mMol/l (106 mg/100 ml) reflected the usefulness of the four routine preprandial blood samples taken to monitor blood sugar in the ward before the study. Closer inspection of their diurnal profiles, however, showed definite deviations from the normal. During the day their mean glucose concentration was 6-47 mMol/l (116-6 mg/100 ml; normal 4-69 mMol/l (84-6 mg/100 ml)), while at night hypoglycaemia developed with a mean for the lowest glucose concentration of 2-9 mMol/l (53-8 mg/100 ml; normal 3-7 mMol/l (67-1 mg/100 ml)). This difference between day and night values was associated with an increased diurnal variability which was nearly three times that of normal women at the same period of gestation.

Though control was satisfactory so far as the mother's health was concerned such an unstable glucose environment may have adverse effects on the developing fetus. Many workers have suggested that poor diabetic control in early pregnancy may be responsible for abnormal fetal development; neurological defects have been seen in the offspring of diabetic mothers. More specifically, the frequent nocturnal hypoglycaemia observed among insulin-treated diabetics may, in severe cases, be a factor responsible for abnormal embryogenesis or perhaps for unexpected death of the hyperinsulinaemic fetus during the last trimester of pregnancy. Thus, every attempt should be made to normalize the maternal plasma glucose so far as possible throughout the 24 hours.

The total area under the three-hour oral glucose tolerance curve was the function which correlated best with the mean diurnal plasma glucose concentration in normal and chemically diabetic women on a standard diet. The fasting plasma glucose concentration contributes directly to the calculation of both the mean diurnal plasma glucose concentration and the total area under the oral glucose tolerance curve, both of which increase as the fasting plasma glucose increases. Thus a strong correlation between the total oral glucose tolerance area and the mean diurnal glucose is inevitable in a group of people with a wide range of fasting glucose values; only three of our patients, however, had a plasma glucose greater than 5-6 mMol/l (100 mg/100 ml): 5-61, 5-72, and 6-33 mMol/l (101, 103, and 114 mg/100 ml).

There was also a highly significant correlation between the G.T.T.-two-hour plasma glucose level and the diurnal glucose levels, which supports the widespread use of the G.T.T.-two-hour value for identifying patients with impaired carbohydrate tolerance. The two-hour plasma glucose level, however, showed much greater variability in the "normal" range than the area under the curve, which limits its usefulness.

The H index has the advantage over other indices of carbohydrate tolerance that it is independent of both the source of the blood sample and also the method of glucose measurement and hence facilitates comparison of the results of different laboratories. It also uses all the information derived from the glucose tolerance test and takes into account the time at which the peak glucose concentration occurs. Lind et al. have shown a progressive rise in the H index with advancing pregnancy in women with glucose tolerance judged to be normal by conventional criteria. We saw no significant difference, however, between the H index at 18 and at 34 weeks of pregnancy in the normal group. Our findings do, however, confirm that raised values occur in chemical diabetic patients. Though this index of glucose tolerance may be valuable for showing changes in the shape of the curve during pregnancy it seems to be of limited use for assessing the glucose concentration prevailing in pregnant women with normal or borderline carbohydrate tolerance. Our findings on maternal carbohydrate tolerance are related to the glucose metabolism of the newborn in Part II.

References

Part II—Relation between Maternal Glucose Tolerance and Glucose Metabolism in the Newborn

Summary
The objective of clinical management of the pregnant diabetic woman is to prevent the serious adverse effects of an abnormal glucose environment on the fetus. Neonatal glucose assimilation and insulin release over the first two hours of life were correlated with various indices of maternal carbohydrate metabolism in the third trimester. Of the 31 mothers studied 21 were defined as normal and 10 as having chemical diabetes.

Neonatal glucose assimilation during the first two hours of life correlated strongly with functions of both maternal glucose tolerance and mean diurnal glucose level, the strongest correlation being with the area under the three-hour oral glucose tolerance curve (P<0.001). Two-hour neonatal plasma glucose values of under 1.7 mMol/l (30 mg/100 ml) were found only in the newborn of women whose glucose tolerance area measured over 416 area units (750 traditional units); thus, even in the borderline diabetic range glucose tolerance testing during the last trimester of pregnancy may be valuable in predicting likelihood of neonatal hypoglycaemia. The findings also shed light on the possible sensitizing role of mild maternal hyperglycaemia on fetal insulin production and secretion.

Introduction
Chemical diabetes in late pregnancy carries an increased risk of unexpected fetal and neonatal death. Part of the problem in patients with chemical diabetes is to know beforehand how
seriously affected the baby is by the abnormal glucose environment to which it is constantly exposed. For this reason there is a need to determine whether it is possible to correlate the indices of maternal carbohydrate tolerance with the metabolic performance of the baby.

Pedersen showed that increasing maternal blood sugar levels during late pregnancy were associated with a decrease in mean neonatal birth glucose during the first 24 hours after birth. He suggested that this was due to neonatal hyperinsulinaemia resulting from exposure of the developing fetus to varying degrees of maternal hyperglycaemia. A year later Cardell showed pancreatic β-cell hypertrophy and hyperplasia in infants born to diabetic mothers. More recently it has been shown that during the first 24 hours of life infants of diabetic women show an enhanced insulin response to glucose with an increase in the glucose disappearance rate after an intravenous glucose load.

Thus, if early neonatal carbohydrate metabolism in some way reflects that of the mother during the latter part of pregnancy it may be possible to predict which baby is likely to develop hypoglycaemia as the result of maternal diabetes. The detailed documentation of carbohydrate metabolism during pregnancy reported in Part I was therefore related to the changes in plasma glucose and insulin levels during the first two hours after birth in infants born to the women studied during pregnancy.

Patients and Methods

The infants of 31 women whose carbohydrate metabolism had been documented during the last trimester of pregnancy and who had not been treated in any way were studied. There were six controls and 25 patients with one or more of the features of overt diabetes. Twenty-one of the women were classified as normal and 10 as chemical diabetics on the basis of a three-hour oral glucose tolerance test (G.T.T.) area of over 41-6 units (750 traditional units) (see Part I).

At birth blood was collected from the vein of a double-clamped segment of umbilical cord. The neonate was then transferred to an incubator and maintained under constant conditions without feeding until two hours after delivery, when capillary blood was obtained from a warmed heel. All blood was collected into heparinized tubes, centrifuged immediately, and the plasma stored at −20°C. Neonatal plasma glucose was measured by a micro glucose oxidase-oxygen electrode method. Neonatal plasma insulin was measured by the method of Albano et al.

To assess the relation between the maternal and neonatal data the indices derived from the maternal study (Part I) were compared with the neonatal findings. The neonatal indices were: (a) the rate of glucose utilization during the first two hours after delivery—"neonatal incremental K value"; and (b) the absolute plasma glucose two hours after delivery. The neonatal incremental K value—a fractional glucose removal rate expressed as %=min− was calculated on the assumption that neonatal plasma glucose falls exponentially towards the value reached at two hours after delivery.

During labour all the patients fasted and all except three received a routine intravenous infusion of 1 litre of 5%, dextrose every eight hours. In all cases the plasma glucose levels remained within the physiological range. Twenty-six infants were delivered vaginally and five by elective caesarean section. No fetal distress was observed. Plasma glucose was measured on all the umbilical vein and two-hour neonatal blood samples and in 58 out of the 62 samples plasma insulin was also estimated.

The normal and chemically diabetic women were well-matched for timing of the maternal study and duration of pregnancy, and did not differ significantly in age, weight, or height. The mean birth weight of infants born to chemically diabetic women was higher than that of those born to normal women (P<0.001). Though the mean plasma insulin concentration at birth in the infants of the chemical diabetics was higher than normal this difference was only significant at a level of P=0.08. The two-hour post-delivery plasma insulin concentration of the neonates of the chemical diabetics, however, significantly higher than normal (P=0.02).

The neonatal insulin:glucose ratio two hours after delivery is shown in fig. 1. The mean:insulin:glucose ratio of infants born to chemically diabetic women was significantly higher than that of those born to normal women (P=0.017) while neonatal hypoglycaemia (plasma glucose <1.39 mmol/l (<25 mg/100 ml)) was invariably associated with inappropriate insulin secretion.

Neonatal Carbohydrate Changes and Maternal Carbohydrate Tolerance.—Neonatal incremental K values and neonatal two-hour glucose levels showed very similar correlations with the various maternal values (table II). The closest correlation was between neonatal two-hour plasma glucose and the total area under the maternal oral G.T.T. profile (fig. 2). High significant correlations (P<0.001) were also found between the G.T.T. two-hour plasma glucose and both the neonatal functions. The best diurnal index correlation was between neonatal two-hour plasma glucose and maximum diurnal plasma glucose (r=−0.51; P<0.005) but the diurnal plasma glucose range, the mean diurnal glucose, and mean daytime glucose all gave correlations greater in the infants of the chemical diabetics than in those of normal women (P=0.001).

The mean plasma glucose concentration at birth and the two-hour post-delivery plasma glucose concentration in the infants of the chemical diabetics was significantly higher than that of those born to normal women (P=0.017) while neonatal hypoglycaemia (plasma glucose <1.39 mmol/l (<25 mg/100 ml)) was invariably associated with inappropriate insulin secretion.

Results

Neonatal Plasma Glucose and Insulin Concentrations after Delivery.—The neonatal plasma glucose and insulin concentrations in blood taken at birth and two hours after delivery from the infants of the 21 normal and 10 chemically diabetic women are shown in table I. At birth the umbilical venous glucose was similar in both groups, but the fall in plasma glucose during the first two hours after birth was significantly

### Table I—Mean (±1 S.D.) Neonatal Plasma Glucose and Insulin Values at Birth and Two Hours Later

<table>
<thead>
<tr>
<th>Neonatal Glucose mmol/l</th>
<th>Neonatal Insulin (mU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal women</td>
<td>Chemical diabetics</td>
</tr>
<tr>
<td>Birth</td>
<td>At 2 Hours</td>
</tr>
<tr>
<td>4.70 ± 0.89 (21)</td>
<td>3.99 ± 0.39 (21)</td>
</tr>
<tr>
<td>4.93 ± 1.17 (10)</td>
<td>1.50 ± 0.58 (10)</td>
</tr>
</tbody>
</table>

Conversion: SI to Traditional Units—1 mmol/l=18 mg/100 ml.

![Graph showing the relationship between plasma glucose and insulin](image)

**Fig. 1—Two-hour neonatal insulin:glucose ratios in infants of 20 normal and nine diabetic mothers.**

Open symbols represent patients with two-hour glucose values of <1.39 mmol/l (<25 mg/100 ml), closed symbols those with values of ≤1.39 mmol/l (≥25 mg/100 ml).

### Table II—Correlation between Maternal and Neonatal Carbohydrate Tolerance Indices

<table>
<thead>
<tr>
<th>Maternal Glucose (mmol/l)</th>
<th>Neonatal Glucose (mmol/l)</th>
<th>Neonatal Glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Chemical</td>
<td>Normal</td>
</tr>
<tr>
<td>0.679*</td>
<td>0.569*</td>
<td>0.629*</td>
</tr>
<tr>
<td>0.593*</td>
<td>0.593*</td>
<td>0.609*</td>
</tr>
<tr>
<td>0.571*</td>
<td>0.571*</td>
<td>0.591*</td>
</tr>
<tr>
<td>0.125*</td>
<td>0.125*</td>
<td>0.145*</td>
</tr>
<tr>
<td>Mean diurnal plasma glucose</td>
<td>Mean diurnal plasma glucose</td>
<td>Mean diurnal plasma glucose</td>
</tr>
<tr>
<td>0.456*</td>
<td>0.456*</td>
<td>0.471*</td>
</tr>
<tr>
<td>Maximum diurnal plasma glucose</td>
<td>Maximum diurnal plasma glucose</td>
<td>Maximum diurnal plasma glucose</td>
</tr>
<tr>
<td>0.473*</td>
<td>0.473*</td>
<td>0.484*</td>
</tr>
<tr>
<td>Diurnal plasma glucose</td>
<td>Diurnal plasma glucose</td>
<td>Diurnal plasma glucose</td>
</tr>
</tbody>
</table>

*P<0.001. †P=N.S. ‡P<0.005. **P<0.05.
with \( P < 0.005 \). The H index did not correlate significantly with either of the neonatal indices.

**Discussion**

Several workers have studied the spontaneous changes in blood sugar which occur during the first two hours after birth in infants born to both normal and diabetic women.\(^3\)\(^8\)\(^9\)\(^1\)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\) McCann et al.\(^4\) showed that the rate of decline of the endogenous blood glucose is most rapid in the infants of insulin-dependent diabetic mothers, least rapid in the infants of normal mothers, and intermediate in the infants of gestational diabetic women. Nobody, however, has correlated the degree of glucose intolerance in normal mothers and those with mild chemical diabetes with any index of neonatal carbohydrate metabolism.

Our most important result was the demonstration of a direct relation between carbohydrate tolerance in the mother and glucose utilization by the newborn; the worse the maternal tolerance the more rapidly is glucose assimilated by the infant. This finding is of interest when one recalls that the tests on maternal carbohydrate tolerance were done, on average, four weeks before birth, and when viewed in conjunction with the insulin data shown in fig. 1 it provides strong evidence in favour of Pedersen's\(^3\) theory that the hyperinsulinism of the newborn of the diabetic mother can be attributed to the abnormal glucose environment provided by the mother in which the fetus has to develop.

An arbitrary cut-off point is usually used to distinguish normal from abnormal glucose tolerance; yet in pregnancy information from the neonate should help to improve this situation. We therefore looked to see what maternal cut-off point would have best identified the neonates who became hypoglycaemic. Seven babies had two-hour plasma glucose values of 1-67 mmol/l (30 mg/100 ml) or less, four being below 1-39 mmol/l (25 mg/100 ml). Selection of the 10 women with oral G.T.T. areas of over 41-6 units would have included the mothers of all but one of these babies, together with those of four whose blood sugar did not fall excessively at birth. The six women with G.T.T. areas of over 44-4 units (800 traditional units) included the mothers of all but two hypoglycaemic babies and of only a single normal one. Twelve mothers had two-hour G.T.T. values above 6-7 mmol/l (120 mg/100 ml), but only four of their babies had a plasma glucose of <1-67 mmol/l (<30 mg/100 ml). Thus in terms of the ratio of false positives to false negatives an oral G.T.T. area of over 44-4 units is the best predictive index of neonatal hypoglycaemia. The finding that the H index in the mother does not provide a good guide to the effect on the fetus in keeping with the weak correlation found between this index and the diurnal glucose functions (see Part I).

The neonatal plasma insulin concentrations at birth and two hours after delivery were similar to those observed by other workers;\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\) we confirmed that infants who have been exposed to hyperglycaemia in utero have higher fasting plasma insulin levels. In this context the significant correlations between neonatal values and the maternal diurnal plasma glucose range are of particular interest. Grasso\(^8\) reported that in premature infants of the same gestational age as the mothers in our study an increase of plasma glucose to about 6-1 mmol/l (110 mg/100 ml) for one to two hours in some way sensitizes their pancreatic \( \beta \)-cells so that a subsequent glucose load induces an increased insulin response. Diurnal studies showed that though concentrations as high as this rarely occur in normal women throughout pregnancy they do occur quite often after meals in women with chemical diabetes. These findings support the concept that even minor impairment of maternal glucose homeostasis in late pregnancy with an increase in diurnal fluctuation may sensitize the \( \beta \)-cells to glucose and result in a state of relative fetal and neonatal hyperinsulinism. They may also explain why the glucose tolerance test correlates so well with the disappearance of glucose and the insulin status of the neonates we have studied.

We thank Dr. D. A. Pyke and Mr. J. M. Brunedell for their permission to study the insulin-dependent diabetic patients under their care at King's College Hospital; Professor Victor Wynn for his advice during the study and for allowing us to use the facilities of the Alexander Simpson Laboratory and the metabolic ward; and Miss C. A. Knight for her help with the illustrations. We acknowledge the generous support of the Welcome Trust and the British Diabetic Association for their grants to Professor R. W. Beard and Dr. N. W. Oakley respectively.

**References**