

# Infants of Diabetic Mothers

Guy Joassin, M.D., Mary L. Parker, M.D., Rosita S. Pildes, M.D.,  
and Marvin Cornblath, M.D., Chicago and St. Louis

## SUMMARY

Of six infants of gestational diabetic mothers (IGDM), the levels of insulin were high in four during the first week of life; levels of free fatty acid and glucose tended to be low. Growth hormone values were within normal limits.

In six infants of overt diabetic mothers, five had significant hypoglycemia; three were symptomatic. Growth hormone levels were within normal limits.

There was a positive correlation between the mother's blood glucose and the infant's insulin level at delivery in five of the IGDM. After birth, a negative correlation was found between the infant's blood glucose and the plasma insulin. There was a positive correlation between weight and insulin levels at birth in twenty normal infants and five IGDM. There was no correlation between growth hormone levels and birth weight. DIABETES 16:306-11, May, 1967.

The infants of the insulin-dependent diabetic mother have an increased morbidity and mortality, are often of excessive size, and frequently have low blood sugar levels.<sup>1</sup> The large size and low blood glucose have been attributed to excessive insulin secretion.<sup>2</sup> The evidence for this includes the hyperplasia of the beta cells of the pancreas,<sup>3</sup> the increased rate of disappearance of exogenous glucose and the increased levels of insulin-like activity (ILA).<sup>4</sup> The immunoassay of insulin in these infants has not been successful because of interference by maternal anti-insulin antibodies.<sup>5</sup> However, Jørgensen et al.<sup>6</sup> have reported high levels when there were minimal or no antibodies present. Infants of gestational diabetic mothers are also of excessive size, have lower levels of blood sugar than the normal, an increased morbidity,<sup>7-9</sup> and elevated insulin levels at birth.<sup>7</sup> Therefore, infants of mothers with gestational diabetes were studied to understand the interrelationship of insulin, growth hormone (HGH), free fatty acids (FFA),

From the Department of Pediatrics, University of Illinois College of Medicine, Chicago, Illinois, and the Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

and glucose homeostasis without the complications of therapy for the maternal diabetes.

The purpose of this paper is to present observations on the clinical course and correlations with growth hormone, free fatty acids, insulin and glucose levels in infants of gestational diabetic mothers, as well as in infants of diabetic mothers.

## PATIENT MATERIAL

From October, 1965, to July, 1966, twelve infants of diabetic mothers born at the University of Illinois Research and Educational Hospitals were studied. They were classified in two groups.

*Group 1:* Infants of gestational diabetic mothers (IGDM) consisted of six infants. All the mothers in this group had an abnormal glucose tolerance test during the third trimester of pregnancy, as compared to the criteria of O'Sullivan and Mahan<sup>10</sup> (figure 1). Five had a previous history of at least one large baby at

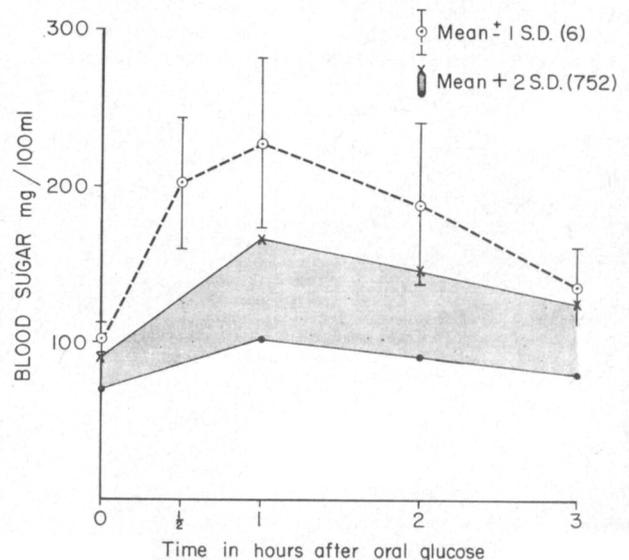


FIG. 1. Blood glucose response to an oral load of 100 gm. of glucose in the third trimester of pregnancy. Mean values  $\pm$  2 S.D. in 752 pregnant nondiabetic women.<sup>10</sup> Mean values  $\pm$  1 S.D. in the six mothers with gestational diabetes (Group 1).

birth. None had received insulin therapy. Five infants were delivered vaginally and one by cesarean section after induction of labor had failed. Labor was induced successfully in three cases. All infants in this first group were large at birth (mean weight was 4.2 kg, range 3.76 to 5.3 kg.) with a mean gestational age of thirty-nine weeks. No infant was less than thirty-eight weeks of gestation. Three infants were white, three were Negro; five were females and one was male. Five infants displayed the characteristic features of the infant of the diabetic mother.<sup>11,12</sup> These infants were plump, sleek, full-faced and plethoric. Some appeared cushingoid.

*Group 2:* Infants of diabetic mothers (IDM) consisted of six infants whose mothers had an average duration of diabetes of nine years. Five mothers were treated with daily insulin and one had received tolbutamide for two and one half years up to and including the first five months of pregnancy and then was controlled with an 1800-calorie diet alone. During the current pregnancy, three mothers had episodes of acidosis, hypoglycemia, or both. Five infants were delivered vaginally after induction of labor, and one was delivered by cesarean section. The mean birth weight was 3.24 kg. (range 2.47 to 3.76 kg.) with a mean gestational age of thirty-seven weeks (range 36 to 38). Four infants were white, two were Negro; three were females and three were males. Four infants displayed the characteristic physical features of the infant of the diabetic mother.<sup>11,12</sup> One baby (An.) died.

All newborn babies were cared for in the Premature Neonatal Nursery. They were kept warm in incubators (rectal temperatures 96 to 98° F.). Blood was obtained from the umbilical vein on the placenta for determinations of Na, Cl, K, Ca and BUN. Hematocrits and radiologic examinations of the chest were done routinely as soon as possible after birth. An electrocardiogram (ECG) was obtained as indicated.

Frequent blood glucose estimations were obtained, using a modification of the Dextrostix<sup>13</sup> during the first few hours of life. Blood samples were obtained in all of the infants at regular intervals, as indicated, for electrolytes, bilirubin and glucose. Urinalyses were done on all infants. Oral glucose solution feedings were started at six hours of age in those infants with an uneventful course. The others were given intravenous fluids and oral feedings as tolerated.

Glucose, FFA, insulin and growth hormone concentrations in the umbilical vein and peripheral blood from birth to seven days of life in normal-term infants are shown in table 1. A total of 102 glucose, 101 FFA, 102 insulin and ninety-four growth hormone determinations were done. These data were obtained from seventy-six infants whose birth weights ranged from 2,360 to 4,140 gm. Fifty-three were Negro and twenty-three were white; there was an equal number of males and females. Of the ninety-four HGH values, nineteen were obtained from sixteen infants studied previously.<sup>13a</sup> Recent HGH values are 50 per cent of those previously reported because a new growth hormone standard of greater immunopotency has been used.

#### ANALYTICAL METHODS

The majority of blood samples were obtained by venipuncture and placed in heparinized tubes. Immediately, 0.2 ml. of blood was laked in water and precipitated with Ba(OH)<sub>2</sub> and ZnSO<sub>4</sub> for glucose determinations.<sup>14</sup> The remainder of the blood sample was kept on ice and the plasma separated as soon as possible in a refrigerated centrifuge. Blood glucose was analyzed by the glucose oxidase method,<sup>15</sup> FFA by colorimetric microdetermination<sup>16</sup> after a Dole extraction,<sup>17</sup> insulin<sup>18</sup> and HGH<sup>19</sup> by the double antibody radioimmunoassay

TABLE 1

Whole blood glucose and plasma free fatty acids, insulin and growth hormone values in seventy-six normal-term infants from birth to seven days of age

	Cord	0-3 hrs.	4-12 hrs.	13-24 hrs.	25-48 hrs.	49-72 hrs.	3-7 days
Glucose (mg./100 ml.)	86±30* (21)†	68±23 (16)	50±9.4 (14)	49±9.5 (13)	50±14 (15)	56±15 (9)	67±20 (14)
FFA (μEq./L.)	358±168 (21)	557±344 (16)	1,214±423 (13)	1,182±458 (13)	1,034±539 (15)	1,406±672 (9)	1,435±593 (14)
Insulin (μU./ml.)	17±12 (21)	18±9 (16)	12±5.2 (14)	18±11 (13)	11±5 (15)	12±7 (9)	15±12 (14)
HGH (mug./ml.)	25±19 (21)	17±13 (16)	25±18 (18)	35±20 (17)	30±22 (8)	23±8 (3)	10±5 (11)

\*Mean ± standard deviation

†Number of determinations

method. Electrolytes were determined in the microchemistry laboratory of the Department of Pediatrics of the University of Illinois College of Medicine, using standard methods.

## RESULTS

### *Group 1, IGDM*

The pertinent clinical observations in these infants were as follows. No congenital anomalies were found. No infants had respiratory distress (R.D.S.), hyperbilirubinemia or hypocalcemia. A high hematocrit or hemoglobin was found in four infants (Ib., Hct. 70 per cent and 75 per cent, Hgb. 22.2 gm. per 100 ml.; De., Hct. 80 per cent; We., Hgb. 21.5 gm. per 100 ml.; To., Hgb. 21.1 gm. per 100 ml.). Serum electrolyte determinations were done in five infants. A sodium level of 128 mEq./L. was found in one infant (Ib.). The electrolytes were otherwise normal.

At the time of delivery, blood glucose values ranged from 55 to 270 mg. per 100 ml. in the mother's peripheral blood and were elevated in three of the five (figure 2). Cord blood glucose values were normal in two infants and elevated in three. In these three, the corresponding maternal blood glucose values were high.

After birth, during their first twelve hours of life, five infants (Ib., De., Pe., We., Cr.) had blood glucose levels that were more than 1 S.D. below the normal values in term infants of comparable gestations. One infant (Ib.) had recurring episodes of hypoglycemia during the first week of life in spite of oral feedings and intravenous administration of glucose solutions. Another infant (To.) had four glucose values within the normal range. Of the total of forty glucose determinations in the six infants, seventeen were low; sixteen were indistinguishable from those in the controls, and seven were higher than expected.

Three infants (Ib., Pe., To.) had high insulin values in the cord. This elevation did not persist in one (Pe.). Five infants had seventeen insulin values out of a total of thirty higher than 1 S.D. above those shown in the controls the first forty-eight hours of life. One (De.) had a single determination at seventeen hours of age which was very high and not associated with hypoglycemia. High insulin levels persisted beyond twenty-four hours in one infant (Ib.) and were associated with low levels of blood glucose. Approximately 50 per cent of the sugar values (seven out of fourteen) were low when the insulin values were high. The majority of high insulin and low glucose values were observed before twenty-four hours of age.

The plasma free fatty acid levels in the umbilical vein were higher than 1 S.D. above the mean value of the controls in two infants (Pe., Cr.). The plasma FFA levels (five values from zero hour to seven days) were persistently low in one infant (Cr.). This low FFA was associated with a low glucose value at one hour of age, but thereafter with normal glucose levels. Concomitant insulin concentrations in this baby (Cr.) were higher than 1 S.D. above those in the controls and growth hormone levels were normal with the exception of one isolated value of 90 m $\mu$ g./ml. (figure 2).

One infant (Ib.) had persistently low free fatty acid levels associated with persistently low glucose, high insulin and normal growth hormone values. The remainder of the IGDM (Pe., De., We., To.) had FFA levels indistinguishable from those in the controls.

Growth hormone values were higher than 1 S.D. above those in the controls in three infants (We., To., Cr.). The cord plasma value was higher in one infant only (To.). Concomitant plasma insulin concentrations were high in two infants (To., Cr.) and normal in the other (We.). There was no correlation between elevated HGH values and the other determinations.

The data from the infants were analyzed to determine if a positive or negative correlation existed between the parameters measured. No significant correlations were found between glucose and insulin, FFA or HGH; between FFA and insulin or HGH; or between insulin and HGH.

### *Group 2, IDM*

Pertinent clinical observations only will be presented for this group. One infant (An.) died at six hours of age with hyaline membrane disease. An exchange transfusion was done in each of two infants (Jo., Me.) who had very low levels of blood glucose during the first twelve hours of life. One (Jo.) was hypoglycemic with lethargy and jerking movements in the extremities. The response to the intravenous administration of glucose was good, but the baby became lethargic again, the hemoglobin was 26 gm. per 100 ml. and, at twenty-eight hours of age, the serum indirect bilirubin was 16 mg. per 100 ml. The other infant (Me.) was markedly hypoglycemic and lethargic and responded well to parental administration of glucose. Jaundice was noticed at thirty-eight hours of age and from that time to the age of seventy-four hours the bilirubin increased from 11.6 mg. per 100 ml. to 21.3 mg. per 100 ml., at which time an exchange transfusion was performed. The clinical course was uneventful in one infant (McN.).

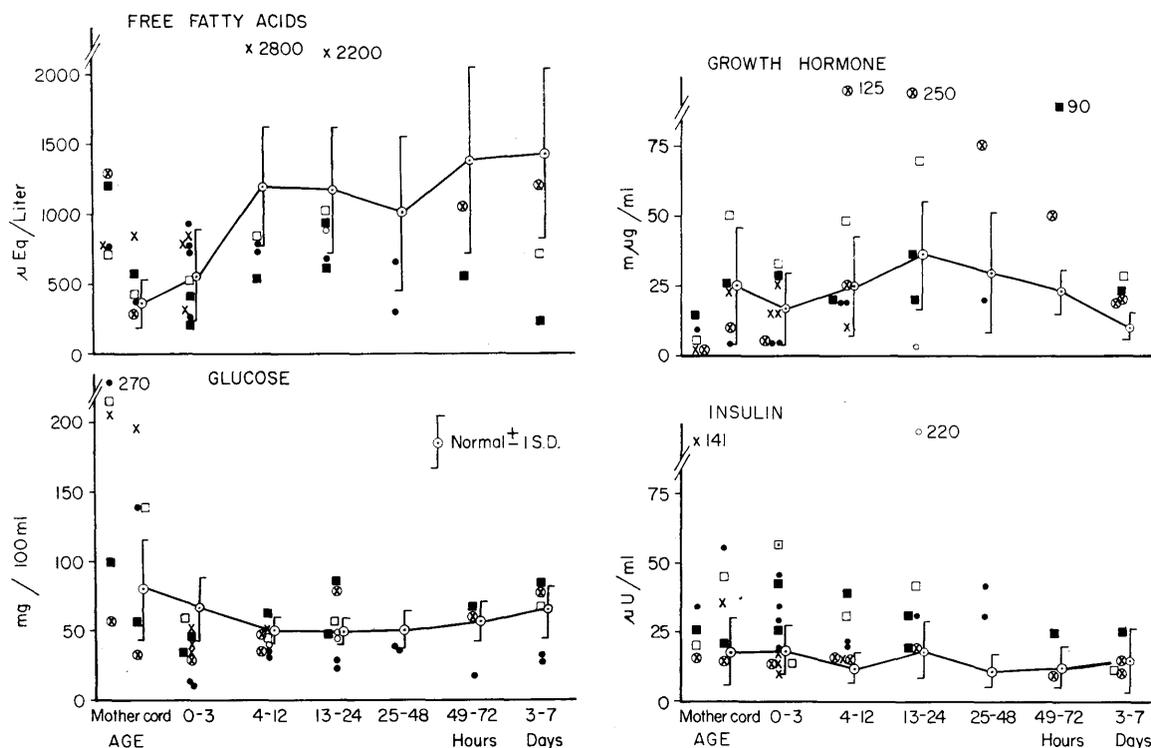


FIG. 2. Group I (IGDM). Maternal, umbilical vein and venous plasma FFA, GHG, insulin and blood glucose concentrations in six infants (● lb., ○ De., × Pe., ⊙ We., □ To., ■ Cr.) as compared to the mean values  $\pm$  1 S.D. in control infants. In the insulin data, □ represents Jo. of Group II whose mother received no insulin.

At birth, blood glucose values were obtained from the umbilical vein in four infants. Two were normal, one elevated, and one very high (McN.) (figure 3).

During the first three hours of life, five infants (all but An.) had eight blood glucose values out of a total of ten determinations less than 20 mg. per 100 ml. Three infants (Jo., Wa., Me.) had lethargy, jitteriness, hypotonia, and duskiess. One (Jo.) responded promptly to parenteral glucose. Hypoglycemia persisted in three infants (McN., Me., Wa.) during the four- to twelve-hour period of age. The first (McN.) had no symptoms and his blood glucose level rose spontaneously. The second (Me.) required parenteral glucose for several hours associated with low FFA and normal growth hormone values. There was no response in the third (Wa.) in spite of the parenteral administration of glucose, fructose, glucagon and invert sugar during the first ten hours of life.

Insulin levels could only be interpreted in one infant (Jo.) because the other infants' mothers had been on insulin therapy. One value obtained at ten minutes of age (figure 2) was high ( $62 \mu\text{U./ml.}$ ) and was associated with low blood glucose ( $31 \text{ mg. per } 100 \text{ ml.}$ ),

normal free fatty acid ( $995 \mu\text{Eq./L.}$ ) and normal growth hormone ( $10 \text{ m}\mu\text{g./ml.}$ ) levels.

Growth hormone values were within the normal range except in two infants (McN., Al.) at the time of birth and the first hours of life (figure 3). There was no correlation between birth weight and plasma GHG values.

#### DISCUSSION

The hypothesis has been advanced that hyperglycemia in the pregnant diabetic mother is an important factor in the pathogenesis of some of the metabolic abnormalities observed in the newborn infant.<sup>2,4,6,7,20</sup> Elevated insulin levels, as determined by immunoassay, have been reported in infants of insulin-dependent diabetic mothers who did not have any antibodies<sup>6</sup> and in infants of gestational diabetic mothers.<sup>7</sup> Insulin levels were found to increase in normal infants whose nondiabetic mothers had received intravenous glucose just prior to delivery.<sup>21</sup> In the present study, the plasma insulin values in umbilical venous samples at birth were high in three infants of gestational diabetic mothers and normal in two. A positive correlation was found between the cord plasma insulin and the mothers' blood glucose in these

INFANTS OF DIABETIC MOTHERS

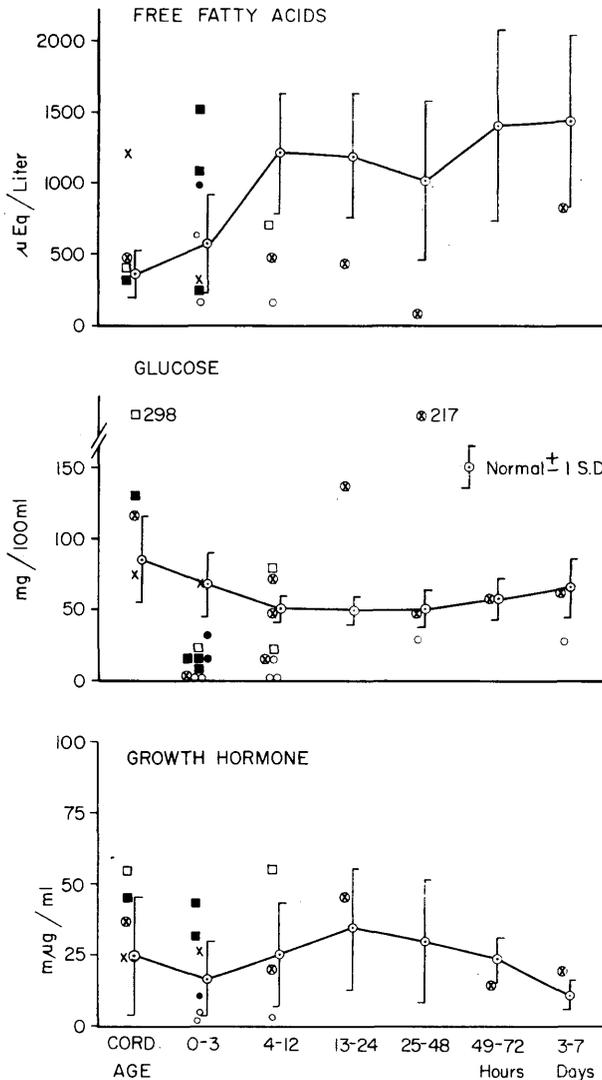


FIG. 3. Group II (IDM). Umbilical vein and venous plasma FFA, GH and blood glucose values in six infants (● Jo., ○ Wa., × An., ⊙ Me., □ McN., ■ Al.) of diabetic mothers are compared to the mean ± 1 S.D. of those in control infants.

infants (figure 4a), suggesting that hyperglycemia in utero produced a relative hyperinsulinism in the fetus and was related to the control of the maternal diabetic condition. In fact, of twelve infants of gestational diabetic mothers, four had plasma insulin values in the umbilical vein at birth significantly higher than those in the mother<sup>7</sup> (figure 3). No correlation was found between the maternal blood glucose and the infants' plasma insulin levels during the first three hours of life (figure 4b). However, during this same period a negative correlation was found between the infants' blood glucose and plasma insulin levels (figure 4c).

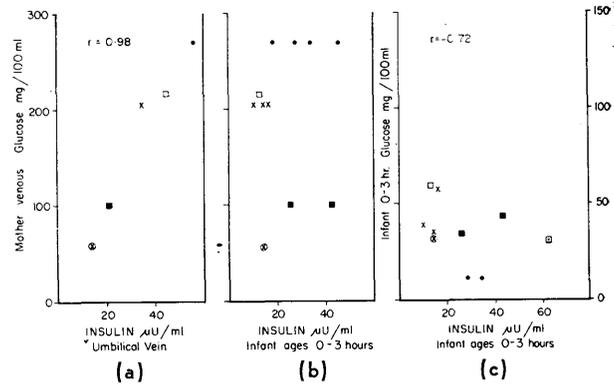


FIG. 4. Group I (IGDM). Plasma insulin values in umbilical vein plotted against maternal blood glucose (● Ib., × Pe., ⊙ We., □ To., ■ Cr.) shows a positive correlation ( $r = 0.98$ ): (a) At 0-3 hours of age, there was no correlation between the infant's plasma insulin and the maternal blood glucose, (b) but a negative correlation with the infant's blood glucose, (c) (□ Jo—Group II).

This suggested that the insulin regulating mechanism was established soon after birth in these infants, a feat not accomplished by the normal newborn (table 1).

Persistently low glucose levels with symptomatic hypoglycemia during the first day of life were present in only one infant of Group 1 (IGDM). This was associated with high insulin levels and occurred in an infant (Ib.) whose umbilical plasma insulin and maternal glucose were the highest. This baby was also the largest of the entire group and presented most of the characteristics of the IDM. In contrast with Group 1, low glucose levels and hypoglycemia with symptoms was a prominent feature in Group 2 (IDM). These observations support the hypothesis that a relationship exists between the severity of the maternal metabolic abnormalities and clinical manifestations in the newborn infant.

Low free fatty acid levels were observed in some infants but the results were variable. Chen et al.<sup>22</sup> reported a slower rise of FFA levels after birth in infants of gestational and insulin-dependent diabetic mothers. More observations will be necessary to confirm these findings.

The growth hormone levels in the IGDM and the IDM did not differ significantly from those in the controls. Using the data of twenty normal-term infants and of five infants in Group 1 (IGDM), a significant positive correlation ( $p = <.01$ ) was found between birth weight and plasma insulin levels in the umbilical vein at birth, confirming the findings of Shima et al.<sup>23</sup> (figure 5). No correlation was found between birth weight and plasma growth hormone levels.

## RELATIONSHIP BETWEEN WEIGHT AND INSULIN VALUES AT BIRTH

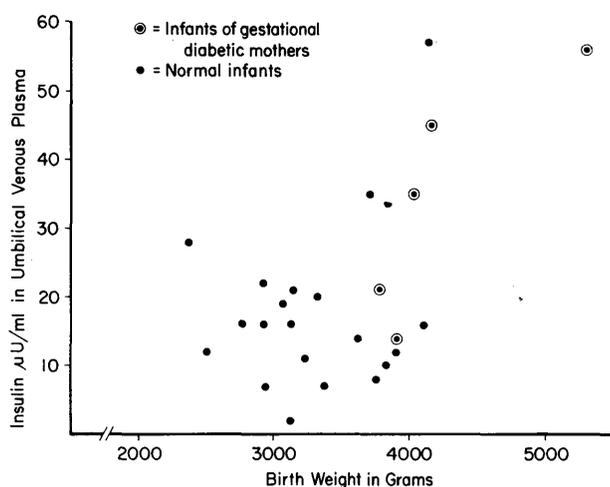


FIG. 5. A positive significant correlation ( $r = +.558$ ;  $p = < .01$ ) was found between weight and plasma insulin values at birth.

## ACKNOWLEDGMENT

This investigation was supported in part by a USPHS training grant (HD-88-03) and in part by Research Grants A-5105, HD-00235-06, and HD-02556-06 from the National Institutes of Health, USPHS, and a grant from the Psychiatric and Research Fund of the Illinois Department of Mental Health.

The authors wish to thank Miss Sandra Levy, Mrs. Lan Chao, and Miss Gertrude Asrow for able technical assistance and Mrs. De Lores Stratten and Miss Susan Klingman for help in preparation of the manuscript.

## REFERENCES

- <sup>1</sup> Cornblath, M., and Schwartz, R.: Disorders of Carbohydrate Metabolism in Infancy. Philadelphia, W. B. Saunders and Company, 1966, p. 57.
- <sup>2</sup> Pedersen, J., Bøisen, B., and Poulsen, H.: Blood sugar in newborn infants of diabetic mothers. *Acta Endocr. (Kbh.)* 15: 33, 1954.
- <sup>3</sup> Cardell, B. S.: Hypertrophy and hyperplasia of the pancreatic islets in newborn infants. *J. Path. Bact.* 66:335, 1953.
- <sup>4</sup> Baird, J. D., and Farquhar, J. W.: Insulin-secreting capacity in newborn infants of normal and diabetic women. *Lancet* 1:71, 1962.
- <sup>5</sup> Grodsky, G. M.: *In* Juvenile Diabetes Mellitus. Report of the Fifty-first Ross Conference on Pediatric Research. Owen, G. M., Ed. Columbus, Ohio, Ross Laboratories, 1965, p. 9.

<sup>6</sup> Jørgensen, K. R., Deckert, T., Pedersen, L., and Pedersen, J.: Insulin, insulin antibody and glucose in plasma of newborn infants of diabetic women. *Acta Endocr. (Kbh.)* 52:154, 1966.

<sup>7</sup> Thomas, K., de Gasparo, M., and Hoet, J. J.: Insulin levels in the umbilical vein and in the umbilical artery of newborns of normal and gestational diabetic mothers. *Diabetologia* 2:221, 1966.

<sup>8</sup> Miller, H. C.: Offspring of diabetic and prediabetic mothers. *Adv. Pediat.* 8:137, 1956.

<sup>9</sup> McCann, M. L., Chen, C. H., Katigbak, E. B., Kotchen, J. M., Likly, B. F., and Schwartz, R.: Effects of fructose on hypoglycemia in infants of diabetic mothers. *New Eng. J. Med.* 275:1, 1966.

<sup>10</sup> O'Sullivan, J. B., and Mahan, C. M.: Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 13:278, 1964.

<sup>11</sup> Hoet, J. P.: Carbohydrate metabolism during pregnancy. *Diabetes* 3:1, 1954.

<sup>12</sup> Farquhar, J. W.: The child of the diabetic woman. *Arch. Dis. Child.* 34:76, 1959.

<sup>13</sup> Cornblath, M., Joassin, G., Weisskopf, B., and Swiatek, K. R.: Hypoglycemia in the newborn. *Pediatr. Clin. N. Amer.* 13:905, 1966.

<sup>13a</sup> Cornblath, M., Parker, M. L., Reisner, S. H., Forbes, A. E., and Daughaday, W. H.: Secretion and metabolism of growth hormone in premature and full-term infants. *J. Clin. Endocr.* 25:209, 1965.

<sup>14</sup> Somogyi, M.: Determination of blood sugar. *J. Biol. Chem.* 160:69, 1945.

<sup>15</sup> Marks, V.: An improved glucose oxidase method for determining blood, C.S.F. and urine glucose levels. *Clin. Chim. Acta* 4:395, 1959.

<sup>16</sup> Duncombe, W. G.: The colorimetric micro-determination of long-chain fatty acids. *Biochem. J.* 88:7, 1963.

<sup>17</sup> Dole, V. P.: A relation between non-esterified fatty acids in plasma and the metabolism of glucose. *J. Clin. Invest.* 35: 150, 1956.

<sup>18</sup> Morgan, C. R., and Lazarow, M. A.: Immunoassay of insulin: two antibody system. Plasma insulin levels of normal, subdiabetic and diabetic rats. *Nutr. Rev.* 20:245, 1962.

<sup>19</sup> Schalch, D. S., and Parker, M. L.: A sensitive double antibody immunoassay for human growth hormone in plasma. *Nature* 203:1141, 1964.

<sup>20</sup> Farquhar, J. W.: Maternal hyperglycaemia and foetal hyperinsulinism in diabetic pregnancy. *Postgrad. Med. J.* 38:612, 1962.

<sup>21</sup> Milner, R. D. G., and Hales, C. N.: Effects of intravenous glucose on concentration of insulin in maternal and umbilical-cord plasma. *Brit. Med. J.* 1:284, 1965.

<sup>22</sup> Chen, C. H., Adam, P. A. J., Laskowski, D. E., McCann, M. L., and Schwartz, R.: FFA and blood glucose in normal and diabetic pregnancies. *Pediatrics* 36:843, 1965.

<sup>23</sup> Shima, K., Price, S., and Foà, P. P.: Serum insulin concentration and birth weight in human infants. *Proc. Soc. Exper. Biol. Med.* 121:55, 1966.