE)

Author & (Year)	Infants	Age	Glucagon dose		Fasting level	Minutes after glucagon administration 30	45	60	90	120	150
Cornblath Levin and Marquetti (1958)	Full-term, various anaesthesia to mothers	3-15 hours	30 µg./kg. i.m.	Mean S.E.± Range No.	55 2.6 28-73	25 - -	- - -	32 - - 8	22 - -	14 - -	- - -
Method: Somogyi Nelson.	Full-term normal	3-15 hours	30 µg./kg. i.v.	Mean S.E.± Range No.	48 35-77	41 5.8 -	46 6.8 -	49 5.9 - 11	48 7.9 -	35 8.3 -	23 7.0 -
	Full-term normal	5-14 days	30 µg./kg. i.v.	Mean S.E.± Range No.	62 - 55-87	43 5.4 -	47 6.3 -	35 6.0 - 9	10 5.3 -	-9 6.7 -	- - -
Cornblath et al. (1961) Method: Nelson Somogyi.	Full-term normal, vaginal, labour-Yes, fluid to mother-none.	0-3 hours	30 µg./kg. i.v.	Mean S.Em.± Range No.	55 3.9 35-73	28 5.3 8-60	- - -	36 3.6 20-55 10	29 4.3 6-48	12 7.0 -16 to 53	- - -

TABLE 6. (CONTINUED)

Author & (Year)	Infants	Age	Glucagon dose		Fasting level	Minutes after glucagon administration 30	45	60	90	120	150
Cornblath et al. (1961) contd.	Full-term normal, vaginal delivery, labour-yes, fluid to mother none.	6-31 hours	30 µg./kg. i.v.	Mean S.Em.± Range No.	51 3.9 39-77	47 6.9 17-84	- - -	56 6.8 27-93 10	51 9.1 15-96	37 8.6 6-75	- - -
	Full-term normal vaginal, labour-yes, fluid to mother-glucose.	0-3 hours	30 µg./kg. i.v.	Mean S.Em.± Range No.	45 4.6 19-95	19 4.3 -3 to 49	- - -	38 3.3 23-55 10	26 7.3 -15 to 156	24 14.5 -22 to 19	- - -
	Full-term normal vaginal, delivery, labour-yes, fluid to mother-glucose.	0-3 hours	300 µg./kg. i.v.	Mean S.Em.± Range No.	44 3.1 18-60	28 2.5 13-47	- - -	51 4.4 27-86 15	64 11.3 42-112	59 3.1 42-84	- - -

TABLE 6. (CONTINUED)

Author & (Year)	Infants	Age	Glucagon dose		Fasting level	Minutes after glucagon administration 5	10	20	30	45	60	90	120
Mulligan & Schwartz (1962)	Full-term normal	2.5-5.5 hours	30 µg./kg. i.v.	Mean		12.3	20.1	29.8	32.6	35.4	32.4	18.2	2.9
				S.Dm.±		7.3	7.7	7.8	8.8	16.4	15.8	17.6	19.6
Method: Somogyi Nelson.				Range									
				No.					15				
	Full-term normal	2.5-7 hours	Epinephrine 3 µg./kg. i.m. + 30 µg./kg. i.v.	Mean		18.4	24.9	37.2	43.9	46.1	45.8	34.4	10.0
				S.Dm.±		7.3	9.8	12.9	13.4	13.8	19.9	27.2	19.9
				Range									
				No.					14				
	Full-term normal	4-5.5 hours	Epinephrine 3 µg./kg. i.m. + glucagon 300 µg./kg. i.v.	Mean		16.6	30.4	47.7	58.7	72.2	74.0	74.2	55.4
				S.Dm.±		9.2	10.4	8.3	9.3	28.0	26.4	36.0	33.8
				Range									
				No.					6				

FIGURE 2a.

PLASMA GLUCOSE, INORGANIC PHOSPHORUS, POTASSIUM, UREA AND TOTAL AMINO ACID NITROGEN CONCENTRATIONS (MEAN) OF THE FULL-TERM NORMAL INFANTS ON THE FIRST (●——●) AND EIGHTH (o——o) DAY OF LIFE AFTER GLUCAGON (30 μg./kg., i.m.) ADMINISTRATION.

FIGURE 2b.

PLASMA GLUCOSE, INORGANIC PHOSPHORUS AND POTASSIUM CONCENTRATIONS (MEAN) OF THE FULL-TERM NORMAL INFANTS ON THE SECOND (●——●) AND EIGHTH (o——o) DAY OF LIFE AFTER GLUCOSE (2.5 G/kg., oral) ADMINISTRATION.

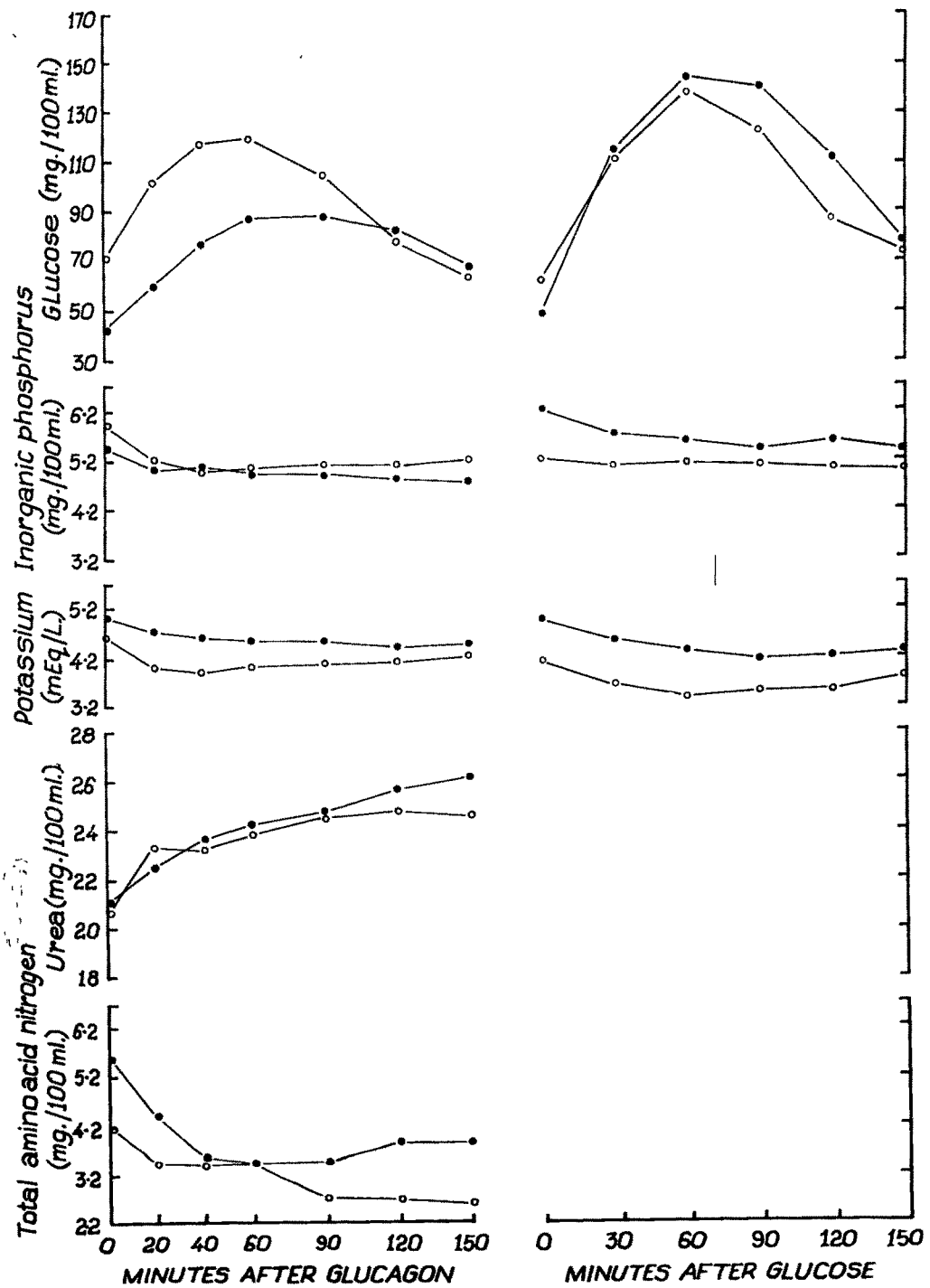
Glucose (mg./100ml.)
170
150
130
110
90
70
50
30
Inorganic phosphorus (mg./100ml.)
6·2
5·2
4·2
3·2
Potassium (mEq/L.)
5·2
4·2
3·2
Urea (mg./100ml.)
28
26
24
22
20
18
Total amino acid nitrogen (mg./100 ml.)
6·2
5·2
4·2
3·2
2·2
0 20 40 60 90 120 150
MINUTES AFTER GLUCAGON
0 30 60 90 120 150
MINUTES AFTER GLUCOSE

Fig. 2a. 2b.

FIGURE 3a.

INCREASE IN PLASMA GLUCOSE CONCENTRATIONS (Δ mg./100 ml.) OF THE FULL-TERM NORMAL INFANTS ON THE FIRST (●——●) AND EIGHTH (○——○) DAY OF LIFE AFTER GLUCAGON (30 µg./kg., i.m.) ADMINISTRATION.

FIGURE 3b.

INCREASE IN PLASMA GLUCOSE CONCENTRATIONS (Δ mg./100 ml.) OF THE FULL-TERM NORMAL INFANTS ON THE SECOND (●——●) AND EIGHTH (○——○) DAY OF LIFE AFTER GLUCOSE (2.5 G /kg., oral) ADMINISTRATION.

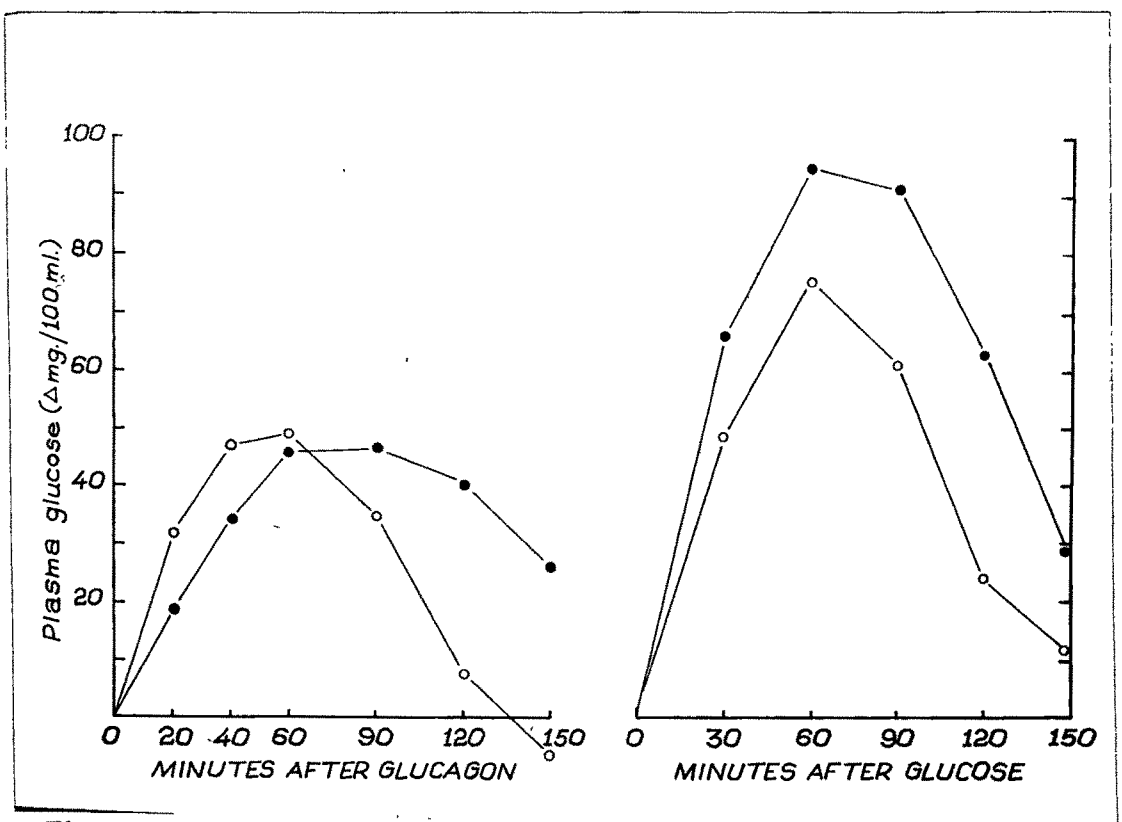
100
80
60
40
20
Plasma glucose (Δmg./100 ml.)
0 20 40 60 90 120 150
MINUTES AFTER GLUCAGON
0 30 60 90 120 150
MINUTES AFTER GLUCOSE

Fig. 3a. 3b.

GLUCOSE TOLERANCE TESTS

Variability of insulin release after rapid intravenous load of glucose in the normal newborn infants has been reported. (Isles, Dickson and Farquhar, 1968). It has also been reported that the parenteral glucose administration represents a far less potent insulinogenic stimulus than the oral glucose load (Dupre, 1964; Elrick, Stimmler Hald and Arai, 1964; Perley and Kipnis, 1967). Further, intravenous route of glucose administration is less physiological than the oral glucose load (Cornblath and Schwartz, 1966). Considering all these factors, oral glucose tolerance tests have been carried out with a view to study the glucose disappearance rates on the second and eighth days of life in 17 full-term normal infants.

RESULTS:

Results of the mean concentrations of plasma glucose, inorganic phosphorus and potassium before and after oral glucose administration on the second and eighth day are given in Table 7 and 8 respectively. The net increases in the plasma glucose concentrations after glucose administration are shown in Table 9. Fig. 2b shows the behaviour of the above mentioned parameters after glucose administration. The net increases are presented in Fig. 3b.

Second day:

The basal plasma glucose concentration of 49.1 $\pm$ 3.02

(mean ± S.E.) mg./100 ml. is observed on the second day of life.

The maximum level of 144.5 ± 6.72 (mean ± S.E.) mg./100 ml. is reached at 60 minutes after oral glucose load, with a net rise of 95.4 ± 3.17 (mean ± S.E.) mg./100 ml. over the basal level. At 150 minutes, a level of 77.6 ± 5.85 (mean ± S.E.) mg./100 ml. is seen with a net increase of 28.5 ± 6.37 (mean ± S.E.) mg./100 ml.

The basal plasma inorganic phosphorus level is found to be 6.21 ± 0.95 (mean ± S.D.) mg./100 ml. A gradual fall throughout the tolerance period is observed. A maximum fall of 0.84 mg./100 ml. is attained at 150 minutes after oral glucose administration.

The plasma potassium level at the initiation of the glucose tolerance test is found to be 4.95 ± 0.72 (mean ± S.D.) mEq/L. Significant fall of 0.80 mEq/L. is observed at 90 minutes after glucose administration ($t = 2.58$; $.01 < P < .02$). A gradual rise is seen upto 150 minutes.

Eighth day:

On the eighth day the last sample collected at 150 minutes after glucagon tolerance test is taken as a basal level for the oral glucose tolerance test. The basal plasma glucose level is found to be 62.7 ± 3.13 (mean ± S.E.) mg./100 ml. which is higher than the basal level observed on the second day of life. The net increase at 30 minutes is significantly lower than that observed in the same infants

on the second day ($t = 2.21$; $.02 < P < .05$).

The maximum level of 138.5 ± 6.27 (mean ± S.E.) mg./100 ml. is attained at 60 minutes after oral glucose administration on the eighth day, with a net increase of 75.8 ± 6.46 (mean ± S.E.) mg./100 ml. The net increase is significantly lower in comparison to that observed on the second day of life ($t = 2.99$; $.001 < P < .01$). The net increases in the plasma glucose levels are significantly lower at 90 minutes ($t = 3.21$; $.001 < P < .01$) and at 120 minutes ($t = 3.85$; $P < .001$) than those seen at similar intervals on the second day.

At 150 minutes the plasma glucose concentration of 74.1 ± 3.78 (mean ± S.E.) mg./100 ml. is found with a net increase of 11.4 ± 3.64 (mean ± S.E.) mg./100 ml.

The basal plasma inorganic phosphorus level of 5.21 ± 0.81 (mean ± S.D.) mg./100 ml. is observed on the eighth day. The maximum fall of only 0.22 mg./100 ml. is seen at 150 minutes.

The basal plasma potassium level is found to be 4.11 ± 0.98 (mean ± S.D.) mEq/L. A maximum fall of 0.73 mEq/L. is observed at 60 minutes after which a gradual rise is seen in the potassium concentration.

Representative data from the literature as regards the blood glucose/sugar concentrations after oral glucose administration during the early neonatal period are summarised in Table 10.

Pildes, Hart, Warrner and Cornblath (1969b) studied the behaviour of blood glucose, plasma insulin, free fatty acids (FFA) and growth hormone levels in the full-term newborn infants and in the infants of gestational diabetic mothers (IGDM) after oral glucose administration. These authors observed a maximum rise of 100 mg./100 ml. in the blood glucose concentration at 60 minutes above the basal level. Blood glucose concentration did not attain the basal level at 120 minutes. The authors observed a prolonged hyperglycaemia, a delayed rise of plasma insulin and an initially high FFA levels followed by a marked decrease in the full-term normal newborn infants. The results of the net increases of plasma glucose concentrations in the present series on the second day of life are in good agreement with the results reported by the above authors within the first 24 hours after birth.

Cole, Bilder, Camerini-Davolos and Grimaldi (1970) carried out oral glucose tolerance tests in the full-term newborn infants and in the infants of gestational diabetic mothers. Simultaneous determinations of plasma insulin and growth hormone levels were also performed during the glucose tolerance tests. These authors observed a maximum rise of about 56 mg./100 ml. in the blood sugar concentration at 30 minutes in the full-term newborn infants. A level less than the basal was recorded at 180 minutes after the oral glucose load. No appreciable rise in the plasma insulin was observed in response to the oral glucose administration in the full-term infants studied by these authors.

DISCUSSION:

In the present series slower rate of glucose disappearance is found on the second day than that observed on the eighth day which is evident from the general appearance of the plasma glucose curves (Fig. 3b). Similar observations were noted in the full-term newborn infants on the first day of life after intravenous glucose tolerance tests by Baird and Farquhar (1962), Bowie, Mulligan and Schwartz (1963) and von Euler et al. (1964). Improved rate of glucose disappearance on the eighth day in the same infants after oral glucose administration is observed in the present series (Fig. 3b). The net maximum rise of about 95 mg./100 ml. in the plasma glucose concentration is seen at 60 minutes on the second day of life, in the present series. This net plasma glucose increase is about 194 per cent on the first day and 121 per cent on the eighth day of life. In the normal adult individual the level rises to a peak value of about 50 per cent of the fasting level within 30 to 60 minutes after oral glucose administration (Cantarow and Trumper, 1962). These observations favour low insulin output on the second day which shows a considerable improvement on the eighth day.

Low plasma insulin activities after intravenous glucose administration in the full-term normal infants during the first day of life were reported by Baird and Farquhar (1962), Milner and Hales (1965), Jorgensen, Deckert, Pedersen and Pedersen (1966) and Spellacy, Gall and Carlson (1967), and a

delayed plasma insulin activity after an oral glucose load by Pildes et al. (1969b). Stegmann and Beck (1955) using two-dose oral glucose tests found that the Staub-Traugott effect was absent during the first day of life, but when the test was repeated in the second week, this effect was seen to be normal in 14 of the 20 infants studied. This also favours the gradual increase of insulin secretion.

Isles et al. (1968) are of the opinion that the newborn infants of the normal mothers are capable of releasing insulin in response to hyperglycaemia. However, unlike the infants of diabetic mothers these normal infants are not exposed to the stimulatory effects of multiple priming loads (hyperglycaemic). The results of the present series do not contradict the opinion of these workers. At the same time, these results indicate that the insulin release mechanism although active, is not as efficient as seen in the normal adult individual.

Persson and Gentz (1966) suggested that the slow rate of utilization of blood glucose during the early neonatal period may be on account of the high FFA concentrations found in the neonatal infants. The presence of high FFA concentration would diminish the utilization of glucose in the tissue by production of a block somewhere in the glycolytic pathway (Randle, Garland, Hales and Newsholme, 1963). Howfar the high FFA level contributes towards reduction of the glucose disappearance rate is difficult to assess.

Decrease in the inorganic phosphorus level is observed on both the second and eighth days. It appears to be intimately related to intermediary glucose metabolism. Inorganic phosphorus is withdrawn during the process of glucose utilization for the formation of hexose phosphate. These changes occur independently of the level of blood sugar and continue beyond the period of hyperglycaemia induced by the glucose administration. It seems that the hypophosphatemia is a reflection of the increased glucose utilization (Cantarow and Trumper, 1962).

The decrease of potassium has been also correlated to the glucose utilization, which is accompanied by a shift of potassium from the extracellular to intracellular fluid space (Cantarow and Trumper, 1962). The basis for this phenomenon is not clear. Transportation of the intracellular water to the extracellular space due to the osmotic variation after glucose administration has been reported (Danowski, 1957).

TABLE 7.

PLASMA GLUCOSE, INORGANIC PHOSPHORUS AND POTASSIUM CONCENTRATIONS (MEAN) OF THE FULL-TERM NORMAL INFANTS ON THE SECOND DAY OF LIFE AFTER GLUCOSE (2.5 G/kg., oral) ADMINISTRATION. (PRESENT SERIES)

	Basal level	Minutes after glucose administration				
		30	60	90	120	150
Glucose (mg./100 ml.)						
Mean	49.1	115.2	144.5	140.4	112.0	77.6
S.E.±	3.02	4.83	6.72	7.43	7.43	5.85
Range	30-69	91-154	106-206	75-186	49-164	45-148
No.	16	16	16	16	16	16
Inorganic phosphorus (mg./100 ml.)						
Mean	6.21	5.71	5.59	5.41	5.59	5.37
S.D.±	0.95	0.81	0.87	0.88	0.98	1.15
Range	4.2-7.3	4.2-6.9	4.1-6.6	3.5-6.9	3.9-6.7	3.6-6.9
No.	11	11	11	11	11	11
Potassium (mEq/L.)						
Mean	4.95	4.56	4.33	4.15	4.19	4.29
S.D.±	0.72	0.77	0.73	0.71	0.79	0.59
Range	3.5-5.8	3.1-5.5	2.8-5.2	3.1-5.3	2.7-5.3	3.2-5.2
No.	11	11	11	11	11	11

TABLE 8.

PLASMA GLUCOSE, INORGANIC PHOSPHORUS AND POTASSIUM CONCENTRATIONS (MEAN) OF THE FULL-TERM NORMAL INFANTS ON THE EIGHTH DAY OF LIFE AFTER GLUCOSE (2.5 G/kg., oral) ADMINISTRATION. (PRESENT SERIES)

	Basal level	Minutes after glucose administration				
		30	60	90	120	150
Glucose (mg./100 ml.)						
Mean	62.7	111.4	138.5	123.8	86.8	74.1
S.E.±	3.13	9.53	6.27	5.08	4.62	3.78
Range	41-79	70-174	110-175	98-148	63-116	54-94
No.	11	11	11	11	11	11
Inorganic phosphorus (mg./100 ml.)						
Mean	5.21	5.08	5.12	5.10	5.02	4.99
S.D.±	0.81	0.95	0.92	0.85	1.00	0.78
Range	4.2-7.1	4.0-6.9	4.0-6.8	4.0-6.8	4.1-6.6	4.1-6.4
No.	8	8	8	8	8	8
Potassium (mEq/L.)						
Mean	4.11	3.64	3.38	3.49	3.52	3.82
S.D.±	0.98	0.77	0.54	1.22	0.67	0.95
Range	2.7-6.0	2.2-4.8	2.2-4.0	2.0-4.2	2.1-4.5	2.2-5.6
No.	8	8	8	8	8	8

TABLE 9.

INCREASE IN THE PLASMA GLUCOSE CONCENTRATIONS (mg./100 ml.)OF THE FULL-TERM NORMAL INFANTS ON THE SECOND AND EIGHTH DAY OF LIFE AFTER GLUCOSE (2.5 G/kg., oral) ADMINISTRATION. (PRESENT SERIES)

	Basal level	Minutes after glucose administration				
		30	60	90	120	150
Second day						
Mean	49.1	66.1	95.4	91.3	62.9	28.5
S.E.±	3.02	2.58	3.17	6.90	7.65	6.37
Range	30-69	55-89	65-138	39-133	8-118	-3 to 118
No.	16	16	16	16	16	16
Eighth day						
Mean	62.7	48.7	75.8	61.1	24.1	11.4
S.E.±	3.13	8.80	6.46	5.32	4.85	3.64
Range	41-79	12-101	41-117	36-95	2-54	-1 to 27
No.	11	11	11	11	11	11

TABLE 10.

BLOOD SUGAR CONCENTRATIONS (mg./100 ml.) AFTER ORAL GLUCOSE ADMINISTRATION OF THE FULL-TERM NORMAL INFANTS. (REPRESENTATIVE DATE FROM LITERATURE)

Author & (Year)	Age	Glucose dose		Fasting level	Minutes after glucose administration					
					30	60	90	120	150	180
Pildes, Hart, warrner and Cornblath (1969). Method: glucose oxidase.	Within first 24 hours	2.0 G per kg.	Mean	60	122	160	151	124	-	-
			S.E.±	3	9	6	7	9	-	-
			Range	-	-	-	-	-	-	-
			No.	-	-	-	-	-	-	-
			Net increase (calculated)	-	62	100	91	64	-	-
Cole, Bilder, Camerini-Davalos and Grimaldi (1970). Method: Autoanalyser using pot. cyanide and pot. ferricyanide.	Within first 24 hours	2.5 G per kg.	Mean	50.6	106.3	102.5	-	61.1	-	46.6
			S.E.±	2.61	8.70	14.0	-	6.57	-	3.02
			Range	37-69	61-129	62-178	-	43-112	-	30-55
			No.				12			
			Net increase (calculated)	-	55.7	51.9		10.5	-	-4.0