THE CHILD OF THE DIABETIC WOMAN

A Thesis presented for the Degree

of

Doctor of Medicine

by

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M.B., Ch.B., Ed., F.R.C.P.E.

The pathology of the present series.

UNIVERSITY OF EDINBURGH

October 1958
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**Factors possibly responsible for the morphology.**

- Inheritance.
  - Maternal build.
- Family birth weight.
- Pre-diabetes and diabetes mellitus.
  - Hyperglycaemia.
  - Pre-diabetes.
- Hormonal factors.
  - Animal experiment.
    - The offspring of diabetic animals.
    - The production of insulin.
    - The role of insulin as a growth hormone.
  - Pituitary growth hormone.
  - Insulin.
  - Corticotrophin and corticosteroids.
  - Sodium-retaining hormone.
  - Gonadotrophins.

**Summary.**

**Factors possibly responsible for the foetal morbidity and mortality.**

- Pre-natal factors.
  - Severity of the maternal diabetes.
  - Insulin requirement.
  - Duration and severity of diabetes.
  - Control of the maternal diabetes.
  - Ante-natal obstetric care.
  - Family mortalities.
  - Mortality and foetal birth weight in the pre-diabetic group.
- Placental insufficiency.
  - Hormonal imbalance.
  - Foetal hypoxia.
  - The cause of placental insufficiency.

- Post-natal factors.
  - Time and route of delivery.
  - Birth weight.
  - Hypokalaemia.
  - Hypocalcaemia.
  - Hypoglycaemia.
  - Adrenocortical disorder.
Post-natal factors (contd.)

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Treatment of the newborn.

Lactation.

Congenital malformations.

The development of surviving children.

The relationship of neonatal condition to later health.

Growth.

Birth weight and later height.

Birth weight and later weight.

The development of diabetes mellitus.

Conclusions.

Summary.

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ACKNOWLEDGMENTS

During the ten years in which the information contained in this thesis has been gathered, a great deal of help has been obtained from many people to whom I gladly express my thanks.

Professor R.W.B. Ellis fostered my first interest in the diabetic pregnancy and he has remained my principal source of inspiration and encouragement. Dr. G. Douglas Matthew, whose work on the subject was well established before I joined his team, has not only stimulated my explorations but has generously provided information obtained from his own studies. Professor R.J. Kellar gave me the use of a room, equipment and technical help in his clinical research laboratory. Professor G.F. Marrian advised me on some of the earlier work, and Dr. W.N.M. Ramsay of his department tutored me in the use of his method for determining the blood sugar level. Professor D.M. Dunlop provided generous amounts of corticotrophin and cortisone when the supply of these materials was subject to strict control, and Drs. J. Baird, L.J.P. Duncan, J.A.L. Gilbert and C.F. Rolland of his department have given much information about the mothers. Professor D. Whitteridge and Dr. R. Passmore helped with the study of hypoglycaemia and neonatal respiration. Professor E.J. King of the Hammersmith Postgraduate Medical School and Dr. C.P. Stewart assisted me in my efforts to master a copper-reduction micro-method for blood sugar level estimation, and it was from Dr. Stewart and from Dr. J.S. Robson that I obtained the assistance which made possible the study of urinary formaldehydogenic steroid excretion.
The autopsy reports have been quoted with the consent of Dr. A.R. Macgregor who also gave me the sections of pulmonary hyaline membrane and of normal pancreas (Figures 11 and 13). Dr. R.F. Ogilvie willingly discussed the foetal pancreas with me many times, and he provided the section which shows Langerhans continents (Figure 12).

Dr. L. Stein and Mr. S. Sklaroff have given statistical assistance. Drs. T.A. Munro, P.K. McCowan, W. Mayer-Gross, D.E. Sands and T. Tennant searched the records of insulin coma units under their charge for particulars of women treated in early pregnancy. A number of Medical Officers of Health in Scotland and elsewhere have assisted in tracing children who changed address. Many paediatric house officers at the Simpson Memorial Maternity Pavilion have taken endless trouble over the care of the infants and over the related observations and experiments. Careful technical assistance was provided for two years by Miss Pat Stevens.

A great deal of secretarial work has been necessary, and this has been carried out efficiently and pleasantly by Miss A. Brown, Miss E. Cruickshank, Miss E. Meiklejohn and Miss D. Trench. Many of the charts were drawn by Mr. C. Shepley or members of his department. The photographs were taken, reproduced and mounted by Miss C. Brydone who, with Mr. R.P. Danskin of the Department of Cardiology, Edinburgh Royal Infirmary, obtained the electrocardiograms. These were reported by Dr. R.A. Miller and cardiologists of the Royal Infirmary.

The nursing staff of the Simpson Memorial Maternity Pavilion
Pavilion has provided a very high standard of care for each baby.

The diabetic mothers of the children have co-operated wholeheartedly with the follow-up examinations. The mothers of the control group, who stood to gain nothing, have been particularly helpful.

Finally, I gladly record thanks to my wife who has helped me in the laboratory, at hospital and at home with the cheerful generosity which is so characteristic of her.

Financial assistance has been received from the George Guthrie Research Fellowship and the Kinghorn Bequest of the University of Edinburgh.
Figure 1

THE BABY OF THE DIABETIC WOMAN

Birth Weight - 5032 g.  Maturity - 36 weeks.
INTRODUCTION

For many married women the development of diabetes mellitus in middle or later life involves little disability. The size of their babies and the sad memory of an unexplained stillbirth will seldom be connected in their minds with the need for some dietary control, the swallowing each day of a few tablets of tolbutamide or the nuisance of injecting themselves with insulin.

For others, however, diabetes is a disease which has existed undiagnosed from childhood or early adult life. It has usually meant the imposition of annoying restrictions on diet and on social activity during the "years of freedom", the discomfort of insulin injection and the upsets of hypoglycaemia, ketosis and hospital admission. In a significant proportion of cases the disease will have created emotional maladjustments as a result of stress and of family deficiencies and discords. Nor is the diabetic woman's marriage necessarily blessed with the satisfaction of motherhood, for she is less likely to bear a live baby or to see that child survive the first week of life than is her non-diabetic neighbour. And if he does survive, then there are still troubling anxieties about his health and his future.

The Edinburgh medical team, operating at the Simpson Memorial Maternity Pavilion, has tried to improve the foetal survival rate in diabetic pregnancy. This work has naturally provided opportunities to enquire into the possible causes of foetal mortality and into the future development of surviving children.
The material is presented in three parts.

**Part A. THE THESIS.**

The Thesis proper is a discussion of the mortality and morbidity, and of the morphology, pathology and later progress of children conceived by diabetic women. It includes the results of personal studies and reviews of relevant literature.

**Part B. INDIVIDUAL ACCOUNTS OF SPECIAL STUDIES.**

This part provides detail of the special studies mentioned in Part A. and of others which, although relevant to the whole investigation, would interrupt the theme of the Thesis if introduced into it.

**Part C. APPENDICES.**

The appendices contain summaries of the progress notes of morbid cases, details of the laboratory methods used, tables of basic data about the cases studied, and the references to the quoted literature.
PART A.

THE THESIS
THE CHILD OF THE DIABETIC WOMAN

Over a century ago Bennewitz, when delivering a diabetic woman, observed that the giant foetus whose head had been born but whose shoulders were stuck fast "seemed anxious and sighed with a clear voice". In this depressed state the infant died, as so many of his kind have done since.

Pregnancy complicating diabetes and the development of children born to diabetic women became problems only with the development of insulin. Some idea of the rarity of pregnancy among diabetic women in the pre-insulin era may be gathered from the fact that Lecorche (1885) reported only 7 gestations in 114 female diabetics, while von Noorden (1917) before 1909 had observed only 5 per cent of pregnancies in 427 diabetics of child-bearing age. This infertility has been regarded as a possible consequence of poor nutrition (Sinden and Langwell, 1949). In the first decade of insulin treatment, however, Skipper (1933) already noted improved fertility, and the infertile diabetic woman is now exceptional in the extensive experience of White (1952), and Stevenson (1956) found that in his Belfast series 70 per cent were pregnant within one year of marriage and that over 90 per cent were pregnant within two years.
FOETAL LOSS IN THE DIABETIC PREGNANCY

Prior to the development of insulin, the infrequent pregnancies were fraught with risk for both mother and child. The foetal loss rate ranged from 40 to 70 per cent (Table 1), and although maternal mortality in diabetic pregnancy has been almost entirely eliminated, a distressing foetal loss persists. Until recently pre-viable abortions were included in the over-all foetal mortality figures. No evidence exists, however, that abortions are any commoner among diabetic than among non-diabetic women (Peel and Oakley, 1950). A figure of 6.4 per cent found by Pedowitz and Shlevin (1955) was well within the normal range in their experience, 10 per cent of abortions were reported by Stevenson (1956), and Barns and Morgans (1949) described a diabetic abortion rate of 10.9 per cent and a non-diabetic rate of 11.8 per cent. Because of these reports, and because an unknown number of abortions in both groups are never reported, it is now customary to compare only the viable foetal loss rates of different series.

The perinatal mortality for all booked pregnancies at the Simpson Memorial Maternity Pavilion has been less than 40/1000 births in recent years, and this contrasts with the figure of 166/1000 births for those diabetic women who were adequately supervised from not later than the twentieth week of gestation, and upon whom or upon whose babies exceptional and co-ordinated care was lavished by a team composed of an obstetrician, a physician and a paediatrician. These results are compared in Table with other American and European /
European series. The Danish and Belfast figures have been calculated for roughly the same years as this series, but later improvement was noted in both. The neonatal death rate is given only where this could be calculated from the figures given.
<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>Place</th>
<th>Number of Cases</th>
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<th>Neonatal Mortality</th>
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<tr>
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<td>39</td>
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<td>226</td>
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<td>280</td>
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<td>Boston</td>
<td>628</td>
<td>111</td>
<td>-</td>
<td></td>
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<tr>
<td>Oppe</td>
<td>1957</td>
<td>Boston</td>
<td>736</td>
<td>180</td>
<td>110</td>
<td>Excluding all diabetic women with nephropathy.</td>
</tr>
</tbody>
</table>

* Over-all foetal mortality (probably including abortions).

* * Expressed in terms of per 1000 viable pregnancies.
Figure 2

TYPICAL LARGE BABIES OF DIABETIC WOMEN
CLINICAL DESCRIPTION AND PROGRESS OF THE NEWBORN

The children born to diabetic men do not differ discernibly at birth from those born to non-diabetic men (Babbott et al, 1958). Those delivered by diabetic mothers, however, (Figure 1) commonly exceed both the mean body weight and crown-heel length for their gestational age (Cardell, 1953a; Pedersen, 1954). Because of their gigantism, and because of a strong tendency toward intra-uterine death after the 36th week, Caesarean birth some weeks before term has been commonly practised, and most of the babies in this series were so delivered.

The infants are remarkable (Figure 2) not only because like foetal versions of Shadrach, Meshach and Abednego they emerge at least alive from within the fiery metabolic furnace of diabetes mellitus, but because they resemble one another so closely that they might well be related. They are plump, sleek, liberally coated with vernix caseosa, full-faced and plethoric. The umbilical cord and the placenta share in the gigantism. During their first 24 or more extra-uterine hours they lie on their backs, bloated and flushed, their legs flexed and abducted, their lightly closed hands on each side of the head, the abdomen prominent and their respiration sighing. They convey a distinct impression of having had such a surfeit of both food and fluid pressed upon them by an insistent hostess that they desire only peace so that they might recover from their excesses. And on the second day their resentment of the slightest noise improves the analogy while their trembling anxiety seems to speak of intra-uterine /
intra-uterine indiscretions of which we know nothing. The
self-description provided by the oysters in 'Alice Through
the Looking Glass' is singularly applicable to these babies.

'But wait a bit', the oysters cried,
'Before we have our chat,
For some of us are out of breath
And all of us are fat.'

Of the 123 viable pregnancies in the series, occurring
in women in whom the diagnosis of diabetes mellitus was
certain, 96 resulted in the birth of a live child, and of
these, 57 survived the newborn period without serious
incident. Most of them showed prolonged Moro embrace
responses which were elicited so easily that even a light
footfall in the room, a hand laid gently on the cot, or the
movement of a camera shutter was sufficient to evoke a series
of movements which have been described by the inexperienced
as twitchings or convulsions.

Those infants whose first feed is delayed, for reasons
which will be given later, until the fourth day will cer-
tainly become restless before then and will show some evi-
dence of dehydration. Physiological jaundice is common and,
as in infants of comparable gestational age, it may be quite
deep and prolonged. Infection of the skin occurs easily
unless strict precautions are taken. Very little breast
tissue is palpable during the first two weeks of life.

Every author who has described the progress of babies
born alive to diabetic women has commented upon the frequency
with which respiratory disorders occur. Respiratory
embarrassment and acute "cyanotic attacks" or "colour
changes" are commonly mentioned. Those babies of the
present /
The duration of dyspnoea

Newborn infants of diabetic women. Edinburgh. 1948-55

Supervision refers to adequate ante-natal care.
Figure 4

DYSPNOEIC INFANT SUFFERING
FROM PULMONARY HYALINE MEMBRANE
present series whose clinical progress was abnormal may be grouped together according to whether they suffered from dyspnoea or cyanotic attacks. Loose as such descriptive terms may be, insufficient evidence exists as yet to support the adoption of others. The disorder of function responsible for them, however, need not be located in the respiratory system alone.

**Dyspnoea.**

Difficult respiration was observed in 21 babies (22 per cent). In some, respiration was established slowly, occasionally only with assistance, and breathing then remained distressed. In others the baby cried immediately on removal head-first from the uterus, quickly became pink, and then after a few minutes or an hour or more dyspnoea gradually developed. In only two cases did respiratory difficulty make its first appearance after the first day, and one of these infants had pneumonia. (See Appendix I for progress notes of individual babies.)

The duration of dyspnoea varied from a few hours to more than three days (Figure 3). Cyanosis of varying degree accompanied the forcible respirations (Figure 4), the sternal and costal indrawing and the strange tremulous expiratory whine which is known to the midwives as "murmuring". Seriously affected babies became very limp, and the Moro response, so very active in the well offspring of the diabetic woman, was lost at least temporarily. All the deaths in this series were preceded by dyspnoea, and in all cases acute cyanotic attacks were superimposed upon the distress and were often the terminal /
terminal event. The survivors showed gradual improvement over periods of up to 24 hours, and where dyspnoea became progressively less noticeable over periods of 6 to 9 hours the baby's recovery could be expected.

**CYANOTIC ATTACKS.**

Cyanotic attacks were observed as unaccompanied abnormalities in 18 babies (19 per cent). Such incidents were unheralded and dramatic, and were characterised by infrequent or temporarily interrupted respiration and profound cyanosis. (See Appendix I for progress notes of individual babies.) They are almost always well established when observed by the nurse, and unless the physician is spending much time simply observing premature babies, he may never see such an attack. The incident is quite unlike that which is superimposed upon respiratory distress and resembles more an exaggeration of the common irregular respiratory pattern of the small immature newborn (Young and Smith, 1950). At one moment he is pink and well, and then before the observer's eyes the pink skin gives way to grey and then to deepening shades of cyanosis. Respiration may be infrequent, or even absent for a minute or longer. The infant is toneless and, in severe cases, apparently lifeless. Bradycardia is profound and may be found as soon as cyanosis is obvious. It need not be the result of the same central discharge which arrests respiration, however, because hypopnoea or apnoea always exists for an undetermined space of time before the changing colour attracts the observer's attention.

Such attacks may occur at any time in the first week, they /
Figure 5

TIME INCIDENCE OF CYANOTIC ATTACKS

NEWBORN INFANTS OF DIABETIC WOMEN
EDINBURGH 1948-55

TIME INCIDENCE OF CYANOTIC ATTACKS

CASE NUMBER
122
108
107
105
104
103
99
98
88
86
85A
74
56
53
51
49
39
23

DAYS
1 2 3 4 5 6 7 8

O = CYANOTIC ATTACK.
• = CYANOTIC ATTACK ASSOCIATED WITH FEEDING.
○ = CYANOTIC ATTACK ASSOCIATED WITH PHARYNGEAL MUCUS.
they may be single or multiple and they are usually brief (Figure 5). Some are associated with small accumulations of mucus which can be aspirated from the pharynx, and others occur when premature attempts are made to feed the baby. Most of them are unexplained. The isolated cyanotic attack has never been lethal in this series. Although treatment may be unnecessary, the infant's appearance is so alarming that action is always taken. A clear airway is assured, and then sensory or chemical stimulation of respiration is added and oxygen is given temporarily. Such treatment is about as scientific as shaking a clock which has stopped, but fortunately the mechanism is intact and requires no more drastic remedy.

POST-NATAL WEIGHT LOSS.

The fact that babies of diabetic women are heavier as a group than those born at the same gestational age to non-diabetic women has been attributed in part to foetal oedema (White, 1952). Pitting oedema is common, according to White, and a diuresis is responsible for the abnormal post-natal weight loss of such babies.

Oedema.

The above opinion is reflected in such well-known textbooks as those of Baird (1950), Gruley and Eley (1952), Nelson (1954), Johnstone and Kellar (1955), Ellis (1956), Price (1956) and Dunlop, Davidson and Alstead (1957). The babies have been described as oedematous also by Rolland (1954), Pedowitz and Shlevin (1955) and Stevenson (1956). According to White, the oedema may be made to pit on pressure, but Gellis /
Gellis (1954) described it as non-pitting. This difference of opinion is of the greatest importance, because if White is correct then the diagnosis of oedema cannot be doubted. If the oedema cannot be demonstrated by pitting, however, then the diagnosis cannot be confirmed without such direct evidence as may be obtained by measurement of the body water or by careful records of body weight and fluid balance. As White and Gellis have probably shared a number of their cases and have discussed them together, (Gellis et al, 1949) the wide divergence of opinion between two such acknowledged authorities indicates that doubt exists about the presence of pitting oedema.

Diuresis.

The occurrence of a diuresis in such babies is mentioned by White (1952), Rolland (1954) and Stevenson (1956), but no real proof of its occurrence has been provided and no record of a fluid balance study has been found. The 24-hour urinary volumes of infants born to diabetic and to non-diabetic women are recorded elsewhere in this thesis (Page The groups are small and they are not comparable with regard to maturity or the route of delivery, but the results strongly suggest that babies of diabetic women do pass rather more urine initially than normal babies. The difference in volume, however, is so small that it cannot be responsible for much difference in weight loss between the groups.

Weight Loss.

The description by White (1952) of the amount of weight lost does not prove that this was abnormal. She did not define /
define what she meant by weight loss and she provided no information about the control group other than that the mothers were non-diabetic women who had been delivered at the same hospital over the same time-interval. She compared only the average weight loss of the two groups and even this was in terms of absolute weight and made no allowance for the greater birth weight or different maturity of the babies of diabetic women. The babies studied by Cardell (1953a) were grouped first according to birth weight. He was then able to show that infants of diabetic women in his series lost significantly more weight (expressed as a percentage of birth weight) than "control babies" of comparable birth weight. He failed to define what he meant by weight loss, although he clearly did not mean the weight lost over a fixed time interval. He gave no idea of the variability of weight loss. His control group did not match his diabetic group with regard to either maturity or the route of delivery.

Neither White nor Cardell provided any detail about the technique of weighing, the environmental conditions under which their diabetic and control series were nursed, or how and when they were fed.

By matching the infants of the present series with as comparable a control group as it was found possible to obtain, it has been shown that the difference in post-natal weight loss between infants of diabetic and of non-diabetic women is not significant. (Page 129)
1. THE PATHOLOGY DESCRIBED IN THE LITERATURE.

The largest series of autopsies (50 and 25 cases respectively) reported in detail are those of Warren and Le Compte (1952) and of Cardell (1953a), but there have been many others. The principal abnormalities recorded by them will now be described.

**Abnormal Weight.**

The excessive size of these babies was noted by Fischer (1935), and in the series published by White and Hunt (1943) 80 per cent of the infants exceeded the average birth weight for gestational age. Since then the finding has been confirmed by many others, including Miller, Hurwitz and Kuder (1944), Peel and Oakley (1950), Warren and Le Compte (1952), Cardell (1953a) and Pedersen (1954).

**Abnormal Length.**

The observed length exceeded the calculated length in 25 of 40 babies studied by Warren and Le Compte (1952). Five others were heavier but shorter than the calculated standard, and two were lighter but longer. The infants of diabetic women were found by Cardell (1953a) to be longer than normal controls of the same gestational age, and this increased length was proportionate to weight. The range of the length to weight ratio of babies born to diabetic and to non-diabetic women was identical. These observations have been confirmed by the measurement of live infants (Pedersen, 1954) as distinct from neonatal deaths.

**Cedema.**/
Figure 6

BIRTH WEIGHT / MATURITY OF NEWBORN INFANTS OF DIABETIC WOMEN.

Figure 7

BABIES OF DIABETIC MOTHERS,
LOWEST POST NATAL WT. / GESTATION

MEAN B.W. OF INFANTS OF NON-DIABETIC PREGNANCIES (ELLIS 1951)
CASE 64. APPEARANCE AT BIRTH AND AT ONE WEEK

Birth Weight 5032 g.
Alteration of appearance in one week

Birth Weight
3799 g.

Birth Weight
4423 g.

Birth
One week
Birth
One week
INFANTS SHOWING LITTLE CHANGE IN APPEARANCE IN ONE WEEK

Birth Weight 3827 g.

Birth Weight 4132 g.
Oedema.

Although oedema has been reported by many authors, including Miller, Johnson and Durlacher (1944), Given et al (1950) and White (1952), a mild degree of it in only 2 of 25 autopsies was reported by Cardell (1953a) and he could find no evidence of it from a limited study of post-natal weight changes. The dramatic change in the appearance of many of these babies during the first week certainly suggests that oedema fluid has been shed (Figures 8 and 9). Such a change does not always take place, however, even in babies of high birth weight (Figure 10). The excessive fluid, if present, is certainly not the only explanation of the high birth weight, because the infants commonly exceed the average for gestational age after having lost weight for days (Figure 7). A more closely controlled study (Page 129) has failed to find evidence from weight changes that these babies are oedematous, and very recently Osler (1958) has measured the total body-water and the extracellular water in the newborn infants of normal and of diabetic mothers. The infants of diabetic mothers contained significantly less water, presumably because the body contained relatively more fat and glycogen than that of infants of normal mothers.

Jaundice.

A baby reported by Rossle (1942) suffered from severe jaundice and died on the 7th day of life. Autopsy revealed areas of acute hepatic necrosis which he attributed to hypoglycaemia. The rarity of jaundice in babies of diabetic women was noted by Miller, Johnson and Durlacher (1944), but White (1946) /
(1946) stated that jaundice was common. A few years later, however, (1952) she modified this statement by saying that although mild jaundice occurred in many cases before 1950, its incidence had declined steeply following the institution of hormone treatment for diabetic women during pregnancy. The infrequency with which neonatal jaundice appears has also been mentioned by Given et al (1950) and by Cardell (1953a).

Visceromegaly.

The enlargement of various viscera has been reported by Miller (1945a) and by Warren and Le Compte (1952). The increased weight of some organs was confirmed by Cardell (1953a) who believed, however, that their weight was simply proportionate to the increased body weight of such babies. The abnormalities of individual organs will now be considered.

The Pancreas.

The pancreas of infants born to diabetic women vary in size, but many of them show hypertrophy and hyperplasia of the islet tissue. This was described first by Dubreuil and Anderodias (1920) and Wiener (1924). Since then pancreatic islet tissue has been described in single cases by Gray and Feemster (1926), Schretter and Nevinny (1930), Bowen and Heilbrun (1932), Ehrich (1934), Jacobsen (1934), Angyal (1936), Bauer and Royster (1937), Hartmann and Jaudon (1937), Rascoff et al (1938), Smyth and Olney (1938) and Brenner (1941). Small series of cases have been reported by Skipper (1933), Gordon (1935, 1936), White and Hunt (1943), Torgersen (1943) and Petersen (1947). More comprehensive studies of the changes in pancreatic tissue have been published by Okkels and /
and Brandstrup (1938), Helwig (1940), Potter et al (1941), Miller and Wilson (1943) and Hultquist et al (1946).

Many of these reports have been criticized because the authors failed to compare the appearance of the pancreas with that of the gland taken from an infant of the same gestational age born to a non-diabetic woman. Islet tissue is plentiful in the pancreas of most newborn babies, and the individual islets may vary in size from one field to another. This criticism has been met, however, in the controlled studies of Tejning (1947) and Cardell (1953b) who made quantitative studies of the volume of islet tissue in the infants of diabetic and non-diabetic women. Tejning found that the total volume of islet tissue was greater than normal if sections of the pancreas showed islets which were larger than normal. In 18 infants studied by Cardell (1953b) the area of islet tissue in infants of diabetic women measured from 1.8 to 9.9 per cent of the total pancreatic tissue as compared with a normal range in the newborn of 0.7 to 2.6 per cent. In 13 of the cases (72 per cent) the increase appeared to be due mainly to an increase of beta cells. A close correlation existed between the amount of islet tissue and the body weight of the infant.

Several authors (including Rascoff, Helwig and Cardell) have reported upon the frequent occurrence and significant degree of cellular infiltration of the pancreas, composed chiefly of eosinophil leucocytes many of which are immature.

The Adrenal Glands.

Enlargement of the adrenal glands, the result of cortical hypertrophy, has been reported by Jacobsen (1934), Torgersen (1943), /
(1943), Ringertz (1943), Miller, Johnson and Durlacher (1944), Hultquist et al (1946), and Petersen (1947). The absence of adrenal abnormality, however, has been claimed by Schretter and Nevinny (1930), Potter et al (1941) and Hultquist et al (1946).

The weights of the adrenal glands in 13 cases described by Cardell (1953a) were considered to be proportionate to the increased body weight and a histological study of the adrenals from 15 cases and 45 controls showed that, when the sections were specially stained or examined unstained with polarised light, no significant difference in the lipoid content could be found. He concluded that "the evidence at present available suggests that there is no abnormality of the suprarenal gland in infants of diabetic women." The infants composing the diabetic group were not comparable, however, with the control group for the former were considerably less mature. Because the foetal adrenal gland rapidly increases in size during the last month of pregnancy, the eventual weight of the adrenal cortex might have been excessive had pregnancy been allowed to go to term. The glands may be heavier because the whole baby is heavier, but this does not exclude the possibility that increased secretion by the gland has contributed toward the increased size of the infant.

The Pituitary Gland.

The pituitary gland has been described as enlarged by Schretter and Nevinny (1930), Okkels and Brandstrup (1938), Bauer and Royster (1937), Smyth and Olney (1938), Poursines and Cerati (1939) and Rossle (1942). Histology has shown hypertrophy /
hypertrophy of eosinophilic cells and accelerated differentiation. The histology of the gland has been reported as normal, however, by Ehrich (1934), Wenig (1941), Bayer (1942), Ringertz (1943), Petersen (1947) and by Warren and Le Compte (1952). Four pituitary glands were examined by Cardell (1953a) who found them identical with 8 control glands and with the description of the foetal pituitary given by Cooper (1923). Although numerous, the eosinophil cells were considered by Cardell to be present in no more than physiological numbers.

The Thyroid Gland.

Histological evidence of increased thyroid activity has been reported by Okkels and Brandstrup (1938), but Potter et al (1941) found the histology normal. Much more recent studies of thyroid function in the perinatal period have shown that the gland is very active in normal newborns during the first few days of life (Pickering et al, 1958).

The Ovaries.

Enlargement of the ovaries with large follicular cysts and advanced maturation has been described by Schretter and Nevinny (1930), Smyth and Olney (1938), Brenner (1941) and Torgersen (1943). The ovaries of 10 cases were examined by Warren and Le Compte (1952). Three showed follicles with theca lutein cells, and in 2 of these cases the mother had had hormone therapy throughout pregnancy. The female genital system of 4 cases was examined by Cardell (1953a). The ovarian follicles were commoner and larger than in 7 control cases. Luteinization of the theca interna in the follicles
and endometrial hyperplasia (one case) were present in the diabetic material but not in the control cases. According to Spivack (1934) and Potter (1952) polycystic ovaries are found not uncommonly in infants of non-diabetic mothers, but luteinization of the theca interna in such cases is rare. The finding of endometrial hyperplasia in one case was not considered significant by Cardell, similar changes having been noted by Spivack (1934) in 5 out of a series of 23 newborn infants.

The Heart.

Cardiac enlargement was observed in 4 of 10 cases by Miller, Johnson and Durlacher (1944), in 4 of 13 by Given et al (1950) and in 19 of 41 by Warren and Le Compte (1952). The latter 19 cases exceeded the calculated weight by over twice the standard deviation, while only 6 hearts from control infants did so. Cardiomegaly has also been reported by Hurwitz and Irving (1937), Rascoff et al (1938), Brenner (1941), Torgersen (1943) and Petersen (1947). Cardell (1953a) considered that 3 of 25 hearts in his diabetic group and 1 of 25 in his control group were excessively heavy.

Increased glycogen in the myocardium has been reported by Hurwitz and Irving (1937), Bayer (1942), Rossle (1942) and Miller, Johnson and Durlacher (1944). Two of 5 hearts analysed chemically by Warren and Le Compte had a high glycogen content, and Cardell found glycogen in the myocardium of 6 of 10 infants of diabetics and of 1 of 4 control cases. Cardiomegaly is sufficiently common to make the finding significant, but although the heart contains more glycogen than normal, the increase /
increase in size cannot be attributed entirely to glycogen.

The Liver.

Enlargement of the liver has been reported by Dubreuil and Anderodias (1920), Gordon (1936), Smyth and Olney (1938), Brenner (1941), White and Hunt (1943), Torgersen (1943), Petersen (1947) and Given et al (1950). No significant degree of enlargement was found, however, in 42 cases studied by Warren and Le Compte or in 25 cases examined by Cardell. An increase in the liver fat and glycogen has been found by Bayer (1942) and Hultquist et al (1946). An increase in the glycogen alone has been noted by Gordon (1936) and Rossle (1942). Glycogen was found in small amounts in 4 of 12 babies specially examined by Cardell and in 2 of 4 controls. Most authors agree, however, that the liver is a site of highly active extramedullary haemopoiesis which is sufficient to increase the size of the organ in some cases.

Extramedullary Haemopoiesis.

Extramedullary haemopoiesis is one of the commonest autopsy findings, particularly in the liver and spleen. It was first demonstrated by Ehrich (1934), and has since been reported by Bauer and Royster (1937), Smyth and Olney (1938), Brenner (1941), Bayer (1942), Miller and Wilson (1943), White and Hunt (1943), Miller, Johnson and Durlacher (1944), Miller (1945a), Hultquist et al (1946), Petersen (1947) and Given et al (1950). It was a significant feature in 37 of 38 livers examined by Warren and Le Compte (1952) and in many examined by Cardell who described the distribution and character of the haemopoietic activity as that which occurs in much less mature normal /
normal infants.

**Normoblastaemia.**

Increased normoblastaemia has been reported by Miller, Johnson and Durlacher (1944) and by Given et al (1950). This has been confirmed in a special study by Berglund and Zetterstrom (1954). It is so pronounced in most infants that the peripheral blood smear may resemble closely that of a baby with mild haemolytic disease of the newborn.

**The Kidney.**

Enlargement of the kidney has been described occasionally (Pedersen, 1952a), but Warren and Le Compte (1952) found the kidneys to be of normal size, and Cardell (1953a) found them to be normal or slightly subnormal in size when compared with the body weight of the baby. Immaturity of the glomeruli has been recorded by White and Hunt (1943), but Warren and Le Compte (1952) and Cardell (1953a) have shown that the maturation of the glomeruli is simply consistent with the gestational age of the baby.

Renal vein thrombosis has been reported by Tveteras and Rudstrom (1956) and by Avery et al (1957). With the one case which occurred in the present series the total number of published cases is only 4, however, and the incidence of the condition in infants of diabetic women is not necessarily significant.

**The Lungs.**

Respiratory distress, or other functional disorder, is so common that the discovery of some significant pathology in the lungs of those who die is not surprising. Pulmonary hyaline membrane /
Figure 11

PULMONARY HYALINE MEMBRANE

(x 170)
membrane (Figure 11) is the most constant autopsy finding in the experience of White (1952) and it has been found in 85 per cent and 77 per cent respectively of neonatal deaths reported by Peel (1955) and Clayton (1956). Cardell (1953a) found hyaline membrane formation with resorption atelectasis in the lungs of 11 of 13 babies. All the infants were of 34 to 36 weeks' gestation and none weighed less than 2,500 grammes.

The Placenta.

The placenta of the diabetic pregnancy was examined by Reis et al (1950). Many sections, from multiple blocks, were stained by different methods. Although they observed infarction and degeneration of the chorionic villi with some oedema and calcification, they did not consider that these changes differed either quantitatively or qualitatively from those found in the placentae of non-diabetic women. Warren and Le Compte (1952) examined 54 placentae and found increased weight to be the only abnormality (195.5 g. per Kg. of baby weight as opposed to 165.5 g. for a control group). The placentae of 12 babies were examined by Cardell (1953a). He thought that several of them "appeared to be bulky", and their weight ranged from 18 to 30 per cent of the infant's weight. Histological examination showed no significant abnormality.

When the placenta is fixed within half-an-hour of delivery, however, Mackay (1952) claims that definite abnormal stromal oedema exists in the larger chorionic villi. This rapidly disappears if the early fixation technique described by him is not employed.

2. THE PATHOLOGY OF THE PRESENT SERIES.
Figure 12

PANCREAS OF CASE 102
(x 100)

(Birth Weight 4508 g. Maturity 35 weeks)
Figure 13

PANCREAS OF BABY OF NON-DIABETIC WOMAN

(x 100)

(Birth Weight about 2500 g. Maturity 35 weeks)
2. THE PATHOLOGY OF THE PRESENT SERIES.

The 8 neonatal deaths and some (7) of the intrauterine deaths which occurred in the present series were submitted to routine autopsy by a number of paediatric pathologists acting under the supervision of Dr. Agnes Macgregor. The pancreas was usually examined by Dr. R.F. Ogilvie. No particular study of other endocrine organs was made.

The principal finding in each neonatal death is given in Table 2, and the autopsy reports are available in Appendix IIIa. Islet hyperplasia was found whenever the pancreas was examined, and a good example of the islet "continents" may be seen in Figure 12 and compared at the same magnification with the islet tissue of a baby of the same gestational age (Figure 13) born to a non-diabetic woman. Only the pneumonic death was preventable. Extreme prematurity cannot always be avoided, but breech delivery was not permitted after 1949. The incidence of pulmonary hyaline membrane (25%) is lower than in most of the larger published series, but it has been reported more commonly since this series was closed at the end of 1955.

The autopsy reports of those intra-uterine deaths which were not so badly macerated that examination was impossible, are available in Appendix IIb. Four of the 7 showed excessive numbers of cornified squames in the lungs, one had "oedematous expansion" of the lungs, and the remaining two were so macerated that histological examination was omitted.
<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>MATURITY</th>
<th>BIRTH WT. (grammes)</th>
<th>NATURE OF DELIVERY</th>
<th>PRINCIPAL AUTOPSY FINDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>37</td>
<td>2764</td>
<td>C/S</td>
<td>Pneumonia. Terminal inhalation.</td>
</tr>
<tr>
<td>18</td>
<td>36</td>
<td>2807</td>
<td>Breech. Forceps to head.</td>
<td>Massive adrenal haemorrhage.</td>
</tr>
<tr>
<td>32</td>
<td>36</td>
<td>2651</td>
<td>C/S</td>
<td>Hyaline membrane.</td>
</tr>
<tr>
<td>35</td>
<td>30</td>
<td>1644</td>
<td>Assisted breech.</td>
<td>Intracranial haemorrhage.</td>
</tr>
<tr>
<td>40</td>
<td>38</td>
<td>2693</td>
<td>C/S</td>
<td>Signs of asphyxia.</td>
</tr>
<tr>
<td>84</td>
<td>37</td>
<td>1701</td>
<td>C/S</td>
<td>Massive cerebral haemorrhage. Hyaline membrane.</td>
</tr>
<tr>
<td>93b</td>
<td>30</td>
<td>850</td>
<td>Spontaneous twin breech.</td>
<td>Atelectasis. Prematurity.</td>
</tr>
<tr>
<td>102</td>
<td>35</td>
<td>4508</td>
<td>C/S</td>
<td>Renal thrombosis.</td>
</tr>
</tbody>
</table>
FACTORS POSSIBLY RESPONSIBLE FOR THE MORPHOLOGY INHERITANCE.

According to White (1952) and Jackson (1952, 1955) the foetal gigantism may be in part an inherited characteristic and not entirely the result of a growth-promoting uterine environment. Jackson has studied the birth weights of children of pre-diabetic and diabetic fathers. Few of these men knew their children's birth weights and had to obtain the information elsewhere, so he controlled this factor by getting the birth weights of a group of babies of non-diabetic fathers in the same way. He was satisfied that the babies of pre-diabetic and diabetic fathers are of above average birth weight and that they are lighter than those born to pre-diabetic and diabetic mothers. More recently, however, Babbott et al (1958) have failed to find any discernible difference in the birth weights of children of diabetic and non-diabetic men.

Maternal Build.

The body-build of the mother is the result of both inheritance and environment and it may be related to the type of diabetes from which she suffers (Draper et al, 1944; Lawrence, 1951; Lister et al, 1951). Her foetus may inherit this somatotype and, for the duration of pregnancy, he shares the same influences. There may be a relationship therefore between maternal build and foetal birth weight.

The birth weight group of only-children in the series has been plotted against the maternal height and weight prior to the onset of pregnancy (Figure 14). In the case of families consisting of more than one child the average birth weight of the /
Figure 14

THE RELATIONSHIP OF MATERNAL BUILD TO FOETAL BIRTH WEIGHT

RELATIONSHIP OF MATERNAL BUILD TO FOETAL BIRTH WEIGHT

- • = 4.0 Kilos or more
- ○ = 3.5 Kilos but less than 4.0
- □ = 3.0 Kilos but less than 3.5
- ▽ = 2.5 Kilos but less than 3.0
- X = 2.0 Kilos but less than 2.5
- △ = Less than 2.0 Kilos

SINGLE CHILD FAMILIES

MULTI-CHILD FAMILIES

(Average foetal birth weight of family)
the family has been plotted against the height and weight prior to the onset of the last pregnancy. The weaknesses in this comparison are acknowledged. The infants vary in maturity, but the only-children are mostly in the 36 - 38 week range and the majority of babies of multiparous diabetic women were delivered at term. The build of mothers of only-children was in fact the build at the time of the child's birth, but in the case of multiparous women their weight when the last child was born does not necessarily represent their weight when childbearing began. These points and the small size of the groups make impossible an analysis of such other possibly important factors as birth rank, maternal age and social group of the father.

In both figures, points low to the right indicate tall slim mothers, points high to the left indicate short stout mothers, and so on. No clear relationship exists in either, between foetal birth weight and maternal build except that with some exceptions infants of less than 3.0 kilograms (Kg.) at birth appear to be commoner among lighter mothers. The birth of babies exceeding 4.0 Kg. to short light diabetic women is unusual. The absence of a direct relationship between foetal birth weight and maternal build when child-bearing begins is illustrated further in this series by one mother of average height who developed clinical diabetes during her first pregnancy when she was a slim school-girl and whose build remained unaltered in further pregnancies although the babies exceeded 4 - 5 Kg. at birth.

**FAMILY BIRTH WEIGHT.**

The birth weights and the maturity of all sibs of the children /
Figure 15

FAMILY BIRTH WEIGHTS AND DURATION OF MATERNAL DIABETES
children in this series were ascertained wherever the information was available, and these have been grouped in families (Figure 15). In order that the diagram may be more easily understood it consists of 12 small graphs with 3 or 4 families on each. The number allotted to each family on the graph is the number of the first case in the family to be included in the present series. The point at which the mother was found to have diabetes mellitus is indicated on the horizontal axis of each small graph, and the years before and after read to the left and right from there. The horizontal broken line on each graph indicates 4.0 kilos (8.8 lbs.) birth weight. The only-children of diabetic women are naturally excluded.

The birth of heavy babies during the pre-diabetic years is as apparent here as it was in the series studied by Miller, Johnson and Durlacher (1944), Gilbert (1949) and Futcher and Long (1954), but many of these large babies in the present series are shown to be sibs.

**PRE-DIABETES AND DIABETES MELLITUS.**

The disordered metabolic environment is the most important cause of those foetal characteristics which have been described already (Page 19). Laboratory animals suffering from experimental diabetes or receiving diabetogenic treatment during pregnancy have produced giant and sometimes oedematous offspring, and clinical observation of the development, severity and control of human diabetes have indicated that these too may influence foetal growth.

**HYPERGLYCAEMIA.**
HYPERGLYCAEMIA.

Maternal hyperglycaemia and the passage of large amounts of glucose from mother to baby were held responsible for foetal overgrowth until the existence of the pre-diabetic state was recognised 25 years ago. The credit for the latter may be given to Bix (1933) who was the first to point out that some women give birth to big babies many years before the first symptoms of diabetes are recognised. This observation has been confirmed by Allan (1939), Miller, Hurwitz and Kuder (1944), Miller (1945a, 1946a), Kriss and Futcher (1948) and Gilbert (1949), and it is again apparent in the present series (Page 42). Because the pre-diabetic woman maintains her blood sugar within normal limits during years when she is bearing giant offspring, the belief that hyperglycaemia is responsible for foetal overgrowth has now been abandoned in favour of different hypotheses relating to the aetiology of diabetes mellitus itself.

PRE-DIABETES.

The pre-diabetic woman may indicate her future by a high foetal loss rate, by the large size of her babies, or by her own obesity (Miller, 1946b; Gilbert and Dunlop, 1949; Jackson, 1952). Her babies are not only big and beset with early hazards, but they have the morphological features of those born to women with classical diabetes mellitus. Those examined by Miller (1945a) had cardiac hypertrophy, adrenal hyperplasia, increased eosinophilia of the anterior pituitary gland, very active extramedullary haemopoiesis and hyperplasia of the pancreatic islets. The latter was also found in babies /
babies of pre-diabetic, diabetic and Rhesus-sensitised non-diabetic mothers (Miller, 1944b) and its occurrence in the still-born infants of diabetic women has been confirmed by Van Beek (1952). The quantitative measurement of islet tissue in infants of diabetic and non-diabetic women has been mentioned already (Page 25). The islet area of the pancreas in babies whose mothers have been diagnosed as pre-diabetic, by the use of the intravenous glucose tolerance test, has been measured by Jackson and Woolf (1957). In every suspected pre-diabetic case the baby's pancreas showed islet hypertrophy. The tissue was studied by Dr. Woolf who was given no prior knowledge of the source of the pancreas. In no case in which an adequate cause for death, other than diabetes, existed was islet hyper trophy found.

The process responsible for the ultimate development of diabetes mellitus may be active for many years before hyperglycaemia and ketosis appear, and it passes across the placenta to promote a consistent embryopathy, irrespective of the phase of diabetic development.

HORMONAL FACTORS.

Growth depends upon, among other things, the powerful anabolic stimulation of Pituitary Growth Hormone (P.G.H.), Insulin, Thyroid hormone and the Androgens. Clinical observations of the newborn of the diabetic woman excludes the excessive secretion of the last two as the cause of foetal overgrowth. Pituitary Growth Hormone, however, has been linked by animal experiment with the aetiology of diabetes mellitus and with the secretion of insulin.

Animal Experiment. /
Animal Experiment.

The possible part played by P.G.H. in the production of diabetes mellitus has received much attention in recent years. Evans et al (1932) treated puppies with daily injections of a growth-promoting extract of the anterior pituitary gland and noted the development of diabetes mellitus in a number after a period of months. Similar observations were made by Houssay and Biasotti (1932) in normal and in partly depancreatized animals using a crude anterior pituitary extract. These findings were confirmed by Young (1936, 1937) in intact dogs and cats using crude anterior pituitary extract and later by using a highly purified anterior pituitary growth factor (Cotes et al, 1949). Young (1951) observed that the young animal responded to P.G.H. with accelerated growth, but, as the latter decelerated, evidence of diabetes mellitus appeared. He concludes that "in the human being a slightly excessive rate of secretion of growth hormone, insufficient to cause overt signs of acromegaly, but lasting a long time, might lead to a prolonged but not excessive restraint upon the processes of carbohydrate and protein catabolism and oxidation, combined with the increase in appetite characteristic of growth hormone activity, so that diabetes ultimately develops."

The offspring of diabetic animals. The injection of pituitary extracts into a variety of animals has promoted prolongation of pregnancy, an increased foetal mortality and the overgrowth of survivors (Teel, 1926; Hain, 1932; Sontag and Munson, 1934). The same effects were observed by Hooper (1933) and Snyder (1934) after injecting pregnant urine extracts.
extracts into rats and rabbits. The injection of pituitary extract into pregnant rats by Watts (1935) resulted in the birth of giant foetuses at term. Houssay and Biasotti (1932) found that the foetuses of depancreatized animals were large. The surviving foetuses of pregnant rats, rendered diabetic by subtotal pancreatectomy, were above normal length and weight and showed splanchnomegaly and oedema (Hultquist and Engefelt, 1949; Hultquist, 1950).

The injection of "prolan" into pregnant rabbits by Lawrence and Oakley (1942) produced foetal overgrowth, and it was also observed by Barns and Swyer (1952) after the injection of anterior pituitary extract or a preparation of growth hormone into pregnant rats. The latter pointed out, however, that the reduction of litter-size by intra-uterine death and foetal resorption in treated groups might have contributed to the greater size of the survivors.

On the other hand, although pregnant alloxan-diabetic rats have an increased foetal death rate, with foetal death and resorption sometimes in early pregnancy, no increase in foetal size has been observed when pregnancy has gone to term (Davis et al, 1947; Levi and Weinberg, 1949; Sinden and Langwell, 1949; Lindan and Morgans, 1950). Similar observations have been made by Miller (1947) on rabbits, dogs and rats.

These experiments show that foetal overgrowth may be observed among animals receiving extracts of the Anterior Pituitary or of pregnant urine during pregnancy and among animals rendered diabetic by subtotal pancreatectomy. It has not /
not been observed among alloxan-diabetic animals. But, whereas in some of the former groups foetal overgrowth may be attributable to prolongation of pregnancy or the reduction of litter size, no overgrowth has occurred in the babies of alloxan-diabetic animals. This would suggest that the growth-promoting influence may be a pituitary one, but the deficiencies of the experiments are clear.

One of the most interesting observations is that not only were the foetuses of subtotal pancreatectomised animals oversized, splanchnomegalic and oedematous but they had a high incidence of pancreatic islet-cell hyperplasia (Hultquist, 1950).

The production of insulin. Hyperplasia of the pancreatic islets follows experimental hyperglycaemia in guinea-pigs (Woerner, 1938), in dogs (Houssay et al., 1942), in rats (Tejning, 1947; Wissler et al., 1949), and in cats (Dohan and Lukens, 1948). This cannot, however, be the cause of islet hyperplasia in babies of pre-diabetic women, but insulin production may be expected to increase in direct proportion to the diabetogenic activity. A normal blood sugar may only be maintained in the pre-diabetic if the pancreatic beta cells are able to respond to the increased load.

Pancreatic islet hyperplasia has followed the injection of P.G.H. (Ogilvie, 1944; Conn, 1945; Young, 1953), and single doses or short courses of P.G.H. may induce hypoglycaemia (Milman and Russell, 1949). Finally the administration of corticosteroids to experimental animals has been followed by beta cell hyperplasia in the pancreatic islets (Frawley, 1953; Hausberger /
Hausberger and Ramsay, 1953), but not by foetal overgrowth when
given to pregnant animals (Jackson, 1955).

Much has been written about the contribution of foetal
insulin to maternal carbohydrate metabolism in experimental
diabetic animals. Among many others Carlson and Drennan
(1911) and Pack and Barber (1929) believed that foetal insulin
either crossed the placenta or effected an influence across the
placenta on the foetal-maternal blood sugar gradient. Allen
(1920) found no evidence that either took place, but Schlossman
(1931) quoted by Bowen and Heilbrun (1932) believed that some
hypoglycaemic effect on the mother cat or dog was demonstrable,
but this was probably the result of sugar crossing from mother
to foetus rather than of insulin moving in the opposite
direction. The increase in diabetogenic activity during
human pregnancy is such that the woman's need of insulin almost
always increases even if the foetal pancreas is rendering
assistance.

The role of insulin as a growth hormone. Attention has
been given to the part which insulin may play as a growth
hormone. It is known that under certain conditions the
stimulation of growth by P.G.H. is dependent upon the avail-
ability of insulin. In Young's experiments it was found that
the growth response of puppies who were subjected to prolonged
treatment with anterior pituitary extract diminished pari
passu with the development of diabetes, and that growth
eventually stopped. At this point further growth could be
induced by the administration of large amounts of insulin with
the pituitary extracts. It seemed clear to Young (1951) from
these /
these experiments that the diabetogenic action of growth hormone could be converted to a growth-promoting one in the dog if enough insulin were administered with the pituitary extract. In 1953 he reviewed the relationship between growth hormone, the pancreas and diabetes mellitus and again expressed the belief that the action of growth hormone in inducing growth depends at least in part on the ability of the pancreas to secrete extra insulin. If the pancreas cannot produce enough of the latter, then diabetes mellitus replaces growth. Milman, De Moor and Lukens (1951) demonstrated the fact that the giving of growth hormone to a depancreatized cat caused no anabolism of protein unless insulin was simultaneously given and the retention of nitrogen induced by growth hormone was not maximal unless a substantial dose of insulin was given in addition to that needed by the animal in the absence of growth hormone. Somatic growth, including skeletal growth, was observed by Salter and Best (1953) in hypophysectomised rats to which insulin had been given in gradually increasing dosage while untreated hypophysectomised rats did not grow at all. The treated rats did eat more than the controls, but Maassen (1951) demonstrated that insulin-treated normal rats grew faster than pair-fed control animals so that food intake alone is unlikely to be a limiting factor.

Finally, the injection of large doses of insulin into adult female mice (Abel, 1931) has been followed by ovarian follicular development and the formation of many corpora lutea (Page 28). These animal experiments are interesting in view of the consistency with which islet hyperplasia is found in the babies of the pre-diabetic and diabetic woman.

Observations /
Observations on Human Diabetes.

Pituitary Growth Hormone. The absence of an assay method for P.G.H. which is suitable for use in clinical studies has prevented investigation of the hormone's participation in diabetes mellitus and in the foetus of the diabetic pregnancy. The recent demonstration by Luft et al (1958) that hyperglycaemia and ketosis develop very quickly in young hypophysectomised diabetic adults who have received injections of P.G.H. purified from human glands, provides some indirect evidence in favour of Young's hypothesis based on the animal experiments quoted previously. The observation at the same clinic by Ikkos et al (1958) that human P.G.H. given to normal adults may produce salt and water retention may have some bearing on the tendency of infants of diabetic women to excrete more urine than is normal during the first 48 hours of life. Young's suggestion that the prolonged pituitary overactivity responsible for diabetes is insufficient to cause acromegaly appears inconsistent with the development of foetal gigantism. Foetal tissue, however, unlike the mother's, grows at tremendous pace and P.G.H. levels, too low to cause maternal acromegaly, may yet serve as an efficient accelerator. The absence of as pronounced gigantism in the foetuses of acromegalic women is an obstacle to the acceptance of P.G.H. overactivity as the cause of foetal overgrowth in diabetes (Jackson, 1955) unless we accept Jackson's suggestion that an inherited susceptibility to over-react to P.G.H. exists in the child of the diabetic or that the foetal morphology is the result of other extrinsic influences in addition to P.G.H.

Insulin.
Insulin. Although the existence of pancreatic islet hyperplasia and of immediate post-natal hypoglycaemia (Pages 25 and 86) have been proved in such babies, no results of the assay of insulin activity in umbilical cord blood have yet been published. If the increased numbers of pancreatic beta cells do not secrete more insulin, then it is difficult to imagine what other function such specialised cells can perform or to believe that the cells are the site of some metabolic block similar to the enzyme defects existent in some forms of goitre. The action of insulin on the baby's metabolism is obvious, but Warren and Le Compte (1952) have suggested that the increased insulin activity may play some part in causing the increased incidence of ovarian follicular cysts with luteinization of the theca interna which is found in these infants (see also Page 28).

Corticotrophin and corticosteroids. The possible role of corticotrophin and the corticosteroids in human diabetes mellitus has received a great deal of attention since they were found to be diabetogenic to non-diabetic subjects (Conn et al, 1948), to aggravate the carbohydrate disorder in established diabetes (Perera et al, 1949) and to be associated with insulin resistance (Sprague et al, 1949). The pancreatic islets may be degenerate at autopsy in Cushing's syndrome. Unlike F.G.H., however, and unlike the "cause" of diabetes mellitus, excess 17-OH steroids do not increase significantly the development of ketonaemia in diabetics (Conn and Fajans, 1956; Kalant, 1958). Nevertheless, increased serum corticosteroids have been reported in diabetic children with ketosis and /
and coma (Klein et al, 1955) and in non-ketotic treated diabetic children (Klein et al, 1956). The level of the serum corticoids in the latter group was directly related to the amount of urinary reducing substance. Further indirect evidence of increased adrenocortical activity is provided by Grayzell et al (1957) who found that the 24-hour urinary excretion of pepsinogen was increased in diabetes. A high incidence of adrenal adenomata has been reported at autopsy in elderly diabetics (Daly, 1956) and much attention is being paid to the possible responsibility of corticosteroids for the vascular degenerative disease of diabetes (Page 73). Finally, some evidence has been advanced by Cohen (1958), but requires confirmation, that the over-eating of simple obesity in children may also produce adrenocortical overactivity and Cushingoid features.

Maternal adrenocortical function is increased even in non-diabetic normal pregnancy (Cope et al, 1951; Gemzell, 1953; Bayliss et al, 1955), and it may be even greater during diabetic pregnancy, according to Hoet (1951) and Hoet and Lukens (1954). Although no glucocorticoid has been demonstrated in the amniotic fluid of non-diabetic women, significant quantities have been shown to exist in that of the diabetic (Hoet, 1954). The excretion of corticosteroids by these babies is believed to be higher than normal (Bjorklund and Jensen, 1955) and this is regarded by Bjorklund (1953a, 1953b) as the probable explanation of the "low" potassium levels which he finds in these babies during the newborn period (Page 79). Hoet believes that the newborn of the diabetic /
diabetic woman presents certain features of Cushing's syndrome and they have been described by Jackson (1955) as "Cushingoid". The characteristics which suggest this description are the superficial ones of obesity, flabiness, oedema and high colour. Striae, hirsutes, the central distribution of obesity, polycythaemia and hypertension are not included. There is evidence that some hormones can cross the human placenta in a number of pathological conditions. The occurrence of thyrotoxicosis in the newborn infants of women whose own hyperthyroidism has been treated effectively (Skelton and Gans, 1955; Lewis and Macgregor, 1957) strongly suggests that thyrotrophin may do so, and studies of the serum butyl extractable iodine of maternal serum and the cord blood of the foetus indicate that a free exchange of thyroid hormone takes place between mother and baby (Grumbach and Werner, 1956; Pickering et al, 1958). Parathormone can exert its influence across the placenta and may be able to cross it (Bruce and Strong, 1955). The stimulating hormone of the foetal adrenal cortex is intimately associated with the mother in that its activities cease on separation of the foetus from his mother, whether this is done gradually by vaginal delivery or abruptly by caesarean section, irrespective of birth weight or gestational age. The development of ovarian follicular cysts (White, 1952) and of Leydig cells in the foetal testes (Wilkins, 1957) indicate the trans-placental influence of gonadotrophins. The breast development of the newborn and the large uterus, which involutes as from birth, can be attributed only to maternal oestrogen, but the milk secretion of the foetal breast may be a response to /
<table>
<thead>
<tr>
<th>Case</th>
<th>Maturity</th>
<th>Cortisone</th>
<th>Signs of Maternal Hyperadrenocorticism</th>
<th>Infants</th>
<th>Birth Weights of Previous Babies in Untreated Pregnancies (lb.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Daily Dose (mg.)</td>
<td>Duration</td>
<td>Infant Birth Weight</td>
<td>Oedema</td>
</tr>
<tr>
<td>1</td>
<td>37</td>
<td>100</td>
<td>A few weeks</td>
<td>+</td>
<td>6.7</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>150</td>
<td>)</td>
<td>+</td>
<td>7.9</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>150</td>
<td>) From 22nd - 26th week until term</td>
<td>+</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>150</td>
<td>)</td>
<td>+</td>
<td>5.6</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>150</td>
<td>)</td>
<td>+</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Notes unavailable
to either maternal or foetal prolactin (Smith, 1951). The observations of Margulis and Hodgkinson (1953) suggest that corticotrophin may cross the placenta, but the fact that babies born to mothers with Cushing's syndrome are neither big nor "Cushingoid" (Jackson, 1955) makes it likely that the placenta is impermeable to corticosteroids and that maternal corticosteroids are not responsible for the Cushing syndrome features of the foetus in diabetic pregnancy. The administration of cortisone to pregnant rabbits has been followed by the delivery of excessively large stillborn foetuses (De Costa and Abelman, 1952). Similar experiments have been carried out by Hoet (1953) and by Brasseur (1953). Evidence that the human placenta does not permit the passage of cortisone is provided by information obtained from Dr. A.J. Slessor of the Department of Materia Medica at Glasgow University. He published a report (1952) about the treatment of a Rhesus-sensitised pregnant woman with cortisone. Although he published no other cases, he did treat some and he provided on request the data given in Table 3. These figures suggest that the prolonged treatment of such women with 100 to 150 mg. of cortisone daily induced obvious evidence of hypercorticism in the mother but that it was not associated with the development of abnormally heavy, "Cushingoid" infants.

On the other hand something certainly crosses the placenta from mother to foetus in every normal pregnancy and stimulates the development of the normal foetal cortex which involutes from birth whatever the gestational age of the foetus (Page 218). Furthermore, the treatment of pregnant women /
women with corticotrophin has been associated with abnormal enlargement of the foetal adrenal cortex (Margulis and Hodgkinson, 1953). These observations may explain the morphological difference between the newborn infants of women with Cushing's disease and those of diabetics. The hyperadrenocorticism of Cushing's syndrome is generally regarded now to be independent of anterior pituitary overactivity and the placental barrier would protect the baby. In diabetes mellitus, however, the anterior pituitary overactivity may include some over-production of corticotrophin which can cross the placenta and stimulate the baby's adrenal cortex (Page 26).

Some added weight is lent to such a belief by the fact that pancreatic islet hyperplasia, adrenal enlargement, cardiomegaly and oedema have been described in erythroblastotic babies whose mothers had been "stressed" by Rhesus sensitisation in pregnancy (Miller, 1944b).

**Sodium-retaining hormone.** The foetal adrenal cortex has been shown by Benirschke et al (1956a) to contain a sodium-retaining hormone.

**Gonadotrophins.** High levels of chorionic gonadotrophin have been found in pregnant diabetic women by White (1952), but only a proportion of the women investigated in the present series had levels above the normal range (Page 70). Warren and Le Compte (1952) have suggested that this gonadotrophin excess may cause the increased incidence of follicular cysts with luteinization of the theca interna in infants of diabetic mothers.

**SEVERITY AND CONTROL OF DIABETES.** /
SEVERITY AND CONTROL OF DIABETES.

Quite apart from survival rates, evidence exists that both the severity and the standard of control of the carbohydrate disorder influence foetal morphology. The babies born to diabetic women with nephropathy are smaller than those of women with the uncomplicated disease (Oppe et al, 1957).

Those women whose diabetic control during pregnancy is so good that Pedersen (1954) admits them to his "long-term treatment group" may produce rather lighter babies than women whose control is less satisfactory, but the difference in weights is not statistically significant. In apparent contradiction is the personal finding that, when infants are grouped according to gestational age (Figure 16), poor control of the maternal diabetes seems to influence weight adversely as pregnancy proceeds. As would be expected, no relationship has been found between the birth weight and the adequacy of ante-natal obstetric supervision (Figure 17).

SUMMARY.

These observations suggest that in human diabetes mellitus there is circumstantial evidence for the belief that more than one secretion of the mother's anterior pituitary gland or placenta (P.G.H., corticotrophin and gonadotrophin) may contribute toward the curious foetal morphology.

Control of the mother's diabetes has been graded for me by the two physicians concerned during the eight-year period. Good control implies that the patients were free from symptoms, were not ketotic at any time and that the blood sugar determined weekly three hours or more after a meal never exceeded 140 mg.%. Control is classed as bad if the patient had two or more ketotic episodes of 24 hours' duration or longer during the pregnancy or if the weekly blood sugar taken three hours or more after a meal exceeded 250 mg.% on more than one occasion. Fair control describes those who were to be found somewhere between the two other groups.
Figure 16

BIRTH WEIGHT OF INFANTS BORN AT 35 - 38 WEEKS

INDICATING THE RELATIONSHIP TO CONTROL OF THE MATERNAL DIABETES

BIRTH WEIGHT AND CONTROL OF MATERNAL DIABETES

○ GOOD CONTROL
● FAIR CONTROL
× POOR CONTROL

WEEKS GESTATION

B W

IN

Kg

35 36 37 38
Figure 17

BIRTH WEIGHT OF INFANTS BORN AT 35 - 38 WEEKS

INDICATING THE RELATIONSHIP TO ANTE-NATAL CARE

BIRTH WEIGHT AND ANTE-NATAL OBSTETRIC CARE

○ ADEQUATE ANTE-NATAL SUPERVISION

● INADEQUATE ANTE-NATAL SUPERVISION
FACTORS POSSIBLY RESPONSIBLE FOR THE

FOETAL MORBIDITY AND MORTALITY

The foetal deaths which take place so commonly before or
after birth, the serious neonatal disturbances which affect
about one in five survivors, and the increased neuromuscular
irritability which is present in all, are presumably the
direct or indirect result of the same fundamental disorder of
the mother. The responsibility of a number of abnormal pre-
natal and post-natal factors has been investigated.

PRE-NATAL FACTORS

Severity of the Maternal Diabetes.

Insulin requirement. No relationship between the foetal
mortality rate and the severity of the maternal diabetes as
judged by insulin requirement has been found by Peel and
Oakley (1950), Given et al (1950), Frankel (1950), Hurwitz
and Higano (1952), Oakley (1953) and Peel (1955). Although
Cramer (1951) took the opposite view, examination of his
figures scarcely supports his opinion.

Duration and severity of diabetes (White's classification).
Diabetes mellitus has been divided into six classes (A to F)
according to severity (White, 1952) and these correlate
roughly with the duration of the disease and with the appear-
ance of vascular degeneration. According to White (1952)
the foetal mortality increases with the severity as judged in
this way, and her findings are supported with varying degrees
of enthusiasm by Cramer (1951), Reis et al (1952) and Pedowitz
and Shlevin (1952). No correlation between the age of onset
of the maternal disease and the foetal mortality was apparent


to Oakley (1953) in the largest British series. This was also the experience of Andersson (1950) and it received later support from Peel (1955). The influence of these factors upon the greater part of the present series was examined by Rolland (1954) who failed to find any relationship between them and the foetal loss, but the number of cases was small.

A study of pregnancy in the diabetic woman with nephritis by Oppe et al (1957) has established the greater risk in severe diabetes with degenerative vascular disease. The viable foetal mortality in their series was 39 per cent compared with 18 per cent for 736 viable pregnancies in diabetic women without nephropathy. All of these women probably had intercapillary glomerulosclerosis, and many of them had other vascular complications of diabetes.

Control of the Maternal Diabetes.

The most important cause of foetal death was judged by Skipper (1933) to be poor control of the maternal disease.

Diabetic ketosis has been regarded as an important cause of foetal death by Lambie (1926), Skipper (1933), Herrick and Tillmann (1938), Given et al (1950), Cramer (1951), Bastiaanse and Sindram (1951) and Pedersen (1952). Minor degrees of ketosis which exist for some days unrecognised are considered to be more dangerous by Eastman (1946) and Pedowitz and Shlevin (1952). It is considered to be unimportant by White and Hunt (1943), Andersson (1950) and Peel and Oakley (1950), and it is no longer mentioned by Peel (1955). Maternal hypoglycaemia does not appear to be the cause of foetal death (Lambie, 1926; Skipper, 1933; Lawrence and Oakley, 1942; White /
Figure 18

FOETAL LOSS AND DIABETIC CONTROL

EFFECT OF DIABETIC CONTROL UPON FOETAL LOSS
115 FOETUSES

NUMBER

FAIR TO GOOD

BAD

Adequate Supervision

Inadequate Supervision

Live

I.U.D.

N.N.D.

S.B.

16.2% 18.8% 18.8% 60%

18.8%
White and Hunt, 1943; Anderson, 1950; Peel and Oakley, 1950; Pedersen, 1952).

Pedersen of Copenhagen is the enthusiastic advocate of a policy of rigid diabetic control and he has shown (Pedersen and Brandstrup, 1956) that a very high standard of medical and obstetric care will not only increase the foetal survival rate to a figure unachieved in this country so far, but it permits vaginal delivery at full term. The number of cases judged to have been poorly controlled in the present series is small, but the mortality is higher than in those whose control was fair or good (Figure 18).

Ante-Natal Obstetric Care.

Such obstetric complications as hydramnios and pregnancy toxaemia are common in the diabetic pregnancy, and their occurrence is associated with increased risk to the foetus. Intra-uterine death in the latter weeks is still common and the time at which pregnancy should be terminated must be carefully selected and skilled delivery of the baby by the safest route must then be undertaken. These matters will have prompt attention only in those cases which receive careful ante-natal care from early pregnancy. Adequate supervision in the present series entailed regular examination by the obstetrician (Dr. G.D. Matthew in almost all cases) and the effect which this had upon foetal survival may be clearly seen in Figure 18.

Family Mortalities.

The families included in the present series are arranged in horizontal lines in Figure 19. The pre-diabetic and the diabetic /
Figure 19

OUTCOME OF VIABLE PREGNANCIES IN EACH FAMILY RELATED TO THE DURATION OF MATERNAL DIABETES

FAMILY MORTALITIES AND DURATION OF MATERNAL DIABETES

- ○ SURVIVAL
- ● N.N.D.
- ■ I.U.D.

TOTAL PREDIAB. DIAB.

V.F.L. 25 (16-3%) 8 (2-1%) 17 (9-5%)
N.N.D. 10 (6-5%) 4 (6-1%) 6 (6-9%)

PRE- DIABETIC YEARS DIABETIC
diabetic years of the mother's life are indicated as in Figure 15. The fate of the foetus is shown by symbols. The viable foetal loss of 121 per 1000 during the pre-diabetic years compares with 195 per 1000 after the establishment of clinical diabetes. The neonatal death rates\(^*\) of 61 and 69 per 1000 are less obviously different. Neonatal deaths among diabetic primipara, however, number 77 per 1000. These figures suggest that mortality rises with the development of clinical diabetes, and when the 23 multiparous mothers who were diabetic in each pregnancy are considered the viable foetal loss is 236 per 1000 and the neonatal deaths are 73 per 1000. These figures contrast with the results of 54 viable pregnancies among 8 of the women whose child-bearing began at least 10 years before the development of diabetes mellitus. Only 6 of these babies died, and 5 of them were neonatal deaths. The viable foetal loss among this group is 111 per 1000 and the neonatal death rate is 93 per 1000. The very low incidence of intra-uterine death contrasts with the situation after clinical diabetes appears. The high neonatal death rate occurred at a time when the rate was significantly higher than now among the general newborn population. The families were mostly big ones and social conditions may have been adverse.

**Mortality and Foetal Birth Weight in the Pre-Diabetic Group.** The groups of mothers whose child-bearing life began at least 10 years before diabetes was diagnosed conclusively bore /

\(^*\) Neonatal deaths are expressed here not in terms of per 1000 live births but of per 1000 viable pregnancies.
### Table 4

**BIRTH WEIGHTS OF CHILDREN BORN TO PRE-DIABETIC WOMEN**

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>NO. OF CHILDREN FOR WHOM WTS. KNOWN</th>
<th>NO. OF CHILDREN WEIGHING 4.0 KILOS OR MORE</th>
<th>TREND IN B.W.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>7</td>
<td>7</td>
<td>Trend sustained</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>2</td>
<td>Trend downward</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>10</td>
<td>Trend sustained</td>
</tr>
<tr>
<td>16</td>
<td>5</td>
<td>4</td>
<td>Only the 4th less than 4 Kg.</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>4</td>
<td>Only the last below 4 Kg.</td>
</tr>
<tr>
<td>59</td>
<td>8</td>
<td>0</td>
<td>Trend upward</td>
</tr>
<tr>
<td>63</td>
<td>7</td>
<td>1</td>
<td>Only the last below 4 Kg. (35 weeks)</td>
</tr>
<tr>
<td>106</td>
<td>5</td>
<td>4</td>
<td>Only the last below 4 Kg. (37 weeks)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>
bore a remarkable number of large babies (Table 4). The birth weights of 52 of them are known and of these, 32 weighed 4.0 Kg. or more at birth.

Thus these mothers who developed diabetes after their first child was at least 10 years old not only produced the typical large babies of diabetic women but they did so at the cost of comparatively few lives and with less than 2% of intra-uterine deaths. This fact is complementary to that apparent in Figure 23, i.e. that death and dyspnoea are commoner among the smaller infants at any gestational age. The growth promoting and the lethal influence upon the foetus are not therefore necessarily identical.

Placental Insufficiency.

The placenta of the diabetic woman is not obviously abnormal on inspection. It has been described as large by White (1952), and, in the opinion of Peel (1955), its function cannot keep pace with the growing foetus so that his life is at risk. The ratio of placental to foetal weight is normal in the present series (Figure 20). If the foetus is large for gestational age then so is the placenta, and no relationship has been found here between the ratio and the clinical state of the foetus. The figures for intra-uterine deaths are not, however, available and they may be important. Most of those who have examined the diabetic placenta have failed to find abnormalities which do not occur so commonly in the placenta of the non-diabetic woman. The exception is Mackay's observation (Page 33) that abnormal stromal oedema can be seen if the placenta is fixed at once after birth. The normal /
THE FOETAL / PLACENTAL WEIGHT RATIO RELATED TO CLINICAL COURSE

RELATION OF FOETAL / PLACENTAL WEIGHT TO CLINICAL COURSE. (TWINS EXCLUDED)
normal placenta is a highly complicated vascular organ with a healthy life of about 40 weeks. Under normal conditions it then degenerates, but where the foetus shows an exaggerated response to maternal hormones, as in diabetes mellitus, the life of the chorionic villi, derived from the same source, may be accelerated also. Evidence of functional impairment of the placenta has been found, however, in hormone and blood oxygen saturation studies.

Hormonal Imbalance. The injection of anterior pituitary extracts into pregnant animals or the rendering of the mother diabetic by partial pancreatectomy or by alloxan (Page 45) is associated not only with the prolongation of pregnancy and foetal overgrowth but with a high foetal mortality (e.g. a foetal mortality of 80 per cent in Hultquist's experiments). Whatever influence P.G.H. and corticotrophin and corticosteroids may have upon foetal survival in diabetic pregnancy, White (1952) has attached much importance to the abnormal gonadotrophin levels previously mentioned (Page 56). This "hormonal imbalance" theory of foetal loss and its treatment originates in the observations of Smith and Smith (1933, 1934, 1938, 1946, 1948a, 1948b, 1949). Briefly this hypothesis states that placental degeneration, the result of pituitary dysfunction and/or pelvic arterial degeneration in the case of diabetes, is responsible for the failing production of oestrogens and pregnanediol and for the consequent over-production of gonadotrophins. Treatment consists of replacement therapy with oestrogens and progesterone, and it is claimed to have a dramatic /
dramatic effect upon foetal survival (White et al., 1953). These observations have been confirmed in part only. Loraine and Matthew (1954) have studied the urinary excretion and serum concentration of Human Chorionic Gonadotrophin (H.C.G.) in 52 pregnant diabetics of the present series. Only 29 per cent of the women had abnormally high urinary H.C.G. levels, and the serum concentration of the hormone was above the normal range in only 27 per cent of those examined. In the total series high levels of H.C.G. either in urine or in serum were found in 33 per cent only. Furthermore, Loraine and Matthew found that when the series was analysed to show the relationship of H.C.G. levels to obstetric complications it was found that foetal death, pregnancy toxaemia and premature delivery were just as likely to occur in pregnant diabetics with normal H.C.G. readings as in those with abnormal levels. Finally, they found that stilboestrol had only an evanescent depressing effect on raised H.C.G. levels. The Medical Research Council found that the survival rates of treated and untreated groups did not differ and results as good as in White's treated group have been obtained without replacement therapy by Pedowitz and Shlewin (1955) and by Pedersen and Brandstrup (1956).

Foetal Hypoxia. The vigorous erythropoiesis and the normoblastaemia of babies born to diabetic women led Berglund and Zetterstrom (1954) to believe that these infants suffered from pre-natal hypoxia, and their investigation of the oxygen saturation of cord blood seemed to confirm this. The possible role of hypoxia /
Figure 21

THE OXYGEN SATURATION % OF UMBILICAL CORD BLOOD OF TEN DIABETIC WOMEN AT DELIVERY

The oxygen saturation % of venous and arterial cord blood (Mackay, 1957) refer to normal pregnancies.
hypoxia in the aetiology of intra-uterine death was mentioned by Peel (1955), but he had no confirmatory evidence to offer. Much attention has been paid recently to the degeneration of placental function (as distinct from architecture) toward the end of pregnancy and in the few weeks which may follow term. The studies of Walker and Turnbull (1953), Walker (1954), Turnbull and Baird (1957) and of Mackay (1957) have shown how rapidly the available oxygen dwindles at this time. The oxygen available to a number of babies in the present series was determined by Mackay (1955) and the results have been plotted in Figure 21 with an indication of the anaesthetic employed at caesarean section and of the mean values found by Mackay for normal pregnancies. No obvious relationship exists between the oxygen saturation per cent and the later clinical behaviour of the foetus. Such oxygen levels may not represent the true situation, but only the conditions prevailing after delivery of the foetus. The oxygen pressure gradient across the haemochorial human placenta has been shown by Prystowsky (1957), however, to fall significantly in abnormal, including diabetic, pregnancy. Foetal anoxia may explain the intra-uterine foetal morbidity and mortality. A placenta which fails gradually from shortly after the 30th week may hinder the growth of the foetus (as in Case 84) so that he dies in utero about the 36th week if allowed to remain there, or he has a stormy and possibly fatal neonatal course if pregnancy is terminated prematurely. Alternatively, if the placenta fails later, at the 36th week, when the foetus is already large, then it is relatively less sufficient for the giant baby /
baby and intra-uterine death may occur unexpectedly.

The Cause of Placental Insufficiency. Although evidence for placental failure is available from these two sources, no proven explanation of the cause of placental failure is available. The suggestion that it results from degenerative changes in the mother's pelvic vessels has not received support from others, and no evidence of it has been found in this or in other British series. The principal factor which promotes foetal growth is probably not primarily responsible for foetal death (Page 67). The lethal factor is probably distinct and the possible role of a corticosteroid is worth consideration. The administration of cortisone to pregnant rabbits has been followed by the delivery of excessively large stillborn foetuses (De Costa and Abelman, 1952). Similar experiments have been carried out by Hoet (1953) and by Brasseur (1953). In normal pregnancy the secretion of maternal corticosteroids accelerates from about the 30th week of gestation (Cope et al, 1951) and the weight of the normal foetal cortex accelerates during the same period (Swinyard, 1943; Clatworthy et al, 1944). Vascular changes in the bulbar conjunctiva (Ditzel and Moinat, 1957) and placental failure occur with increasing frequency in diabetic pregnancy from about the 32nd week. The relationship, if any, between these facts cannot be proved meantime. Studies by Wolfe and Paschkins (1952) and Talbot et al (1951) seemed to show that corticosteroid excretion in the diabetic was low, but later work strongly suggests the opposite in the young patient (Page 51). An attempt has been made by Becker (1952) to /
to relate the occurrence of diabetic retinopathy to over-
activity of the adrenal zona fasciculata and in further work
(Becker et al, 1954) he believed that he had established a
positive relationship between adrenocortical hyperactivity and
diabetic retinopathy and nephropathy. The high rate of
excretion of adrenal 11-oxosteroids in patients with diabetic
angiopathy has been reported recently by Bastenie (1958).

The matter was investigated further in the same clinic by Maengwyn-Davies et al (1956). A significantly higher 24-hour urinary
output of 17-hydroxy corticosteroids was found among the
retinopathic diabetics than among the non-retinopaths, but,
although the mean figure for the former did exceed that of the
non-diabetic control group, the difference was not significant.
The high figures found among the retinopaths certainly did not
approach those found in Cushing's syndrome. The authors
stressed, however, that the techniques used could not detect
an abnormal steroid. This suggestion has received no support
from the work of Rifkin et al (1958), but further work on the
possible role of individual normal or abnormal corticosteroids
continues. The occurrence of classical vascular degeneration
in cases of pure pancreatic diabetes (Lawrence, 1950; Duncan
et al, 1958) supports the belief that it may result from the
metabolic disorder caused by insulin lack and that an inherited
vulnerability or dyspituitarism are not necessarily involved.
Insulin deficiency, however, is unlikely to be responsible for
the foetal deaths during the pre-diabetic years, and it is
interesting that in this series intra-uterine deaths were less
common before the development of clinical diabetes (Figure 19).

Strict /
Strict diabetic control is now advocated as the only way by which vascular degeneration may be prevented or delayed (Dunlop, 1954) and whether placental insufficiency is the result of insulin deficiency, corticosteroids, or an as yet undetermined factor, strict diabetic control certainly increases the chance of foetal survival.

**POST-NATAL FACTORS**

**Time and Route of Delivery.**

If pregnancy is allowed to continue to term intra-uterine death may occur, but if the infant is delivered prematurely by caesarean section then the risk of neonatal death, often with pulmonary hyaline membrane, is increased. This is the dilemma in which the obstetrician dealing with the diabetic pregnancy is placed.

During most of this study the obstetric management involved caesarean section at 35 to 37 weeks, the actual time depending upon the estimated size of the foetus, the previous obstetric history and the presence or absence of pregnancy complications such as hydramnios or toxaemia. This policy increases the risk of neonatal morbidity, but under present conditions this is probably smaller than the risk of intra-uterine death.

A higher morbidity and mortality exists among infants born to non-diabetic women by caesarean section than among infants of comparable maturity born spontaneously. This may result from the maternal or foetal illness which dictates the need for section or from circulatory stresses imposed by the method of delivery. A comparison has been made of infants of the /
Figure 22

COMPARISON OF MORTALITY AND MORBIDITY IN GROUPS OF INFANTS DELIVERED BY C/S TO DIABETIC AND NON-DIABETIC WOMEN

CAESAREAN SECTIONS AT 35-38 WEEKS GESTATION (WOMEN NOT IN LABOUR)

- # = APNOEIC ATTACKS
- # = DYSPNOEIC ATTACKS
- # = DEATH

DIABETIC

NON-DIABETIC

NUMBER OF INFANTS

70
60
50
40
30
20
10

76
the same maturity born by elective caesarean section to groups of diabetic and non-diabetic women who had not been established in labour (Page 151). Both groups of women were patients in the same hospital between 1948 and 1955. Three infants born to diabetic women died, but of these, one had suffered pre-natal exsanguination and another had very severe erythroblastosis foetalis and kernicterus. They have been excluded from consideration as in neither case was death a result of diabetes mellitus or caesarean section. The third child died of pulmonary haemorrhage. The mortality and certainly the morbidity are significantly higher among the infants of diabetic women than among those of the control group. They are, however, observed more carefully and some cyanotic attacks may pass unnoticed among the normal babies (Figure 22). The comparison strongly suggests that diabetes and not caesarean section is the principal harmful influence.

The time of delivery is probably more important than the route, although malpresentation and prolonged labour will seriously embarrass the foetus who has little available oxygen.

Birth Weight.

The influence of birth weight upon the progress of the live-born baby of the diabetic woman in the present series is apparent from Figure 23. The curve of mean birth weight at varying gestational ages, the latter based on the date of the last menstrual period, is derived from the figures of Ellis (1951). The dyspnoeic babies who died and the dyspnoeic who survived /

* Cyanotic attacks are indicated as apnoeic attacks in Figure 22.
THE RELATIONSHIP OF BIRTH WEIGHT AND MATURITY TO CLINICAL BEHAVIOUR

BIRTH WEIGHT, MATURITY AND CLINICAL BEHAVIOUR OF THE NEWBORN INFANTS OF DIABETIC WOMEN

MEAN B.W. OF INFANTS OF NON DIABETIC PREGNANCIES (ELLIS 1951)

TWINS
N
D
C
DEATH
survived occurred more commonly among babies who were lighter than others of comparable gestational age or among babies of 1700 g. birth weight or less. Uncomplicated cyanotic attacks are also commoner among the lighter babies. Only one baby of over 3.0 Kg. (6.6 lbs.) birth weight died.

This information should be considered with the already observed facts that (i) some pre-diabetic and diabetic women may produce many big babies and yet have a low incidence of intra-uterine death and a comparatively small neonatal loss (Page 67); (ii) some pre-diabetic and diabetic women have a significantly higher foetal mortality than others (Page 65); (iii) women whose diabetes is poorly controlled or complicated by vascular degeneration give birth to smaller babies (Page 57) and have a higher foetal mortality (Page 61) and (iv) the foetal mortality may not rise with the appearance of clinical diabetes (Page 64).

These findings suggest that the growth-promoting and infanticidal factors are distinct and that, although the former is almost always present, the latter need not co-exist. The lethal influence, although it is associated with diabetes, is more active in some women than in others: it increases with the development of hyperglycaemia, with the maintenance of poor diabetic control and with the development of vascular degeneration. It may interfere with foetal growth.

Hypokalaemia.

The serum potassium of babies born to diabetic women is low, according to Björklund (1953) who found "suppression or sagging" of the S–T segment, pathological negative T and U waves /
Figure 24

EXAMPLE OF E.C.G. CHANGES IN

THE NEWBORN INFANT OF A DIABETIC WOMAN

A. At age 1 day.

B. At age 22 days.

**Figure 25**

**ELECTROCARDIOGRAPHIC ALTERATIONS IN HYPOPOTASSAEMIA**

A. Normal: 3.8 to 6.0 mEq./Liter

b. Hypopotassemia: 2.5 to 3.0 mEq./Liter

C. Hypopotassemia: 1.8 to 2.4 mEq./Liter

d. Hypopotassemia: 1.0 to 1.8 mEq./Liter

waves and prolongation of the QT interval on their electrocardiograms (Figure 24) but no such changes in a control group. These abnormalities disappeared within 15 days of birth and usually within 5 days. They were present whether the baby showed clinical disturbance or not, but in no abnormal baby was the E.C.G. normal. Such E.C.G. changes in adults have been ascribed to potassium deficiency (Figure 25). The serum potassium levels of 4 such babies were found by Björklund to range from 16.3 to 21.4 mg. per cent. The average potassium level of normal umbilical cord blood was found by Bakwin and Rivkin (1927) to be 38.1 mg. per cent, and the average serum potassium of normal newborn infants was reported by McCance and Young (1941) to be 30.4 mg. per cent. By these standards then the babies reported by Björklund were indeed hypokalaemic, but their potassium levels mostly fall within the 17.5 - 21.1 mg. per cent normal range for serum at this age given recently by Hill (1954). Three of the infants in Björklund's series who had hypokalaemia by the standards which he accepted had normal electrocardiograms. Depression or sagging of the S-T segment was apparent in 10 of 11 E.C.G. tracings obtained from babies in the present series (Page 323). Some of the infants were asymptomatic and others who were dyspnoeic showed no other evidence of potassium deficiency. No systematic study of serum potassium levels has been carried out as part of this study, but the level has been within the normal range in ill babies whose serum has been analysed.

e.g. Case 119. /
e.g. Case 119. Caesarean section at 37 weeks. Dyspnœic from birth and during the first 48 hours. Slow improvement from the third day and normal by the fifth day. At one day the E.C.G. (Figure 89) showed low inversion of the T waves in leads I, II and V4 and diphasic T waves in leads III and V2 consistent with hypokalaemia, but the serum potassium was 27.4 mg. and the blood sugar was 96 mg. The E.C.G. abnormality persisted on the second day when the serum potassium was 29 mg. per cent and the blood sugar was 73 mg. per cent. No treatment other than oxygen was employed. The child recovered, but when re-examined at the age of 18 months she had a large patent ductus arteriosus which required ligation.

The T wave abnormalities at this age are not believed to be specific of hypokalaemia but may represent a metabolic disorder. They may exist in the absence of symptoms and the infants may be symptomatic in the absence of E.C.G. change. Depression or inversion of the T waves is more likely to relate to intracellular potassium levels than to serum levels and McCanse (1955) does not believe that they truly reflect potassium deficiency. Although potassium treatment has been mentioned as a possibility (Peel, 1955) no good evidence exists for giving it and, because of haemoconcentration, it may be dangerous. In one clinic where parenteral potassium has been given the neonatal mortality is higher than in the Edinburgh series.

Hypocalcaemia.

Low serum calcium levels in infants born to diabetic women and in premature babies of non-diabetic women have been reported by Craig and Buchanan (1958). The babies in the diabetic group were also mostly prematurely born. The levels recorded are certainly below the accepted normal range and the authors suggest that the neuromuscular irritability which is so common
PLASMA VALUES AND CLINICAL BEHAVIOUR DURING EXCHANGE TRANSFUSION

(Citrate v. calcium ion)
PLASMA VALUES AND CLINICAL BEHAVIOUR DURING EXCHANGE TRANSFUSION

(Potassium v. Calcium ion)
on the second and later days of life (Page 9) may be hypocalcaemic tetany, a condition which bears little resemblance to tetany in the more mature subject (Talbot et al, 1952; Wilkins, 1957). Unfortunately the series includes no proper control study so that there is no real evidence that the low calcium levels are directly responsible for symptoms. No suggestion has been made by them that dyspnoea or cyanotic attacks are of hypocalcaemic origin. The infants of non-diabetic women studied by Farquhar and Smith (1958) during exchange transfusion for haemolytic disease did not show increased neuromuscular irritability at very low levels of calcium ion (Figure 26) even when this was potentiated by high potassium levels (Figure 27). Possibly the formation of calcium citrate is incomplete during transfusion and the reaction proceeds towards completion in the presence of excess of citrate ion after withdrawal of the serum specimen and before analysis. Certainly Walker and Neligan (1955) found that calcium administration during exchange transfusion could be omitted without harm although depression of calcium ion by citrate in vivo may then proceed without interruption for some hours. Calcium was not found by Craig and Buchanan (1958) to relieve symptoms, and better results were obtained with chloral hydrate.

**Hypoglycaemia.**

The blood sugar falls more consistently, more rapidly and further (Figure 28) in infants born to diabetic mothers (Page 171) than in normal babies of non-diabetic mothers (Page 158) and blood sugar levels below 20 mg. per cent are not /
ARITHMETIC MEANS OF SERIAL BLOOD SUGAR DETERMINATIONS ON INFANTS OF DIABETIC AND NON-DIABETIC WOMEN.
not uncommon. This hypoglycaemia is maximum at 2 – 3 hours, it is corrected spontaneously in 4 – 6 hours, and it is unrelated to the birth weight of the child.

Hartmann and Jaudon (1937) were of the opinion that cyanosis, irritability, listlessness, hypotonicity, hypertonicity, twitchings and even death might result from hypoglycaemia. They stated "there can be no question, however, of the greater tendency in the abnormal (diabetic) group to develop extreme grades of hypoglycaemia with clinical manifestations severe enough to be fatal or so alarming as to require constant watching and sometimes frequent treatment to raise low blood sugar levels." Miller and Ross (1940) noted symptoms in three of six infants and although the infants were biochemically hypoglycaemic they noted other abnormalities in the babies; congestive failure in two and possible birth injury or erythroblastosis foetalis in another. They noted a lag in the response of the infants to glucose, but felt this was analogous to the delayed response of a hypoglycaemic non-diabetic adult to glucose. Reis et al (1950) enumerated the dangers to which these newborn infants were exposed and included hypoglycaemia without giving their reasons. John (1950) stated that the physiological hypoglycaemia of healthy newborn infants was benign and unproductive of symptoms, but that the hypoglycaemia which the offspring of diabetic women developed was malignant, leading to shock and to death unless it were treated early and energetically. Komrower (1954) in a comprehensive study observed signs which were considered to be suggestive of hypoglycaemia in 4 of 40 such infants whose
blood sugar levels had been followed carefully from birth. In 3 the levels were less than 20 mg. per cent, and the fourth baby had been subjected to a large and very rapid drop in blood sugar. On the other hand, Komrower found 3 infants who were symptom-free with sugar levels of 20 mg. per cent or less. There is, however, some individual variation in the response of adults to hypoglycaemia and the epileptic in particular may respond with convulsions to a blood sugar level which might not upset the normal person. All of the deaths in Komrower's series appeared to be explicable on the basis of the pathological findings, without his requiring to incriminate hypoglycaemia. In 11 of 27 infants born to diabetic and prediabetic women, Reardon, Field and Baumann (1955) determined the blood sugar value at 4 hours. Seven of these had values of less than 15 mg. per cent, and 4 of them died. Referring to the low blood sugar levels attained by normal infants of non-diabetic women, Donald (1956) stated "the sharp change may well tax the child's endurance and metabolic resources overwhelmingly." Pedersen (1952a) whose work is the exception to the finding that infants of diabetic women have a more profound and more rapid fall in blood sugar, discovered no clinical evidence of hypoglycaemia in his group. Such abnormalities as did present in the first 24 hours of life were attributed to intracranial haemorrhage in one (diagnosed by cranial puncture), congenital heart disease in one (diagnosed by auscultation and radiography), widespread atelectasis in two (diagnosed by auscultation and autopsy in one and by auscultation and radiography in another) and probable atelectasis in the /
the fifth in which the diagnosis could not be verified. He did not note the blood sugar to be abnormal in the presence of cyanosis in these babies.

Those obstetricians and paediatricians who have feared the effects of hypoglycaemia upon the infants of diabetics have suspected that, although such low levels may not be productive of symptoms at the exact moment when the trough of hypoglycaemia was reached, nevertheless the structure and the function of, for example, the brain, the heart, the lungs, or the vessels might have been so altered by it that symptoms might develop later, even after the blood sugar had been somewhat restored.

Hartmann and Jaudon (1937) recommended that the hypoglycaemia of these babies should be prevented by the very early institution of regular carbohydrate and milk feeds and that where symptoms developed the babies should have epinephrine and dextrose parenterally. Reis et al (1950) recommended that a 50% glucose solution should be given orally by medicine dropper in the first hour of life and that after the first 2 hours the infant should receive $\frac{1}{2}$ to 1 oz. feeds two-hourly of breast milk, and 5% glucose alternately during the first day of life. Whitely, Adams and Parrott (1953) recommended the subcutaneous administration of glucose to the newly born infant. Drury (1953) also recommended its parenteral administration. Komrower (1954) studied two groups, one of which received no glucose, whereas the infants of the other received 2 g. glucose by mouth as a 50% solution in the first 8 hours of life. There was no significant /
significant difference in the blood sugar levels of the two groups, and Komrower, therefore, decided to give glucose only when symptoms attributable to hypoglycaemia developed. Pedersen (1952a) and Pedersen et al (1954) saw no point in using glucose at all. The results of this investigation make it clear that there is no need to use glucose in the infants of diabetic women.

During the years 1948 - 51 an effort was made in the present series to prevent this hypoglycaemia or at least to retard its development because of the possible harmful effects. Glucose was given by mouth, but vomiting and serious inhalation occurred on several occasions and the practice was discontinued. Some babies were then given glucose solution by the umbilical vein, but the majority were given intramuscular injections of 25 to 50 per cent glucose when trials had shown that such were well tolerated. Experience showed that even with this precaution the blood sugar level could not be maintained consistently during the first 3 to 4 hours and that a trend exists toward spontaneous correction by 6 hours (Table 27, Page 254).

A study of the clinical importance of the hypoglycaemia showed that no correlation exists between the speed of blood sugar fall, the lowest level reached, the development of symptoms or the later progress of the child (Page 179). All attempts at prevention were then discontinued, and glucose has been withheld, without harm, from all cases since 1952.

Read (1951) claimed that the intravenous glucose tolerance of newborn infants of diabetic women did not alter between the first and second weeks of life and that there was no evidence of /
of increased tolerance during the first week. Scrutiny of
his statistical evidence, however, shows that his conclusions
are not justified and that his results have no bearing upon
conditions prevailing during the first 16 hours of life
(Page 252).
Adreno-cortical Disorder.
Corticosteroids have been suspected of playing some part
in the morphological development of these babies (Pages 51 to
56). The possibility that they also have something to do
with the vascular degeneration of diabetes mellitus and with
the functional impairment of the placenta has been mentioned
(Pages 73 to 75). If they are involved in these matters,
then it is possible that an adreno-cortical disorder is related
to the neonatal morbidity. Peel (1951) hinted vaguely at
"death ...... possibly associated with a suprarenal crisis",
but four years later (Peel, 1955) he had advanced no further
than to say that theoretical considerations had justified
experiments in his department with corticotrophin and cortisone
in the treatment of these babies.

The dangers of both hyperadrenocorticism and hypoadreno-
corticism in adults are well recognised. If the foetal
adrenals have been over-stimulated (Page 26) then this may be
followed by adrenal insufficiency when the stimulus is abruptly
removed and this may occur in the absence of obvious patho-
logical changes in the gland (Banks, 1949). A clinical picture
of dyspnoea, "pseudopneumonia infantum", which is associated
with adrenal haemorrhage in newborn infants has been described
by Goldzieher and Gordon (1932). No convincing evidence of
such /
such a relationship has been discovered, however, in a personal study (Page 318).

The normal neonatal absolute eosinophil counts of the peripheral blood in previous investigations rise from birth to about the third day of life and then begin to fall (Forkner, 1929; Klein and Hanson, 1950). Such eosinophil changes are quite the opposite of what happens to the blood sugar levels. These fall from birth to about the third day and then rise. Because the eosinophil count and the blood sugar levels may be influenced in opposite directions by the secretions of the adrenal cortex and because hypoglycaemic levels are found in the normal newborn and more pronounced ones occur in the infant of the diabetic woman, further investigation of adrenal insufficiency as a cause of symptoms was undertaken.

**Eosinophils.** Serial observations upon the absolute eosinophil counts of such babies shows that significant reductions in eosinophil levels follow birth in each case (Page 211) and that these are greater (Figure 29) and more consistently present than are the reductions which are achieved by the normal infants of non-diabetic women (Page 202). No relationship exists, however, between the eosinophil counts and the blood sugar levels (Page 218). A detailed study of the Thorn test (corticotrophin - eosinolysis test) shows that it has even greater limitations at this age than it has in adults, and it was judged to be unsuitable for this investigation (Page 259).

**Urinary excretion of corticosteroids.** The only measurement of corticosteroid excretion which was available to this study /
ARITHMETIC MEANS OF SERIAL EOSINOPHIL COUNTS ON INFANTS OF DIABETIC AND NON-DIABETIC WOMEN
study (by the kind co-operation of Dr. C.P. Stewart) was the careful determination of the urinary formaldehydogenic steroids (A.S.F.S.) by the method described by Tompsett and Smith (1954) (Page 303). The limitations of formaldehydogenic steroid methods have been indicated by Marrian (1951) who believed that the various techniques then available probably measured only a proportion of the total corticosteroids present in urine. A difference in the urinary excretion of A.S.F.S. was found in this study. The babies delivered by caesarean section to diabetic women excreted more urinary A.S.F.S. during the first 24 to 48 hours of life than did normal infants of almost comparable maturity born to non-diabetic women by the same route or normal infants delivered spontaneously at term to non-diabetic women (Page 305). The amount excreted is independent of urine volume or surface area. No relationship to the development of symptoms has been found. The 17-keto-steroid excretion of infants of diabetic and non-diabetic women is roughly equal. These findings provide some evidence of increased adrenocortical activity but none of a relationship between the latter and neonatal morbidity.

Pulmonary Hyaline Membrane.

Pulmonary hyaline membrane occurs most commonly in pre-maturely born infants and in babies born by caesarean section. Perhaps because his birth is both premature and caesarean the infant of the diabetic woman is unusually susceptible. Although present in less than half of the small number of neonatal deaths in this series it was found in 85 per cent of deaths by Peel (1955) and in 77 per cent by Clayton (1956).
Figure 30

Volume of gastric contents at birth in 23 infants of diabetic women.

<table>
<thead>
<tr>
<th>Volume (in millilitres)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>12</td>
</tr>
<tr>
<td>2-4</td>
<td>10</td>
</tr>
<tr>
<td>4-6</td>
<td>4</td>
</tr>
<tr>
<td>6-8</td>
<td>2</td>
</tr>
<tr>
<td>8-10</td>
<td>0</td>
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<td>10-12</td>
<td>0</td>
</tr>
<tr>
<td>12-14</td>
<td>0</td>
</tr>
<tr>
<td>14-16</td>
<td>0</td>
</tr>
</tbody>
</table>

VOLUME OF GASTRIC CONTENTS AT BIRTH IN 23 INFANTS OF DIABETIC WOMEN
It was the commonest autopsy finding in the experience of White (1952).

The belief that the membrane was formed by the irritating presence of particulate material from the amniotic sac (Farber and Wilson, 1932) seemed to receive substantial support from the work of Claireaux (1953) who reproduced the histological picture by incubating inhaled squamous cells in rat lungs. Morison (1952) believed that the membrane might sometimes follow vomiting and inhalation. The danger of inhaling foreign material into the lung probably prompted the investigation by Gellis et al (1949) into the gastric contents of babies born to diabetic women by caesarean section. Because of the abnormal volumes found by them (average of 20 ml. compared with average 2 ml. in control group), they recommended routine aspiration of the stomach at birth. Large volumes have not been found in infants of this series (Figure 30). The inhalation theory was challenged by Emery (1953) and later work has almost certainly disproved it completely.

Pre-natal injury to the epithelium of the terminal air passages was suggested by Miller and Hamilton (1949), but the condition was never apparent in stillbirths. Several apparently unrelated recent observations relating to the integrity of the plasma compartment in the newborn, perinatal dynamic changes in the circulatory system, the histology of the membrane and its development at different ages may contribute toward a better understanding of its etiology and of the fundamental cause of perinatal death in the diabetic pregnancy. These will now be described briefly.

(1) /
(1) Post-natal Plasma Migration. In work as yet unpublished Gairdner (1958) has shown that the hitherto unexplained post-natal rise in the haemoglobin level of normal babies results from migration of up to 25 per cent of the plasma from the vascular compartment into the extracellular space. Such migration begins within minutes of delivery and is rapidly progressive. The leak includes protein and electrolytes, and this confirms the observations of Baar (1956) that the interstitial fluid of the newborn, and mainly of the premature, has a protein of 3.5 to 7.0 grammes per cent and that the albumin content is little lower than that of plasma. He believed that this resulted from increased capillary permeability due in turn to anoxaemia and to changes in environmental pressures.

(2) Pulmonary Hypertension. The work of Dawes et al (1953) and of Born et al (1954) has shown in lambs that, before the lungs expand, the initial pulmonary vascular resistance is high and that it can be increased by the asphyxia which follows the tying of the umbilical cord before the onset of respiration. This may be effected by ability on the part of this vasculature, probably the arterioles, to contract and so to impede the onward flow of blood to the capillaries (Bonham Carter, 1957), and it may be associated with a compensatory high cardiac output. The same sort of process may occur in neonatal hypothermia where the capillaries are so badly damaged, presumably by anoxia, that they leak badly when the pulmonary blood flow increases during heating and massive haemorrhage results. The membrane seemed to Potter (1952) to resemble the pneumonia associated with rheumatic fever. Similar pulmonary hyaline membranes /
membranes have been found at autopsy among adults whose hypertension has been treated with chemical ganglionic blockade, and also in those dying from uraemia or rheumatic fever (Perry et al., 1957). The authors believe that the membrane is caused by damage to the pulmonary capillaries and possibly by co-existent left-sided cardiac failure and increased pulmonary pressure. Left-sided cardiac failure was suggested as the probable cause of the membrane in newborn infants by Lendrum (1955).

(3) Histology of the Hyaline Membrane. By using a fluorescent antibody and dye-staining technique Gitlin and Craig (1956) were able to refute the earlier hypothesis that the hyaline membrane of newborn infants represents the residue of inhaled amniotic fluid, and they have shown that it consists largely of fibrin derived from the effusion of plasma through the pulmonary capillaries. The endogenous origin of the membrane and that it is a blood derivative were also shown by Duran-Jorda et al. (1956). An electron-microscope study of the membrane (Van Breemen et al., 1957) has provided convincing evidence that the membrane consists of blood plasma which has leaked from the vascular compartment into air spaces, and that the hyaline matrix is fibrin in various stages of clotting. They observed capillary breakage in the alveolar walls and haemorrhage into air spaces. The epithelial linings of ducts and alveoli and the endothelial lining of capillaries was altered sufficiently to allow the passage of plasma proteins, and evidence of red cell sludging was also seen. The capillary damage seems to result from abnormal oxygen tensions.
Hyaline membrane can follow experimental or aviation hyperoxia (Bruns et al., 1954) but in the newborn the most closely associated factor of aetiological importance is generally believed to be perinatal hypoxia.

The dwindling oxygen supply of the foetus in the pregnant diabetic (Page 70) probably accounts for the intra-uterine death of some babies, and in less seriously affected cases it may produce pre-natal capillary damage in the lungs and elsewhere. Surely the physiological seepage of plasma in the newborn, and particularly in the premature infant, may become a microscopic flood when the retaining dykes of the vascular compartment are weakened by cracks and when the full tide of pulmonary hypertension is hammering at them. And so the sequence of events would be pulmonary oedema, hyaline membrane, collapse and, in some cases, varying degrees of haemorrhage. The same mechanism of pre-natal anoxic capillary damage followed by local peri-natal hypertension may cause vascular disaster at other sites.
The treatment of the newborn infant consists of skilled resuscitation where that is necessary, continuous observation of the naked baby in a warm premature-room for three days or more, delay until the third or fourth day before starting feeding, and the efficient treatment of infections.

The hypoglycaemia does not require correction, the giving of potassium salts is probably both unnecessary and dangerous, the injection of calcium has no effect on the irritability, and sedation is probably undesirable. No evidence has been found which would indicate the usefulness of corticotrophin or steroids, and oxygen should be given only when indicated.

Nursing supervision must be conscientious or the dramatic cyanotic attacks may be missed. When one develops, the baby's pharynx should be gently aspirated and respiration may then be stimulated by flicking the baby's foot. Oxygen may be given for a few minutes. Chemical stimulation (0.5 ml. of lobeline for infants by intramuscular injection) is rarely required.

The treatment of the dyspnoeic syndrome is unsatisfactory. Oxygen may be given but the concentration in the inspired air should not exceed 35 per cent, as high concentrations may contribute toward the development of hyaline membrane. Water vapour mists and detergents have not been effective (Hsia et al, 1957). The dyspnoeic infants should be left undisturbed except for the intermittent aspiration of his upper respiratory tract. Should he remain symptomatic for /
for three or more days and become dehydrated, then he may be too distressed to take oral fluids. On the one occasion where this happened in the present series, the baby was successfully treated by gently washing out his bowel and then giving him a continuous glucose infusion through a self-retaining catheter placed high in the descending colon. Assisted respiration by means of mechanical devices may help, but this is less important than trying to prevent the hypoxia which precedes the membrane's formation. Strict diabetic control alone is the most effective preventative so far, particularly when it permits vaginal delivery at term.

Minor skin infections, to which the babies are susceptible, should be treated with aqueous gentian violet, or in severe cases by the systemic use of the effective antibiotic.
Lactation

Normal lactation in diabetic women has been reported by Wilder and Parsons (1928), Merkler (1929) and Peckham (1931) but it is more commonly described as poor. It was deficient in all the cases reported by McIlroy et al (1931), and in the experience of Peel (1951) only half these mothers are able to breastfeed adequately. Lactation may start normally and then fail (Barns and Morgans, 1952), or it may be established only with difficulty but remain adequate afterward (Peel and Oakley, 1950). In contrast, excessive lactation is said by Jackson (1952) to be a feature of pre-diabetes.

Inadequate maternal nutrition was held to be responsible by Skipper (1933) and to be partly responsible by Shemmack (1949). Not all such mothers are obviously malnourished now and the improvement in diabetic nutrition is the recognised explanation for the altered fertility among such women. Premature delivery may be partly responsible (Peel, 1951; Barns and Morgans, 1952; Rolland, 1954). An immature baby certainly may provide poor stimulation for the breast even if suckling were permitted during the first few days. Prolactin deficiency is suspected by Shemmack (1949) and "a pituitary abnormality" by Peel (1951). The lactation even of non-diabetic women, however, is established more slowly after caesarean than after spontaneous delivery.

The breast feeding history of 60 non-diabetic women who were delivered by caesarean section has been studied (Figure 31, inset). Half of them were breast-feeding their babies fully at discharge from hospital and only a third had failed /
Figure 31

BREAST FEEDING HISTORY OF INFANTS BORN TO DIABETIC WOMEN

BREAST FEEDING HISTORY OF 96 INFANTS BORN TO DIABETIC WOMEN

(The inset shows the method of feeding at discharge)
( of 60 infants born by C/S to non-diabetic women )
failed completely. The composition of this group is described elsewhere (Page 133) and differs mainly by being rather more mature than the diabetic group. In contrast to this the breast feeding history of diabetic women, most of whom had been delivered by caesarean section, in the present series is poor (Figure 31). Considerably more than half the women either abandoned the attempt in the first week, or less commonly no attempt was made. A further large group failed during the first 4 to 6 weeks. Some, however, were fully or partly successful until weaning was established at 6 to 9 months. More detailed information about these groups is available later (Page 148). No consistent relationship has been found between the pre-diabetic and diabetic obstetric histories of the mothers or the size of the babies and the success or failure of breast feeding.

Although the hypothesis that first adequate and then inadequate lactation is but one facet of a complicated metabolic disorder involving the pituitary, no convincing evidence for this has been advanced so far. If Jackson's observation concerning pre-diabetic excessive lactation is correct, then the factor influencing lactation (presumably prolactin) behaves quite differently from the factors responsible for foetal overgrowth and mortality. Stimulation of milk-secretion appears to fail with the appearance of clinical diabetes, growth promotion remains unaltered in the majority but it is depressed with the appearance of diabetic vascular complications, and the infanticidal influence increases with the appearance of hyperglycaemia. It is as if different anterior /
anterior pituitary fractions dominate the metabolic machinery at different stages in the disease so that the secretion of, or the response to, first prolactin and then the growth hormone must be displaced in favour of the third and dangerous infanticidal factor. As there is evidence that prolactin and luteotrophin may be identical (Astwood, 1953), the suggestion that the hormone becomes deficient with the development of diabetes is hardly consistent with the normal fertility records of diabetic women. However, Astwood has pointed out that the evidence for the single identity of the hormones, although suggestive, is not conclusive, and this has been stressed by Loraine (1958).

Whatever truth eventually emerges from this, more diabetic women could breast feed if every encouragement were provided by enthusiastic medical and nursing staffs. That she should do so is not, however, a matter of great consequence nowadays.
CONGENITAL MALFORMATIONS

Early this century, Herman (1902) referring to diabetic pregnancy stated that "the chances are two to one that the child will die in utero. Its life is therefore not of much account." With the improved survival rate, however, the fate of the survivors assumes greater importance.

The incidence of congenital malformations in those series which include 40 or more cases ranges from none (Patterson and Burnstein, 1949; Hall and Tillman, 1951) to 80 per cent in the large Boston series (White, 1952). Most published series quote an incidence of from 2 to 3 per cent. In the United Kingdom an incidence of 10 per cent was reported by Barns and Morgans (1949). Peel and Oakley (1950) found 6.3 per cent, but this figure rose later to 8 per cent (Peel, 1955). In Europe an incidence of 6 per cent has been found by Hagbard (1956), and of these 30 babies with congenital malformations, two-thirds died during the first week and further deaths occurred in the next few months. The probability that early death from malformation had removed many cases was accepted by Fredrikson et al (1957) as the explanation for their having found only one child with a congenital anomaly in a follow-up examination of 123 surviving children derived from an originally much larger group.

Few of these authors examined a control group of babies born to non-diabetic women, and where they did so no description of the control material was given. An incidence of congenital malformations in controls of 0.94 per cent (Peel and Oakley, 1950) compares with 0.5 per cent in babies examined /
examined by Pedowitz and Shlevin (1952) and 1.8 per cent by White (1952). Of all of these reports quite the most extraordinary contrast lies in White's claims of 80 and 1.8 per cent of congenital malformations in babies born to diabetic and non-diabetic women respectively. Her statement (1949) that these anomalies were severe in only 10 per cent of the diabetic group and lethal in only 2 per cent raises doubt as to whether she looked for the same range of abnormalities in both groups.

Several explanations can be found for these wide variations in incidence. Some authors may have included every trivial abnormality found on clinical examination, whereas others used technical aids to diagnosis or recorded only the lethal malformations discovered at autopsy. Some have mentioned anomalies which are obvious in the first week, whereas others have followed their cases and have added those malformations which were discovered later. Should such congenital abnormalities be inherited (White, 1952) or should they result from the metabolic disorder there is no clear indication as to which system is most vulnerable in the human subject. The most detailed study, including technical aids, would then be required in order to discover each deviation from what had been decided as normal in a control group. The nearest approach to such a study so far is probably that of Cardell (1953a) who found an incidence of 25 per cent and 20.2 per cent at autopsy in babies of diabetic and non-diabetic women respectively. The difference was not considered significant. Abnormalities of the eye, such as congenital cataract, and of other systems may not always be apparent at autopsy.
According to White (1952) the congenital malformations are probably of genetic origin, but animal experiment and a few human observations have suggested that the metabolic disorder may be partly responsible. The experiments of Duraiswami (1950) have shown that unchecked insulin hypoglycaemia of chicks during the first few days of incubation induces multiple abnormalities of the cartilaginous skeleton and of the eyes. The possible application of this observation to the foetus of the diabetic pregnancy is obvious. Of less certain application are experiments which show that cortisone may produce congenital malformations. The experimental evidence for this has been reviewed by Harris and Ross (1956) who reported the occurrence of cleft palate in the foetus of a woman who had received cortisone early in pregnancy for the treatment of idiopathic steatorrhoea. The teratogenic effects of hypervitaminosis-A in rats are greatly potentiated when cortisone is added (Miller and Woollam, 1957), and Harris and Ross admitted that only this knowledge justified publication of their case as no proof existed that cortisone played any part in causing the child's deformity.

An unsuccessful attempt to discover the influence of prolonged hypoglycaemia upon the human foetus forms part of the present study (Page 350). Since then, however, almost all of the surviving children in this series, and a closely matched group of children born to non-diabetic mothers, have been re-examined personally. A medical history was taken in each case and the children were submitted to a standard clinical /
clinical examination. Technical investigations such as X-ray (Figures 93 to 99) were undertaken only if some positive lead existed, e.g. recurrent urinary infections, scoliosis.

Only those malformations which were considered to be disabling, potentially disabling, in need of surgical correction, or disfiguring were included, and such trifling deformities as mild plagiocephaly, small pilonidal sinuses, prominent ears or small naevi normally covered by clothing were excluded.

The incidence of congenital malformations in the two groups was not found to be significantly different. (Figure 92).
THE DEVELOPMENT OF SURVIVING CHILDREN

THE RELATIONSHIP OF NEONATAL CONDITION TO LATER HEALTH.

Almost all the surviving children in the series have been re-examined on at least one occasion, at ages ranging from 2 to 10 years. Their progress is shown in Figure in relation to their neonatal condition. In each group the absolute figures are given and these are then expressed as percentages. Those groups of infants who were originally dyspnoeic or affected by cyanotic attacks contain a relatively greater number of abnormal babies than the groups whose neonatal course was uncomplicated.

GROWTH.

Reports concerning the physical progress made by children of diabetic women have, until recently, emanated mainly from Boston. From the large numbers available to White et al (1953) 105 children were selected because they lived near the Joslin Clinic. The children were stated to be commonly above average height and weight, but the information given does not constitute proof that, as a group, they were necessarily abnormal.

Selecting their cases only by response to their invitation to them to submit to examination, Fredrikson et al (1957) examined 123 surviving children from a much larger group born to both pre-diabetic and diabetic women. When the heights and weights were compared with Swedish normal values the children who were born before the onset of maternal diabetes were found to be below average, and the difference was /
Figure 32

NEONATAL CONDITION AND LATER DEVELOPMENT

NEONATAL CONDITION AND LATER DEVELOPMENT

DYSNOEIC

CYANOTIC ATTACKS

NORMALS

- BIFID THUMB
- SCOLIOSIS
- SACRAL AGENESIS
- M. D.
- DIED IN INFANCY
- UNTRACED

- NORMAL

- POST. MENIN. M.D.
- R. D.A.

- MONGOL RETROLENTAL F.
- MILD TORTICOLLIS
- HYDRONEPH.

- NORMAL

- DIED

- UNTRACED

- NORMAL

- 100%

- 50%

- 40%

- 30%

- 20%

- 10%

- 0%
Figure 33

STANDING HEIGHTS OF CHILDREN
BORN TO DIABETIC AND NON-DIABETIC WOMEN

STANDING HEIGHTS OF CHILDREN BORN TO DIABETIC AND
NON-DIABETIC WOMEN
(Compared with the crown-heel length of normal Edinburgh children)
Figure 34

NAKED WEIGHTS OF CHILDREN BORN TO DIABETIC AND NON-DIABETIC WOMEN

(Compared with the naked weights of normal Edinburgh children)
was claimed to be significant statistically. Those born after the onset of the disease were on average slightly taller than normal, but the difference was small and statistically not significant. The weights of the children did not differ from the normal.

The surviving Edinburgh cases were re-examined in 1955 and again in 1957. Almost all were examined and measured personally with the same measuring rod and beam balance. The very few exceptions were mostly overseas where they were examined by doctors employing the same techniques. The standing height was measured with the child stripped and erect against a wall, and the naked weight was measured by an Avery beam balance of checked accuracy. In the case of children of 18 months or less the total length, rather than the standing height, was measured with the apparatus devised by Thomson (1956). The heights at one or both examinations are shown in Figure 33. The heights and weights of children in a carefully matched control group (described on Page 355) were also recorded. The unbroken line represents the mean height derived from cross-sectional data for Edinburgh preschool (Thomson, 1956) and school-age children (Provis and Ellis, 1955) of the present decade. The broken lines represent ±1 and ±2 standard deviations (S.D.) about the mean at each year. No abnormality of linear growth is so far detectable in the diabetic group.

The weights of children in the diabetic group at one or two examinations and those of the children in the control group are shown in Figure 34. The normal mean and standard deviations /
deviations for weight from the same Edinburgh studies are recorded. A few children lie above or below the ± 2 S.D. lines, but four lie above + 3 S.D. and three of these are in the 9th or 10th years of age.

These simple measurements are so different from those in the Boston series that no attempt has been made so far to find the changes in the smaller blood vessels of the bulbar conjunctiva (Ditzel et al, 1954) which are said to correlate positively with growth disorder.

Birth Weight and Later Height.

The birth weight, which is subject to the limitations previously mentioned, is recorded against the later height and age in Figure 35. Those children who weighed 4 Kg. or more and who were weighed on two later occasions are linked on the graph. The only child to gain weight steeply in the interval between examinations is indicated. He was of lower birth weight. There is no indication that those babies who are very big at birth "grow away" from the others with the passage of years. They do tend to remain among the taller children, but there are exceptions and some of the lighter babies at birth are later found among the taller children.

Birth Weight and Later Weight.

The birth weight is recorded against the later weight and age in Figure 36. There is no indication that those babies who exceeded 4 Kg. at birth are excessively heavy later. There is perhaps instead a tendency for them to be of average weight by the age of 7 years. Of the three children whose weight exceeded + 3 S.D. of the mean in the 9th and 10th years none /
THE RELATIONSHIP BETWEEN BIRTH WEIGHT AND LATER HEIGHT

- $4.0$ Kilos or more
- $3.5$ Kilos but less than $4.0$
- $3.0$ Kilos but less than $3.5$
- $2.5$ Kilos but less than $3.0$
- $2.0$ Kilos but less than $2.5$
- Less than $2.0$ Kilos

**Figure 35**
Figure 36

THE RELATIONSHIP BETWEEN BIRTH WEIGHT AND LATER WEIGHT

THE RELATIONSHIP BETWEEN BIRTH WEIGHT AND LATER WEIGHT

![Graph showing the relationship between foetal birth weight and later weight in kilos and years of age.](image)

- \(\bullet\) = 4.0 kilos or more
- \(\circ\) = 3.5 kilos but less than 4.0
- \(\square\) = 3.0 kilos but less than 3.5
- \(\square\) = 2.5 kilos but less than 3.0
- \(\times\) = 2.0 kilos but less than 2.5
- \(\triangle\) = Less than 2.0 kilos

Y YEARS OF AGE

B BODY WT.

IN KILOS

KILOS
none exceeded 4 Kg. at birth and two weighed 3.5 Kg. or less. These three had shown a sharp increase in weight in two years, but other children of comparable birth weight were of average or low weight later. (For individual figures see Appendix VI.)

THE DEVELOPMENT OF DIABETES MELLITUS.

The previous sections indicate that if the infants of diabetic women survive the newborn period then they are likely to be as healthy and to grow as normally as the children of non-diabetic women, at least until the age of 10 years. There is a possibility, however, that a population is being salvaged which will live to develop and to propagate diabetes mellitus and, although "the danger of being a potential diabetic is indeed the very least of the hazards to which the fertilized ovum is subjected ..... in the diabetic uterus" (Oakley and Peel, 1955), the prospect is a dreary one for the child, his parents and the community. The child of the diabetic woman was not considered by Skipper (1933) to be specially liable to the disease, but Peel and Oakley (1950) believe that where both parents are diabetic the child will probably develop the disease, and that the presence of diabetes in the families of both parents increases the risk of diabetes in the child even if the parents themselves are unaffected. The probable development of the disease in 1 in 4 children born to diabetic women was forecast by Reis et al (1952).

There is little doubt that the predisposition to diabetes mellitus is often inherited (Pincus and White, 1933; Harris, 1950-51; Bartels, 1953; Steinberg, 1955). A study of 1241 diabetic propositi (Harris, 1950-51) showed that of the 1418 children /
children born to them only 10 became diabetic, and he estimated that about 1.4% of children of a diabetic parent may be expected to develop the disease by the age of 40 years. The inherited predisposition is not the only factor and both Hoet (1954) and Jackson (1955) have pointed out that the pre-diabetic and diabetic internal environment may adversely affect the child and indeed it has already had an influence on the foetal pancreas in utero. This idea has some experimental backing in that Bartelheimer and Kloos (1952) and Bartelheimer (1953) have claimed that rats made mildly diabetic with alloxan may bear progeny which first become larger than normal and later diabetic. Boulin (1958) has stated that diabetic mothers have nearly three times the tendency of diabetic fathers to hand down the diabetes to their children.

By means of oral glucose tolerance tests White et al (1953) found that 28 of 105 children had plainly diabetic curves, and Jackson (1955), on re-examining the results, claimed that the proportion was even higher.

Ditzel et al (1954), also at the Joslin Clinic, found that of 75 children of diabetic mothers 7 were already diabetic and a further 13 were "borderline" diabetics. This incidence is surprising even when taking into account the fact that two-thirds of the diabetics and less than half the suspects were over the age of 10 years. The chances of the children of any one diabetic parent eventually developing diabetes were later estimated to be 22 per cent for their whole life span (White, 1957), but she added that as 1 in 3 of the normal population is an hereditary carrier of the disease "I do not think we should/
should carry genetic teaching too far." In contrast, of the 123 children studied by Fredrikson (1957) only one was found to be diabetic. The children of the present series have not been subjected to glucose tolerance tests, but none has developed diabetes so far and none shows glycosuria after oral loading with glucose. None of them has developed the precocious growth described by Ditzel et al (1954) as being associated closely with reduced glucose tolerance and vascular changes. The numbers, of course, at each age are relatively small, but the total is no smaller than the Boston group and it has the virtue of being unselected. Selection of cases from the area conveniently placed to a large diabetic clinic could introduce considerable bias into the results.

The prediction of diabetes mellitus in the present series by using the steroid-glucose tolerance test (Fajans and Conn, 1954) has not been attempted so far. The obese children in a small series investigated in this way by Komrower (1957) showed no evidence of being pre-diabetic. Kelly (1957), using prednisolone, found that positive results were less commonly found in younger than in older subjects, and he suggested that the test was of only limited ability in the prediction of eventual diabetes mellitus.

The chances of inheritance when both parents are diabetic may be high, but the risk when only the mother is diabetic is still uncertain. Time will provide the answer more effectively and with less likelihood of making mothers anxious and children unhappy than the purely mechanical use of laboratory prediction methods with the associated need for explanation and hospital admission.
CONCLUSIONS

(1) The development of insulin has improved the fertility of the diabetic woman but it has created the problem of the diabetic pregnancy.

(2) A high foetal mortality still exists although it has been remarkably reduced by entrusting the care of the diabetic woman and her foetus to a small team consisting of an obstetrician, a physician and a paediatrician.

(3) The greater part of the viable loss rate is due to intra-uterine death and the remainder to neonatal death.

(4) The majority of babies are excessively heavy and long for their gestational age.

(5) The pathology of these infants is identical with that of babies born to pre-diabetic women and it has also been found in the affected infants of Rhesus-sensitised non-diabetic women. The principal undoubted abnormalities are pancreatic islet hyperplasia affecting the beta cells, some increase in cardiac glycogen and pronounced extra-medullary erythropoiesis. A high percentage of the neonatal deaths have pulmonary hyaline membrane disease.

(6) Many babies suffer from prolonged dyspnoea or from cyanotic attacks during the first few days of life. Of these, those with dyspnoea have the poorest prognosis.

(7) The babies seldom show pitting oedema, and they lose no greater a percentage of their birth weight during the first week than do babies born by caesarean section to non-diabetic women and submitted to the same feeding schedule.

(8) /
Circumstantial evidence of foetal hyperinsulinism exists. This, and excessive foetal growth, may be the result of stimulation by maternal Pituitary Growth Hormone and possibly by corticotrophin in the pre-diabetic woman, and by these and hyperglycaemia in the established diabetic.

No clear relationship exists between maternal build and foetal birth weight. The value of this observation is limited by the variable gestational age of the babies.

The mortality and morbidity are highest among the smaller babies at any gestational age.

The birth weight may be remarkably consistent in families. Some women almost always produce giant offspring, among whom there is no increase in mortality.

The risk of foetal death is greater in some women than in others. The babies of such women are not necessarily large. Foetal overgrowth and foetal death therefore do not result necessarily from the same maternal factor.

Among the possible causes of intra-uterine death the likeliest appears to be functional placental degeneration.

Placental failure leads to hormonal changes in the mother and to oxygen deficiency in the foetus.

Hormonal replacement therapy has not compensated for placental failure.

The placenta may degenerate because of poor diabetic control, because of acceleration of the placental life or because of adrenal corticosteroids.
The neonatal morbidity and mortality commonly result from pre-natal hypoxia. Hypoglycaemia plays no part in the cause of symptoms and the influence of low serum potassium and calcium levels has yet to be proved.

The treatment of the foetus is limited to resuscitation, continuous observation in a premature-room, the maintenance of a clear air-way and delay in instituting feeding. Uncomplicated cyanotic attacks respond to the stimulation of respiration. The dyspnoeic baby should be disturbed as little as possible. He may be given limited amounts of oxygen and complicating cyanotic attacks or dehydration may require special measures. Antibiotics should be used only where necessary and must be used efficiently.

However common excessive lactation may be in the pre-diabetic mother, breast feeding commonly fails in the established diabetic. To any possible maternal endocrine cause for this may be added many extrinsic factors which interfere with the feeding situation.

The incidence of important congenital malformations may be no higher among children born to diabetic women than it is among children of non-diabetic mothers.

Those infants whose neonatal course is uneventful are less likely than others to show later evidence of abnormality.

The heights and weights of children at various ages up to ten years differ very little from those of children born to non-diabetic mothers in the same city.
(23) The size of the baby at birth bears no consistent relationship to his or her later growth.

(24) None of the 88 babies who have survived the newborn period has so far developed clinical diabetes mellitus. None shows glycosuria after oral glucose loads. No steroid-glucose tolerance tests have been undertaken.

(25) These observations upon the child of the diabetic woman suggest that diabetes mellitus is associated with the over-production of various anterior pituitary secretions. Of these a growth-promoting hormone is the most consistently abnormal. Prolactin may be excessive in the pre-diabetic years and deficient once diabetes becomes established. A third hormone, responsible for placental degeneration and foetal death, may exist and may be a stimulant of the adrenal cortex.
SUMMARY

This thesis consists of personal observations made upon 96 children of diabetic women from their intra-uterine life up to the age of ten years, and of information about their mothers and their siblings.

The curious morphology shared by the infants of pre-diabetic and diabetic women includes foetal overgrowth, pancreatic islet hyperplasia, extramedullary haemopoiesis and possible adrenal enlargement. The principal autopsy finding in neonatal deaths is pulmonary hyaline membrane.

Animal experiments and the observations of others on these babies suggest that the morphology is due to an anterior pituitary disorder and to an excess of Pituitary Growth Hormone in particular. The personal observations in this series suggest that the morphology results from the action of a maternal diabetogenic growth factor, to which the influence of adrenal corticosteroids, and later of hyperglycaemia, may be added. Neither the growth factor nor the hyperglycaemia appear to be the principal causes of foetal death, but the latter probably contributes to it.

Failure of placental function is probably responsible for intra-uterine death, for interference with growth stimulation, and for the hypoxia which, with the perinatal circulatory changes, is responsible for much of the neonatal morbidity and mortality. The premature placental failure occurs in many, but not in all, pre-diabetic and diabetic women, and it may be caused by adrenal corticosteroids.

The /
The laboratory studies which form part of this thesis establish the normal range of the blood sugar level during each of the first ten days of life and prove that the hypoglycaemia, which occurs so commonly in infants of diabetic women, is not responsible for the neonatal clinical disturbance and that it does not cause irreversible cerebral damage. They also suggest that increased adrenocortical activity exists in the foetus.

Important congenital malformations occur no more commonly in these babies than they do in children of non-diabetic women, and no significant difference in growth or in the incidence of diabetes mellitus has been noted up to the age of ten years.

Further observations of such a group over a period of twenty years or more will probably be necessary before the risk of such children becoming diabetic can be fully assessed.
PART B

INDIVIDUAL ACCOUNTS OF SPECIAL STUDIES
STUDY I
THE POST-NATAL WEIGHT LOSS OF BABIES BORN TO
DIABETIC AND NON-DIABETIC WOMEN

The fact that babies of diabetic women are heavier as a group than those born at the same gestational age to non-diabetic women has been attributed in part to foetal oedema. Apart from their oedematous appearance, however, such infants are said to lose more weight in the immediate newborn period than babies of healthy women, and it has been concluded that this is the result of water loss. The object of this study is to review the evidence for a significant difference in post-natal weight loss between the babies of diabetic and non-diabetic mothers and to present the results of a comparative study of post-natal changes in weight with special reference to the type of "normal" babies used as controls.

The Problem.

Because the evidence in favour of foetal oedema is inconclusive, it was decided to examine in greater detail the post-natal weight loss of babies born to diabetic and non-diabetic women.

Most of the infants in the Edinburgh series, like those delivered in the hospitals from which both White and Cardell (Page 18) have published their papers, have been delivered by caesarean section. It was decided to compare the weight loss of the diabetic group not only with that of infants delivered spontaneously to non-diabetic women but also with that of babies born by caesarean section to non-diabetic women.
The diabetic group has been subdivided into two according to the feeding history. Between the years 1948 and 1951 most of these babies were fed early because of a fear that they might suffer from hypoglycaemia. When it became recognised that this was not harmful and that inhalation occurred rather easily on the first and second days, feeding was delayed in those infants born during the years 1952 to 1955.

Consideration has been given to the comparability of the groups and also to the environmental conditions in which the infants were nursed.

**Composition of the groups**

**A. Diabetic Mothers**

The infants of diabetic mothers delivered by caesarean section during the years 1948 - 55 are divided into two groups, one of which (A1) consists of 31 babies who were fed within the first 24 hours. The second group (A2) consists of 29 infants who were unfed until aged 72 hours.

**B. Non-Diabetic Mothers**

The infants of non-diabetic mothers are divided into two groups, one of which (B1) consists of 60 babies born by caesarean section to women who had not been in labour before operation. The second group (B2) consists of 60 babies born spontaneously by the vertex per vaginam. These two groups are matched with one another for maternal age and parity.

The mothers of infants in group B1 were delivered in the years 1948 - 49 and 1953 - 54. They had caesarean sections.
sections performed because of placenta praevia in almost half the cases, because of pregnancy toxaemia in less than one sixth and because of disproportion or previous uterine scar in the remainder. So that they might be compared in ways other than those mentioned in this study, as many as possible of the cases were of 36 to 38 weeks' gestation.

Infants in both groups B₁ and B₂ were fed during the first 24 hours. Those in group B₁ usually received a bottle whereas those in group B₂ were put to the breast. Infants were excluded from groups B₁ and B₂ if they died later during the newborn period or if they had lost blood, were pyrexial or had any congenital malformation, infection or gastro-intestinal disorder which was considered by the clinician to have a possible influence upon the weight behaviour.

Comparability of the groups

Sex, maternal age, social class (husband's occupation) parity, birth weight and maturity have all been shown to be relevant to birth weight. It was not known to what extent these would also affect weight loss but since they were readily available they were all taken into account. It was clearly impossible to match the groups according to all these criteria, but where possible maternal age and parity were selected for matching. (see footnote). These are accepted as being of fundamental importance in birth weight studies. The other characteristics are also presented for comparison.

* No relationship between the infants' weight loss and maternal age or parity was found by Naish & Edwards (1952) in their study of normal babies. It was decided, however, that for the better comparison of these abnormal and normal groups these two factors should be taken into account.
POST-NATAL WEIGHT LOSS OF BABIES AS A PERCENTAGE OF BIRTHWEIGHT
SHADING INDICATES ± ONE STANDARD DEVIATION ABOUT THE MEAN

BABIES OF DIABETIC MOTHERS
(CAESAREAN)

FED BABIES (31) GROUP A1

MEAN LOSS %

2 3 4 5 6 7 8 9 10 11 12 13 14

DAYS AFTER BIRTH

UNFED BABIES (29) GROUP A2

MEAN LOSS %

2 3 4 5 6 7 8 9 10 11 12 13 14

DAYS AFTER BIRTH

BABIES OF NON-DIABETIC MOTHERS

CAESAREAN DELIVERIES (60)
GROUP B1

MEAN LOSS %

2 3 4 5 6 7 8 9 10 11 12 13 14

DAYS AFTER BIRTH

SPONTANEOUS VAGINAL DELIVERIES (60)
GROUP B2

MEAN LOSS %

2 3 4 5 6 7 8 9 10 11 12 13 14

DAYS AFTER BIRTH

EXAMPLES OF THE VARIATION IN POST-NATAL WEIGHT LOSS IN THE
FOUR GROUPS

BABIES OF DIABETIC MOTHERS

FED BABIES (31) GROUP A1

25 20 15 10 5 0

MEAN LOSS %

2 4 6 8 10 12 14

DAYS AFTER BIRTH

UNFED BABIES (29) GROUP A2

25 20 15 10 5 0

MEAN LOSS %

2 4 6 8 10 12 14

DAYS AFTER BIRTH

BABIES OF NON-DIABETIC MOTHERS

CAESAREAN DELIVERIES (60)
GROUP B1

25 20 15 10 5 0

MEAN LOSS %

2 4 6 8 10 12 14

DAYS AFTER BIRTH

SPONTANEOUS VAGINAL DELIVERIES (60)
GROUP B2

25 20 15 10 5 0

MEAN LOSS %

2 4 6 8 10 12 14

DAYS AFTER BIRTH
A. The Diabetic Groups

Because these groups formed the consecutive halves of a naturally occurring series no previous matching according to the above criteria was possible. The two groups are evenly balanced for foetal sex, and there is no marked difference in parity. Group A2 contains rather more babies in higher social classes than group A1 (Figure 40). There are rather more of the heavier babies in Group A1 than in A2 because of the greater variability of birth weight in A1. There is also greater variation in the maturity of infants in group A1, so that the group contains relatively larger numbers of more mature infants than does group A2. The lower birth weight and lesser maturity of infants in group A2 reflects the adoption of a more rigid policy about caesarean section at the 36th - 37th week which was adopted about 1951.

B. The Non-Diabetic Groups.

The spontaneous deliveries (B2) were matched with the non-diabetic caesarean deliveries (B1) for maternal age and parity (Figure 40). The two groups are evenly balanced for foetal sex. Rather more of the infants in group B1 are of social classes IV and V. There is no marked difference in birth weight, but the babies in group B1 are distinctly less mature.

C. Diabetic and Non-Diabetic Groups

As a result of the comparative infrequency with which caesarean section is carried out prematurely in the non-diabetic woman, the number of babies available for inclusion in this group was rather limited, and it was found impossible to /
to match them for maternal age and parity with either diabetic group. Older women make up a greater proportion of the non-diabetic caesarean group (B₁) than in either A₁ or A₂, but there is less difference in parity. Birth weight is less scattered in the non-diabetic caesarean group (B₁) but the maturity is more evenly spread over the period 36 to 40 weeks than in the diabetic groups. It may be seen from Figure that the infants of group B₂ are clearly more mature than those of group B₁, which in turn are more mature than those of groups A₂ and A₁.

**Environmental Conditions During the Period of Measurement**

The babies of the diabetic groups were nursed nude in premature rooms at a temperature of 80°F. Those in group A₁ were moved to the main nursery after 2–3 days, and those in group A₂ graduated there on the fourth or fifth day. Only a small proportion of the babies in group B₁ (non-diabetic caesarean controls) was admitted to the premature rooms and then usually for no longer than 24 hours. Most of them were retained in the main nursery at an environmental temperature of 70°F and normal humidity. The babies of group B₂ (spontaneous deliveries) were admitted to the main nursery from the labour ward. In the nursery all infants wore a napkin and gown. They were rolled in a cotton sheet and woollen blanket and covered by another blanket and a light cotton coverlet.

**Method of Weighing**

All /
All the babies have been weighed naked on Avery scales which are tested regularly and which are accurate to \( \frac{1}{2} \) ounce (7.1 g.). They are weighed on arrival from the labour room and at the same hour each morning thereafter. The majority of babies in groups A₁, A₂, and B₁ were born in the forenoon by elective caesarean section. The beginning of the second day on the weight chart therefore corresponded to an age of about 22 hours. Unfortunately in group B₂ the actual age at the beginning of the second day on the chart ranged from 8 to about 30 hours. The retrospective nature of the study made this unavoidable. Weights were graphed on the infant charts and the plotting of the points was found to be accurate to about half an ounce (14.2 g.) when compared with the written record. The weights of the infants in group B₂ were recorded daily from birth. This applied also to the great majority of babies in group B₁. In groups A₁ and A₂, however, the weight records during the first 48 hours were incomplete at times as some infants were nursed with the minimum of disturbance, and others were attached to experimental apparatus the efficiency of which would have been prejudiced by movement or disconnection.

RESULTS

Criteria of weight changes.

In defining what is meant by weight changes the features to be considered are the time interval over which the/
POST-NATAL WEIGHT LOSS ON FOURTH DAY AS A PERCENTAGE IN RELATION TO BIRTHWEIGHT.

Babies of diabetic mothers (caesarean) fed babies (29)

Babies of non-diabetic mothers (caesarean deliveries) (60)

Unfed babies (31)

Spontaneous vaginal deliveries (50)

Comparison of the groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Maternal Social Parity</th>
<th>Birth Weight (100g)</th>
<th>Maturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fed babies of diabetic mothers (caesarean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfed babies of diabetic mothers (caesarean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic caesarean controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal spontaneous vaginal deliveries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N.S. = NOT STATED
the alteration occurs and the weight change in either absolute or relative terms. In this paper the relative weight loss each day is expressed as a percentage of birth weight.

**Percentage weight loss in relation to birth weight.**

The relationship between percentage weight loss and birth weight has been examined for several of the days after birth. No association was discovered on any of these days, and Figure illustrates this lack of any relationship on the fourth day in all of the four groups. The variability of % weight loss changes with age. It is least at the 3rd, or 4th. day after birth and increases thereafter.

**Method of presentation.**

The individual weight record of each infant in the four groups has been studied and examples of the variability of individual weight changes within each group are shown in Figure 38. The main results, however, are presented as group averages with standard deviations (Figure 37).

**Group differences in the pattern of weight change. (Figure37)**

(a) A significant difference in the pattern of weight change clearly exists between the two diabetic sub-groups. The unfed group (A₂) loses more weight than the fed group (A₁) and the rate of regain may be a little more rapid during the period up to fourteen days.

(b) There were no significant differences in the trend of mean % weight changes between the fed diabetic caesarean group (A₁) and the non-diabetic caesarean group (B₁). The statistical significance of the differences between the means for /
for each day after birth was assessed by the "F" test. In no case did the magnitude of the observed difference correspond with a probability of less than 1 in 5 (p < 0.02) of occurrence by chance in random sampling from a common population.

Although the % weight losses of the non-diabetic caesarean group were slightly more variable than those of the fed diabetic group, there was no significant difference in their respective variability up to the 11th day as assessed by Fisher's "F" test (Snedecor, 1956).

(c) A significant difference in the pattern of weight change clearly exists between those of all the caesarean groups (A1, A2, and B1) and that of the spontaneous group (B2). The latter loses less weight, and an earlier and more rapid regain of weight occurs.

**DISCUSSION**

The newly born infant of the diabetic woman commonly has a puffy, sometimes even a bloated, appearance which he loses during the first week of life. This puffiness has been attributed to oedema partly because it "looks like oedema", partly because it changes so quickly, but mostly because pitting oedema has been demonstrated in some cases. The shedding of this fluid has been taken as the explanation of the apparent excessive post-natal weight loss. As we have stated already the babies were found by White (1952) to have pitting oedema and yet the same infants were found by Gellis /
Gellis (1954) to have non-pitting oedema. Neither author mentioned any exception. Oedema was accepted as the explanation of the appearance of such infants by the clinician in the Edinburgh series of over 100 cases. The baby charts appeared to show abnormal post-natal weight losses, but pitting oedema was rare and "occult oedema" was assumed in the majority. In the second half of 1957 not one of ten such babies showed convincing pitting oedema although most of them were described as "puffy" or "flabby". The largest of these weighed 5.0 kilos when delivered at the 36th. week of gestation. He was stated by a midwife to have shown pitting oedema at birth but when examined at three hours by one of us no evidence of it could be found. The greatest percentage weight loss of the ten occurred in a baby who had shown no pitting oedema at birth and in whom even the characteristic puffy appearance was missing.

Direct measurement of the urine volume during the first 48 hours of life, however, showed that a group of babies born to diabetic mothers passed an average of only 60 ml. more urine than more mature infants born to non-diabetic mothers, and by the third day the urine volumes of the two groups were similar (Page 295). Although this did in fact mean that the infants of the diabetic group passed three times as much urine on average than those of the non-diabetic group, such a difference would add comparatively little to the weight loss of infants in the diabetic group. Unless such babies lose relatively greater amounts of fluid from the skin, the lungs or the bowel, and no evidence of this has been reported, then /
then some other explanation of their reported greater weight loss must be sought. In the first place the criteria and the consistency of weight loss should be examined.

The Criteria and Consistency of Weight Loss.

When it is remembered that the birth weights of infants born to diabetic women are often above average than it is clear that if their weight loss is to be compared in terms of absolute weight with that of infants born to non-diabetic women then the birth weights of the two groups must be given. This was not done by White (1952) who gave only the average absolute weight loss of the two groups. A proper comparison can be made only when the weight loss of each infant in the groups is expressed on each day as a percentage of birth weight. Although Cardell (1953a) did express the weight losses of his diabetic and control groups in such relative terms he did not specify what he meant by weight loss. He probably did not take the amount of weight lost over a fixed time interval, such as from birth to the fourth day, and it may be assumed that he selected the maximum amount of weight lost irrespective of the time interval. A study of individual weight patterns in the present groups, however, has shown how difficult the selection of "the point of maximum weight loss" may be. Quite commonly the regain of weight which follows the initial loss is interrupted by a further fall in weight which may be the result of inadequate feeding, infection or some unrecognised factor. The present paper shows the variability of individual weight patterns but the means and standard deviations for each day and for each group.
group have also been calculated and compared.

The Comparability of Diabetic and Control Groups.

The control cases recorded by both White and Cardell were born spontaneously and were usually some weeks more mature than their infants in the diabetic groups, most of which were delivered by caesarean section. The possible influence of maternal age and parity was not considered in either. For these reasons their control cases were imperfect and it was decided that in the present investigation the diabetic groups would be compared with two groups of infants, one of which had been delivered spontaneously, and the other by caesarean section, to non-diabetic mothers. Lack of knowledge about the exact age in hours of the present vaginal delivery group at the time of weighing probably makes very little difference to the group's general pattern of weight loss. The retrospective study of Naish and Edwards (1952) suffers from the same defect. The average weight loss increases to 6.7% of birth weight by the fourth day and from then steady regain of weight occurs. The pattern is similar to that described by Gregory (1871), Holmes (1896), Griffith and Gittings (1907) and Kotz and Kaufman (1939), and it is quite different from that of any of the caesarean section groups.

If the percentage of birth weight lost were to increase as birth weight increases then group comparison of relative loss would be possible only if the groups were evenly matched with regard to birth weight. For this reason the relationship /
ship of birth weight to the percentage of birth weight lost was studied for each of the present groups and no correlation whatsoever was found. This finding opposes that of Griffith and Gittings (1907) but confirms that of Naish and Edwards (1952) with regard to vaginal deliveries and extends the observation to infants delivered by caesarean section either to diabetic or non-diabetic mothers.

Delayed feeding.

The influence of delayed feeding upon the weight of the newborn baby has been studied by Griffith and Gittings (1907) and by Rott (1910). They demonstrated that the less fluid an infant receives during the first three days the more weight he will lose. The giving or withholding of extra fluid before lactation was established was believed to have been responsible for either an increase or a decrease respectively in the weight loss of infants studied by Naish and Edwards (1952) and the time of the first feed was found by Salber and Bradshaw (1954) to influence subsequent weight behaviour. The withholding of fluids until after 72 hours in group A2 was expected to influence weight loss and the likelihood of this was increased by the high environmental temperatures in which these babies were nursed. This group did in fact lose more weight than group than group A1, the infants of which received fluids on the first day and were moved to a cooler nursery after twenty-four hours. Infants which have been dehydrated by simple water deprivation will regain weight quickly when fluids are given and this may explain why group A2 /
A2 regains weight a little more rapidly than group A1.

**Foetal Maturity.**

Although the greater weight loss and slower weight regain of group B₁ when compared with group B₂ is associated with the lesser maturity of group B₁, the slightly greater maturity of group B₁ when compared with group A₂ is not associated with a similar difference in group pattern of weight loss. The small immature baby is said by Smith (1951) to lose a greater percentage of its birth weight than the mature infant, because the less mature the baby and the lower his birth weight the longer will feeding be deferred. The present study strongly suggests that deferred feeding and possibly environmental temperature exert a considerable influence on weight loss. There is no clear indication that differences in maturity alone explain the wide differences between the two non-diabetic groups, but if there is an association between maturity and the pattern of weight loss in the non-diabetic groups then this clearly does not extend to the diabetic groups.

**Route of delivery.**

The post-natal weight loss of infants delivered either spontaneously or by caesarean section to non-diabetic women has been studied by Furuhjelm (1954). He subdivided his caesarean section group into those women who had been in labour before operation and those who had not. When he compared his three groups he found that the mean weight loss of
of all three was equal by the third day, when it constituted about 7.2% of birth weight. This corresponds closely to the behaviour of the two non-diabetic groups in the present paper. After the third day Furuhjelm's vaginal deliveries no longer lost weight, but both caesarean section groups continued to lose weight for two more days. The group of infants who had been born by caesarean section to labouring women then began to gain weight parallel to the vaginal group. The group of infants who had been born by caesarean section to non-labouring women, however, gained weight much more slowly. This also corresponds to the behaviour of the two closely matched non-diabetic groups in the present paper.

CONCLUSIONS

Had the present study been concerned only with a comparison of the post-natal weight loss of babies born by caesarean section to diabetic women and those delivered spontaneously to non-diabetic women, then agreement would have been achieved with White and with Cardell. The conclusion that the greater weight loss of the diabetic group was the result of shedding oedema would probably have been reached. The inclusion of a non-diabetic caesarean section group and the effort made to match this with the vaginal group and to consider the other factors previously mentioned have altered the picture completely. No evidence has been found to confirm the belief that infants born by caesarean section to comparable groups of diabetic and non-diabetic mothers /
mothers differ significantly in their post-natal weight patterns. It cannot be said, therefore, that the excessive weight loss of infants born to diabetic women is evidence of their having been oedematous.

No explanation is offered for the striking difference in post-natal weight between babies delivered by caesarean section to non-labouring women and those delivered after normal labour.

It is true that lactation is established more slowly in the woman delivered by caesarean section, and during the waiting period complementary feeds may be kept small in order that the infant's hunger might act as a stimulus to the breast.

The process of labour was considered by Furuhjelm to be responsible for the differences in weight pattern between caesarean and spontaneous groups, but the underlying condition for which caesarean section is performed may be responsible. Furuhjelm failed to specify why the caesarean sections were carried out on his patients, but if this were the explanation then, in the present study, diabetes mellitus would appear to have no greater influence on the post-natal weight of the foetus than placenta praevia, disproportion or previous uterine scar, which were the principal reasons for section in the control caesarean group.

When ligature of the cord is delayed until the placenta is expelled the infant receives considerably more placental blood. According to Zweifel (1898) such babies lose less weight /
weight post-natally than those whose cords were cut immediately after delivery. The cord is of course likely to be clamped more rapidly after delivery by caesarean section than by the vagina, but Zweifel compared absolute weight losses, and his comparisons may not be valid.

Further studies will be required to explain this difference in weight behaviour, and in these the reason for caesarean section, the nature of the labour, the time allowed to elapse before the cord is clamped, the maturity of the child and the details of feeding should be examined with greater care than has been possible in a retrospective study.

SUMMARY

The abnormal heaviness of infants born to diabetic women has been ascribed in part to oedema.

The evidence in favour of the claims that because of this such infants lose more weight than normal babies in the post-natal period has been reviewed. Because of differences in the criteria of weight loss and in the management of the newborn and because of the faulty construction of control groups this evidence has been found inconclusive.

The weight loss of babies delivered by caesarean section to diabetic women has been compared closely with that of babies similarly delivered to non-diabetic women and with babies born spontaneously to non-diabetic women.

When infants of diabetic women are subjected to prolonged fluid deprivation they lose more weight than when fluids are given early and more weight than infants of non-diabetic women.
women by whichever route these have been delivered.

Infants of diabetic and non-diabetic women delivered by caesarean section lose similar amounts of weight when nursed under similar conditions.

Infants delivered by caesarean section to diabetic or non-diabetic women lose more weight over a longer period than infants delivered spontaneously to non-diabetic women. They also regain weight more slowly.
The intention of this study is to compare the results of breast feeding in groups of diabetic and non-diabetic mothers.

Method

Because lactation is delayed and in some cases deficient after caesarean section, the diabetic mothers were compared with a group of non-diabetic women delivered in this way. This group has been described in Study 1, page 129.

The maternal and infant records were examined in each case and augmented, wherever possible, from the register of the sister-in-charge of the breast feeding clinic. In the case of non-diabetic women, the incidence of breast feeding at hospital discharge only was considered. Diabetic women were followed further. Where they had not reported in the months after delivery at either the post-natal or infant welfare clinics of the Simpson Memorial Maternity Pavilion, the further breast feeding history was obtained either from them by personal questioning or from the dietetic out-patient department at which their diabetes was supervised.

RESULTS

Fifty per cent. of the non-diabetic group were breast feeding wholly and a further 17 per cent. were partially successful.
successful at the time of hospital discharge. In contrast only 17 per cent. of the diabetic group were breast feeding wholly at two weeks and a further 7 per cent. were partially successful.

Analysis of the reasons either for not attempting breast feeding or for abandoning it are given in Table 5.

**COMMENT**

Considerably more than half of the diabetic women in this series either abandoned breast feeding in the first two weeks, or less commonly no attempt was made. A further large group failed during the first 4 to 6 weeks. Some succeeded in fully or partly breast feeding until the baby was weaned at 4-6 months.

Although the incidence of breast feeding at hospital discharge was lower than in non-diabetic women delivered by caesarean section there is evidence that this does not result from a pituitary disorder alone but from medical or obstetrical problems of the puerperium and from an appreciation that breast feeding is no longer a matter of primary importance.
# Table 5

## Feeding Record of 88 Surviving Babies of Diabetic Women

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Duration</th>
<th>Analysis of Reasons for Failure or Interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Feeding Not Attempted</td>
<td>6</td>
<td>-</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Previous failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal refusal</td>
</tr>
<tr>
<td>Breast Feeding Abandoned in First 7-10 Days</td>
<td>51</td>
<td></td>
<td>Inadequate lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Puerperal infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal non-infective illness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prematurity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refusal to fix</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor sucking</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Illness of baby</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mongolism</td>
</tr>
<tr>
<td>Breast Feeding Only</td>
<td>17</td>
<td></td>
<td>Maternal refusal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inadequate lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mother &quot;too busy&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failing lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Husband's advice</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failing lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insulin reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failing lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast abscess</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast abscess</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weaning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(abundant lactation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Feeding With Complement</td>
<td>10</td>
<td></td>
<td>Inadequate lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disinterest in breast</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failing lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medical advice (reason unknown)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failing lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&quot;Crying baby&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failing lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Failing lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete Information</td>
<td>4</td>
<td></td>
<td>Three were fully and one was partly breast fed</td>
</tr>
<tr>
<td>(contact lost because of death of mother or</td>
<td></td>
<td></td>
<td>at the time of hospital discharge.</td>
</tr>
<tr>
<td>child, or because of emigration or adoption)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
STUDY 3

A COMPARISON OF THE MORTALITY AND MORBIDITY IN GROUPS
OF INFANTS DELIVERED BY CAESAREAN SECTION TO DIABETIC
AND NON-DIABETIC WOMEN.

Intention

The intention of this study is to compare the mortality
and morbidity in groups of infants delivered by caesarean
section to diabetic and non-diabetic women in order to dis-
cover if the mode of delivery is responsible for neonatal
clinical disturbance.

Method

A non-diabetic group was obtained by scrutinising the
238 case records of all women subjected to elective caesarean
section during the four years 1948, 1949, 1953 and 1954.
None of the women had been in established labour, although
nine of those with placenta praevia had had some ante-partum
bleeding. Because the majority of women in the diabetic
group were delivered electively somewhere between the 35th.
and 38th. weeks of gestation (Table 6), only 57 non-dia-
betic pregnancies of comparable gestation were found.
(Table 7).

Table /
**TABLE 6**

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>41</td>
<td>1</td>
</tr>
</tbody>
</table>
## TABLE 7

**Gestation of non-diabetic group**

<table>
<thead>
<tr>
<th>Year</th>
<th>28</th>
<th>30</th>
<th>32</th>
<th>34</th>
<th>36</th>
<th>38</th>
<th>40</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>1948</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>1949</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1953</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>1954</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
**TABLE 8**

**REASONS FOR CAESAREAN SECTION IN NON-DIABETIC GROUP**

<table>
<thead>
<tr>
<th>Reason for caesarean section</th>
<th>No. of babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta praevia.</td>
<td>24</td>
</tr>
<tr>
<td>Contracted pelvis (disproportion).</td>
<td>10</td>
</tr>
<tr>
<td>Bad obstetric history.</td>
<td>7</td>
</tr>
<tr>
<td>Toxaemia of pregnancy.</td>
<td>8</td>
</tr>
<tr>
<td>Elderly</td>
<td>2</td>
</tr>
<tr>
<td>Previous uterine scar</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Previous ectopic pregnancy and aortic embolism.</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total:** 57
The reasons for abdominal delivery of the non-diabetic group are provided in Table 8. and they indicate that these babies were subjected to a number of hazards unrelated to diabetes mellitus.

RESULTS

Sixty-nine live infants resulted from the caesarean section of 69 diabetic women. Five of them died (Table 9), 10 suffered from dyspnoea and a further 15 from cyanotic attacks. Two of the dyspnoeic babies also had cyanotic attacks.

Fifty-seven live infants resulted from the caesarean section of 57 non-diabetic women. Three of them died (Table 9), 2 suffered from dyspnoea but cyanotic attacks were observed in none.

As the aim of this comparative study, however, is to determine the relationship, if any, between the mode of delivery and the foetal morbidity and mortality, the deaths due to Kernicterus complicating erythroblastosis foetalis and exsanguination complicating ante-partum separation of the placenta may be excluded. The third death was of a 3 lb. infant who developed mild costal recession within the first six hours, but who remained reasonably well. She was found dead in her cot on the fourth day and at autopsy, she had pulmonary hyaline membrane with atelectasis and some bilateral pulmonary haemorrhage.

The clinical courses of the 2 dyspnoeic infants in the non-diabetic group were as follows -

Case D.1074 /
### TABLE 9

**INFANTS DELIVERED BY CAESAREAN SECTION AT 35 - 38 WEEKS GESTATION**  
(WOMEN NOT IN LABOUR)

<table>
<thead>
<tr>
<th></th>
<th>TO NON-DIABETICS</th>
<th>TO DIABETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1948 - 49</td>
<td>1953 - 54</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>57</td>
<td>69</td>
</tr>
<tr>
<td><strong>Abnormal</strong></td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Haemolytic disease, kernicterus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Exsanguination (A.P.H.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 3. Pulmonary haemorrhage  
Hyaline membrane  
(Birth weight 3 lbs.) |              |              |              |
| **Abnormal but survived** |              |              |              |
| 1. Dyspnoea (2 cases) |                  |              |              |
| **Deaths**           |                  |              |              |
| 1. Pneumonia         |                  |              |              |
| 2. Hyaline membrane  |                  |              |              |
| 3. Asphyxia          |                  |              |              |
| 4. Massive cerebral haemorrhage |              |              |              |
| 5. Renal thrombosis  |                  |              |              |
| **Abnormal but survived** |              |              |              |
| 1. Dyspnoea (10 cases) |                  |              |              |
| 2. Cyanotic attacks (15 cases) |              |              |              |
CASE D.1074  B.W. 2495 grammes. gestation 36 weeks.
Whining expiration with costal indrawing and poor air entry were noted from birth. The baby was not cyanosed and a diagnosis of partial atelectasis or mild pulmonary hyaline membrane was made.

CASE E.6178  B.W. 3204 grammes.
The mother was an elderly primipara with hypertension. The infant's respiration was easily established within two minutes. He had two cyanotic attacks on the first day and was nursed in oxygen. On the second day his respiration was irregular and the baby became cyanosed out of oxygen. Slight costal recession was present and the presence of moist sounds was suspected at the left base. No antibiotic was given. On the third day the baby still developed deep cyanosis out of oxygen but the chest seemed clear of signs and congenital heart disease was suspected. Tube feeding was begun and a portable x-ray showed some doubtful atelectasis. He gradually improved and on the seventh day he was feeding well and was acyanotic out of oxygen. At the age of thirteen months he was walking and no cardiac or respiratory abnormality could be found.

The two groups have been compared on Figure 22.

Page 76. The two deaths mentioned above have been omitted from the non-diabetic group so that its total is given as 55. The mortality is certainly higher in the diabetic group and the surviving babies are much more frequently troubled with dyspnoea than those of the non-diabetic group (15.6% v 3.7%). The absence of minute-to-minute observation of all members of the non-diabetic group makes it impossible to be certain that any true difference exists in the incidence of cyanotic attacks.
STUDY 4

THE BLOOD SUGAR LEVEL OF THE NORMAL NEWBORN BABY

The normal plasma chemistry values for adults are not necessarily the same for newborn infants (Fraser, M.S., 1956, (in Ellis 2nd. ed. Child Health & Develop.)

The blood sugar illustrates such a difference very well because, not only does the normal range differ from that of adults, but it varies from hour to hour on the first day and, later, from day to day. Furthermore, there is a tendency toward an upward trend in the level from birth to the tenth day.

In most of the earlier studies (Table 10) single analyses were carried out on the blood of infants whose ages ranged from a few hours to several weeks. In 1913, however, Gotsky showed that the mean blood sugar level of a small group of newborn babies varied from day to day. More detailed studies, from about 1920 onwards (Table 11), confirmed this variation in the group mean and most of them indicated that, after an initial fall during the first 48 to 72 hours there is a gradual rise. To these may be added the papers of Hartmann & Jaudon (1937) and Pedersen (1952), which although agreeing in principle with the others, are unsuitable for tabulation. A smaller number of more recent papers has provided information about the blood sugar level on the first day of life (Table 12). Most of these deal with serial levels in the same groups of babies but the hours at /
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Fasting Period (in hours)</th>
<th>No. of babies</th>
<th>Age of babies</th>
<th>Blood sugar value mg.%</th>
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<tbody>
<tr>
<td>Coblinger</td>
<td>1911</td>
<td>Frank</td>
<td>-</td>
<td>9 - 21 days</td>
<td>Mean 85 Min. 70 Max. 98.5</td>
</tr>
<tr>
<td>Mogwitz</td>
<td>1914</td>
<td>Bang (triplicate)</td>
<td>24 - 4</td>
<td>7 hrs. - wks. Only 3 were less than 11 days old.</td>
<td></td>
</tr>
<tr>
<td>Cannata</td>
<td>1917</td>
<td>Lewis - Benedict Bass</td>
<td>From birth</td>
<td>First 24 hours</td>
<td>77.9 10 98</td>
</tr>
<tr>
<td>Nysten</td>
<td>1921</td>
<td>Bang</td>
<td>-</td>
<td>1 - 5 days</td>
<td>100.0</td>
</tr>
<tr>
<td>Brown</td>
<td>1925</td>
<td>Maclean</td>
<td>3 - 4</td>
<td>First two wks.</td>
<td>87.0 72 97.0</td>
</tr>
<tr>
<td>Svensgaard</td>
<td>1926</td>
<td>Hagedorn - Jensen</td>
<td>5 - 5½</td>
<td>4 - 14 days</td>
<td>83.0 66 99</td>
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<tr>
<td>Bentivoglio</td>
<td>1926</td>
<td>Bang</td>
<td>4</td>
<td>Marious ages</td>
<td>75 100</td>
</tr>
<tr>
<td>Schiff and Choremis</td>
<td>1926</td>
<td>Hagedorn - Jensen</td>
<td>24</td>
<td>First four</td>
<td>90.0</td>
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<tr>
<td>Haass</td>
<td>1931</td>
<td>Hagedorn - Jensen</td>
<td>-</td>
<td>Prematures 24 hours to 14 days.</td>
<td>79 95.0</td>
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<tr>
<td>Kohler</td>
<td>1932</td>
<td>From birth</td>
<td>31</td>
<td>First 24 hrs.</td>
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<tr>
<td>Miller and Ross</td>
<td>1938</td>
<td>Folin and Malmros</td>
<td>-</td>
<td>First 48 hrs.</td>
<td>50.0 13</td>
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<tr>
<td>Ketteringham and Austin</td>
<td>1938</td>
<td>Jeghers - Myers Folin and Malmros</td>
<td>3½ - 4</td>
<td>Prematures in first 48 hrs.</td>
<td>32.0 12</td>
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Single analyses in all cases means no information available. S.D. means standard deviation.
### TABLE 11
BLOOD SUGAR LEVELS AT AGES ONE TO TEN DAYS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Method</th>
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<tr>
<td>Gotsky</td>
<td>1913</td>
<td>Bang duplicates</td>
<td>$\frac{1}{2} - 4$</td>
<td>Variable 1-5 on each day</td>
<td></td>
<td>72</td>
<td>83</td>
<td>78</td>
<td>85</td>
<td>99</td>
<td>102</td>
<td>88</td>
<td>83</td>
<td>77</td>
<td>86</td>
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<tr>
<td>Sedgwick and Ziegler</td>
<td>1920</td>
<td>Folin</td>
<td>-</td>
<td>Variable 1-11 on each day</td>
<td>Certainly not serial levels as on group.</td>
<td>-</td>
<td>-</td>
<td>70</td>
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<td>90</td>
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<tr>
<td>Lucas et al</td>
<td>1921</td>
<td>Folin</td>
<td>4</td>
<td></td>
<td></td>
<td>Mean 66</td>
<td>51</td>
<td>68</td>
<td>82</td>
<td>64</td>
<td>78</td>
<td>77</td>
<td>85</td>
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<td>77</td>
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<td>Shermann et al</td>
<td>1925</td>
<td>Folin &amp; Wu</td>
<td>-</td>
<td>23</td>
<td></td>
<td>Mean 115.4</td>
<td>97.7</td>
<td>98.7</td>
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<td>Martinolli</td>
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<td></td>
<td>Mean 67.5</td>
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<td>94</td>
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<td>70.3</td>
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<td>Jegas &amp; Myers &amp; Polio-Mähros</td>
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<td></td>
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<td>boys</td>
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<td>120</td>
<td>105</td>
<td>114</td>
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<td>6</td>
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<td>15</td>
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<td>68.3</td>
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<td>1950</td>
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<td>2-3</td>
<td>33</td>
<td>premature babies.</td>
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<td>55.2</td>
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<td>58.5</td>
<td>65.0</td>
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<td>65.6</td>
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<td>Hagedon- Jansen</td>
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<td>35</td>
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<tr>
<td>Hanley and Horn</td>
<td>1943</td>
<td>Jeghers- Myers of Folin &amp; Malmros</td>
<td>From birth</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Peas et al</td>
<td>1950</td>
<td>Shaffer- Hartmann</td>
<td>From birth</td>
<td>19</td>
<td>115.5 80.3 77.3</td>
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<tr>
<td>Ward</td>
<td>1953</td>
<td></td>
<td>From birth</td>
<td></td>
<td>Prematures 47.4</td>
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<td>Creery &amp; Parkinson</td>
<td>1953</td>
<td>King &amp; Garner</td>
<td>3 hours</td>
<td></td>
<td>79.6 50.7 52.4 55.5 55.5 51.8 51.8</td>
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<tr>
<td>Konrower</td>
<td>1954</td>
<td>Haslewood &amp; Strockman</td>
<td>From birth</td>
<td>21</td>
<td>98 92 83 76 72 90</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
at which samples were taken vary widely. A downward trend is apparent in all. The lowest group mean level is usually achieved at about six hours and, in the experience of Reis et al (1950) and Creery and Parkinson (1953) it remains there until twelve hours. Komrower (1954) on the other hand found the lowest level at six hours and a significant rise by twelve hours.

Criticism of previous studies.

Among these investigations very few have been concerned with the serial blood sugar levels of large groups of infants both during the early hours of life and on succeeding days. The best of them (Pedersen, 1952a; Creery and Parkinson, 1953 & Komrower, 1954) deal only with the first neonatal day. Norval's otherwise sound study failed to appreciate that changes might occur during the first few hours while Reis et al, in an otherwise comprehensive investigation made no reference to the accuracy of the chemical method and described their results only in group, and not at all in individual, terms. Of those who have followed serial levels, Mckittrick regarded $3\frac{1}{2}$ hours as a satisfactory fasting period, Norval accepted 4 hours and Reis et al did not mention the duration of the fast. None of these studies has taken a fast which would be acceptable at any other age, the reason probably being an unwillingness to interfere with the infant's feeding routine.

Economy in blood is essential in small babies and this has /
has led to single specimens only being analysed. Very little contamination or deterioration of reagents introduces quite wide errors and duplicate specimens are, therefore, more reliable. It is true also that the scrupulous conditions applied to testing a method's accuracy may not always be employed in later use. Wooton and King (1953) have shown how scattered the results on a known glucose solution may be when analysed in different laboratories. The Folin and Wu copper method, and its many modifications, can certainly be troublesome in relatively inexperienced hands and it has been a source of irritation even to biochemists (see Appendix 3). Many of the investigators of neonatal sugar levels have relied, however, on single determinations by this method. Skilful handling of an accurate method is obviously essential to any investigation. Pedersen comments upon the "staggering range" of the blood sugar in a large series published by Zondek and Wolfschon (1951) and states that their report indicates that the technical difficulties of taking blood samples from newborn infants had not been overcome.

**Intention**

The intention of this study was to determine the behaviour of the blood sugar level during the first six hours of life and on the succeeding ten days.

**Method**

The infants studied were born spontaneously after normal /
normal pregnancy, pethidine and gas and air being the only analgesics. All were over 5\(\frac{1}{2}\) lb. birth weight and breathed within two minutes. Their course in hospital was uncomplicated and no congenital abnormalities were present.

All specimens were taken personally at 5.30 a.m. in order to avoid disturbing the feeding routine which would have been occasioned had specimens been taken later. The infants had fasted eight hours. Glucose determinations were made personally in duplicate by the method of Ramsay (Appendix 3).

In this study, the accuracy of the method was tested before beginning the investigation, and was found to be extremely good. Three sets of 12 readings (six duplicate analyses) at various known concentrations of glucose were analysed; the result gave a very small scatter even in the very dilute solution (25 mg.\%). The highest scatter in any set of 12 gave a standard deviation of only 1.8\% of the mean. The same standard of accuracy was maintained throughout the investigation, frequent checks being made against glucose standards, and duplicate analyses of the blood specimens were made throughout in order to reduce possible error. Occasionally specimens were lost due to breakage or error while toward the tenth day some cases were lost from the series owing to premature discharge from hospital.

The blood sugar was determined at birth, half-hourly until two hours and then two-hourly till six hours. Thereafter it was determined daily until the tenth day.

RESULTS /
Figure 41

SERIAL BLOOD SUGAR LEVELS
OF 32 NORMAL FULL TERM NEWBORN INFANTS

x = males

o = females
RESULTS

At each day. The average values for blood sugar readings were studied in various ways. The average values, standard deviations and coefficients of variation were calculated for each time unit (Table 49).

Taking the immediate birth period first it may be seen from the time-trend diagrams (Figure 41) and from (Table 13) that the mean blood sugar level for the group as a whole fell rapidly during the first two hours of life and that this was arrested before a similar period of time had elapsed:

that is, the average blood sugar for the group fell by 11.2 mg. in the first two hours, by 1.1 mg. in the following two hours and by 0.1 mg. only in the next two hours.

In the next period, from the second to tenth days, the mean blood sugar level for the group as a whole increased steadily from 65.5 mg.% on the second to 82.7 mg.% on the ninth and 81.3 mg.% on the tenth day.

Mean values cannot be taken as adequate descriptions and in this series the scatter of values around the group mean at any time unit was great. This can be seen both from the time-trend diagram which illustrates also the daily scatter of the actual observations, and from the coefficients of variation in Table 49. The coefficient of variation (= S.D./mean expressed as a percentage) rose from 19% to 29% in the first hour and settled with some fluctuations thereafter to 12%. This is a high coefficient of variation.

Day-to-day Mean Increments. Although the scatter of actual /
actual values on individual days decreased slightly suggesting stabilization, the actual scatter of increments of individual infants from day to day did not decrease.

**The Individual Child**

Although the trend of the group mean suggests that the blood sugar level rises gradually from the third day the serial levels of individual babies show considerable day to day variations (Table 13, Figure 56, p. 237).

The common trend, however, is toward a rising sugar level. Scatter diagrams, not reproduced here, failed to show a relationship between birth weight and the foetal blood sugar level at birth.

**COMMENT AND SUMMARY**

Previous work on the neonatal blood sugar levels is open to some criticism but it was confirmed that the variation between individuals at any time unit was wide and also that considerable variation occurred in individual infants at each time interval.

This scatter of individual values at any time unit was so great as to render the arithmetic mean of the group valueless as representing the behaviour of individuals.

The blood sugar level tended to fall fairly rapidly in the first hours after birth but was stabilised by about four hours.

An upward trend in blood sugar values over the 10-day period occurred in the majority.

From scatter diagrams, not reproduced here, there was no /
# Table 13 (a)

**Individual Pattern of Movement of the Blood Sugar (mg.%)**

*In 32 Normal Infants Born to Non-Diabetic Women From Birth to 6 Hours*

<table>
<thead>
<tr>
<th>No.</th>
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<th>½</th>
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<th>4</th>
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**Note:** The table continues with similar data for each column, representing individual patterns of movement of the blood sugar (mg%) in 32 normal infants born to non-diabetic women from 2 to 10 days.
no correlation between body weight and the blood sugar level.

The importance of selecting a long fasting period, as used in this study, has become more apparent from the work of Cornblath, Levin & Gordon (1956) who have shown that capillary blood sugar levels in the newborn are related to the capillary-venous differences under fasting conditions only.
STUDY 5

THE BLOOD SUGAR LEVEL OF NEWBORN INFANTS
OF DIABETIC WOMEN

Intention

The intention of this study is to determine the range of the blood sugar level during the first ten days of life in babies of diabetic women.

Method

The blood sugar level of 17 consecutive live-born infants was determined at birth and then at the same time-intervals as in the normal group (Study 4. Page 158). The two investigations ran concurrently and the same chemical method was used with the same accuracy in both. The daily blood samples were taken at 5.30 a.m. after a fasting period of 8 hours and they were analysed in duplicate.

RESULTS

The individual results for the first six hours of life are given in Table 14. and those for the second to ninth days appear in Table 15. The individual graphs are shown in Figure 58. (Page 243). The scatter of values is greater on the first than on other days and the range becomes less as the infants grow older (figure 42). It is clear, however, that the pattern of movement is quite different from that in the normal group and that a characteristic fall in the blood sugar /
## Table 14

### Individual Patterns of Movement of the Blood Sugar (mg.
%)

**In 17 Infants Born to Diabetic Women from Birth to 6 Hours**

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### Table 15

**Individual Patterns of Movement of the Blood Sugar (mg%) in 16 Infants Born to Diabetic Women from Second to Tenth Days**

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<td>53.01</td>
<td>55.58</td>
<td>63.81</td>
<td>69.98</td>
<td>72.42</td>
<td>76.48</td>
<td>75.7</td>
<td>80.48</td>
</tr>
<tr>
<td>S.D.</td>
<td></td>
<td>12</td>
<td>12.7</td>
<td>12.1</td>
<td>11.4</td>
<td>9.7</td>
<td>4.8</td>
<td>5.2</td>
<td>4.2</td>
<td>6.1</td>
</tr>
</tbody>
</table>
Figure 42

SERIAL BLOOD SUGAR LEVELS OF
17 NEWBORN INFANTS OF DIABETIC WOMEN

SERIAL BLOOD SUGAR LEVELS OF
17 NEWBORN INFANTS OF DIABETIC WOMEN
RELATIONSHIP BETWEEN BIRTH WEIGHT OF INFANTS BORN TO DIABETIC WOMEN AND THE LOWEST BLOOD SUGAR IN FIRST SIX HOURS.

![Graph showing the relationship between birth weight of infants born to diabetic women and the lowest blood sugar in first six hours.](image-url)
sugar occurs. The latter begins at birth and it is maximum at one to two hours after delivery. In all these babies except in Case 84 (who died at 16 hours) the blood sugar was rising again from four hours after birth and it remained fairly stable thereafter. The difference in the behaviour of the two groups, taken as a whole, is fairly accurately reflected in the arithmetic means of the groups at each time interval (Figure 28, Page 87).

No relationship has been found between the lowest post-natal blood sugar level and the birth weight of the babies.

**Comment**

The literature contains many references to the blood sugar levels during the first day of infants born to diabetic women. Most of them are concerned only with one or two determinations in single cases and they were published at a time when the normal neonatal blood sugar range on the first day of life was unknown. The first important study was conducted by Hartmann, & Jaudon, (1937) They investigated about 8 infants and 12 controls. Duplicate blood analyses were carried out by the Shaffer-Hartmann or the Shaffer-Somogyi methods. Unfortunately they did not tabulate the results and their composite graphs are so obscured by crossing lines that there is no possibility of "reading-back" the individual figures. The authors found that both groups tended "to fall deep into the hypoglycaemic zone" on the first day and to remain there for several days. The diabetic group, however, tended /
tended to have lower levels. Miller & Ross (1940) determined in duplicate the blood sugar levels of 17 normal full term babies, 20 prematures and 6 infants of diabetic women by the method of Folin and Malmros. The blood samples were taken "in the first 48 hours of life" and the fasting period was not mentioned. The mean levels and standard deviations of the groups were, full term babies 50 ± 13, prematures 32 ± 12, and infants of diabetic women 30 ± 12 mg. per cent.

In a comprehensive study of the neonatal blood sugar level Pedersen (1952) found no difference between the average blood sugar levels in infants of diabetic and non-diabetic women. On the other hand, Komrower (1954) in as careful a study as Pedersen's has shown that in infants of diabetic women the blood sugar falls further and more rapidly than in normal babies and that this fall can be modified only partially by giving them glucose.

In the unfed babies of his series the group mean sugar level reached its lowest point two hours after birth and in the infants who received glucose this point was reached at three hours. When the graphs reproduced by Pedersen (his Figures IV and V on pages 108 and 109 of his monograph) are studied carefully then a difference between the groups is apparent. The blood sugar levels of his diabetic groups at two hours tend to be lower than the levels of the non-diabetic group at the same time interval. The distribution of points at two hours looks fairly normal on both graphs but 8 of the 27 infants in the diabetic group have blood sugar levels of less /
less than 50 mg. per cent. as compared with 4 of 28 infants in the non-diabetic group. Five of the diabetic group and only one of the non-diabetic group have levels below 40 mg. per cent. The arithmetic means of the diabetic and non-diabetic groups (calculated as carefully as possible from the graphs) are 55 and 71 mg. per cent. respectively at two hours. Thus, although it was not apparent to their author, these results indicate that at two hours the blood sugar level is subnormal even for the newborn. These findings are confirmed by the results of the present study.

SUMMARY

The blood sugar level of babies born to diabetic women falls more consistently, more rapidly, and further than it does in normal babies. The curve of the group mean, which closely reflects the individual trend, reaches its lowest point at about two hours after birth. The lowest sugar levels achieved are unrelated to foetal birth weight. The blood sugar level returns spontaneously to normal by the age of four to six hours and it rises steadily from the third day of life. The variability around the mean decreases over the same period.
STUDY 6

THE SIGNIFICANCE OF HYPOGLYCAEMIA

The discovery that the newborn infants of diabetic women commonly had low blood sugar levels led to the belief that the high morbidity and mortality might be due to hypoglycaemia. Alternatively, a rapid and profound fall from a prenatal hyperglycaemia to a post-natal hypoglycaemia has been considered to be an important cause of clinical disturbance.

Intention

The intention of this study is to show that there is no relationship between the development of a morbid neonatal course and the blood sugar level at the time or the extent and rapidity of the fall. The absence of relationship between the degree of hypoglycaemia or the gradient of the change in levels and abnormality later in the first two weeks or in later childhood will also be shown.

Plan of the Investigation

90 infants born to proved diabetic women in the Simpson Memorial Maternity Pavilion, Edinburgh, have been studied. All were observed continuously by experienced nurses and the nature of any abnormal incident was recorded. Where these lasted for longer than a minute or so they were observed by an experienced paediatric house physician or by myself. All the abnormal incidents which persisted for 15 minutes or more were /
were observed personally and on repeated occasions the development and the course of the cyanotic attacks were witnessed by myself.

In many of the earlier cases the blood sugar level was determined only if the course was abnormal and only in the presence of symptoms. As only a proportion of the cases (about one third) was symptomatic and as a doctor was not always on the spot with the necessary apparatus when symptoms actually developed, the blood sugar level at the time of abnormal incidents is not available for each case. These blood sugar determinations form the preliminary part of the study and answer the first question, Do the incidents occur in association with hypoglycaemia? These findings must be considered also in relation to the second part of the study.

Although personal doubt was expressed about the need to give glucose to these infants after birth, its intramuscular use was found safe and it was given until 1952. Before 1948 glucose was given intravenously but, following a short and highly unsatisfactory experience of oral administration, a change was made in that year to the almost invariable use of intramuscular injections of 20% to 50% solutions. The fact that some infants received glucose in no way invalidates the use of this group.

RESULTS

'Respiratory incidents' (slow establishment of respiration, dyspnoea or cyanotic attacks) were observed in 34 of the
THE RELATIONSHIP BETWEEN CHANGES IN THE BLOOD SUGAR LEVEL BETWEEN BIRTH AND TWO HOURS AND THE CLINICAL COURSE OF INFANTS OF DIABETIC WOMEN

![Figure 44](image-url)
the 90 infants studied and the blood sugar level at the time of symptoms was determined in 23 of these. The results in 21 of the symptomatic cases are recorded in Table 16 along with an indication of the severity and of the duration of the clinical disturbance. It is clear that no correlation exists between severity and hypoglycaemia. The blood sugar level may be high or 'normal' or low during continuous mild or severe disturbances or at the time of brief upsets. The opportunity arose in 1954 of comparing the widely different clinical progress of dizygous twins, neither of whom had been given glucose. These observations and the blood sugar levels are recorded in Table 17 and again there is no relationship between clinical behaviour and the sugar value.

Having demonstrated the dissimilarity of the blood sugar levels occurring in normal babies (Study 5) and in babies of diabetic women (Study 6) and the fact that the blood sugar level of infants born to diabetic women reached its lowest point at one to two hours after birth, it was then possible to examine the behaviour of such infants in the whole series for whom serial blood sugar values in the first few hours of life were available. The value at birth was plotted graphically against the lowest level at 1 to 3 hours and the point was marked with a symbol signifying the nature of the clinical course (Figure 44). The segment of the circle is divided into three sections in the uppermost of which lie points which signify that a fall occurred in excess of 50 per cent. of the birth level. In the central section lie points where...
TABLE 16
SYMPTOMATIC CASES AND COINCIDENT BLOOD SUGAR LEVELS

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Severity</th>
<th>Time of Incident</th>
<th>Chemical Method</th>
<th>Blood Sugar Levels (mg%, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Delayed establishment of respiration.</td>
<td>Birth</td>
<td>H-J</td>
<td>127</td>
</tr>
<tr>
<td>3</td>
<td>Continuous, moderate severe (inhalation)</td>
<td>Birth to 6 hr.</td>
<td>&quot;</td>
<td>&quot; 66, 50, 70</td>
</tr>
<tr>
<td>6</td>
<td>Continuous, moderate severe (inhalation)</td>
<td>Birth to 6 hr.</td>
<td>&quot;</td>
<td>&quot; 120, 298, 156</td>
</tr>
<tr>
<td>8</td>
<td>Continuous, mild.</td>
<td>Birth to 10 hr.</td>
<td>&quot;</td>
<td>&quot; 60, 78, 74, 74, 64</td>
</tr>
<tr>
<td>14</td>
<td>Continuous, severe (inhalational)</td>
<td>4 to 6 hr.</td>
<td>&quot;</td>
<td>&quot; 138, 342</td>
</tr>
<tr>
<td>18</td>
<td>Continuous, moderate</td>
<td>Birth to 8 hr.</td>
<td>&quot;</td>
<td>&quot; 254, 180, 180, 86, 52, 114</td>
</tr>
<tr>
<td></td>
<td>Fatal deterioration</td>
<td>47 to 68 hr.</td>
<td>&quot;</td>
<td>Terminal level unknown</td>
</tr>
<tr>
<td>19</td>
<td>Continuous, severe initially with gradual improvement.</td>
<td>Birth to 24 hr.</td>
<td>&quot;</td>
<td>(522), 160, 132, 66, 74, 74, 78</td>
</tr>
<tr>
<td>35</td>
<td>Continuous to death.</td>
<td>Birth to 22 hr.</td>
<td>&quot;</td>
<td>&quot; 84, 120, 128</td>
</tr>
<tr>
<td>40</td>
<td>Continuous, moderate</td>
<td>Birth to 3 hr. 50 min.</td>
<td>&quot;</td>
<td>Terminal level 71</td>
</tr>
<tr>
<td></td>
<td>Sudden fatal deterioration</td>
<td>3 hr. 50 min. to 4 hr.</td>
<td>&quot;</td>
<td>&quot; 43, 51, 57. Terminal level 62</td>
</tr>
<tr>
<td>41</td>
<td>Delayed establishment of respiration</td>
<td>Birth</td>
<td>&quot;</td>
<td>&quot; 248</td>
</tr>
<tr>
<td>45</td>
<td>Continuous, mild</td>
<td>Birth to 2 hr.</td>
<td>&quot;</td>
<td>&quot; 55, 52, 46, 63</td>
</tr>
<tr>
<td>46</td>
<td>Continuous, moderate</td>
<td>Birth to 9 hr.</td>
<td>&quot;</td>
<td>&quot; 53, 58, 60, 62, 60</td>
</tr>
<tr>
<td>53</td>
<td>Continuous, moderate</td>
<td>3 to 6 hr.</td>
<td>&quot;</td>
<td>&quot; 56, 60</td>
</tr>
<tr>
<td>69</td>
<td>Continuous, severe</td>
<td>Birth to Day 4</td>
<td>&quot;</td>
<td>&quot; 62, 60, 48, 79, 74, 60, 48, 43</td>
</tr>
<tr>
<td>84</td>
<td>Rapid fatal deterioration</td>
<td>16 hr.</td>
<td>&quot;</td>
<td>&quot; 265 (3 hr. after 1 g. glucose intramuscularly)</td>
</tr>
<tr>
<td>85a</td>
<td>Twin. Acute, severe, short</td>
<td>Day 3</td>
<td>R</td>
<td>111</td>
</tr>
<tr>
<td>98</td>
<td>Continuous to death</td>
<td>3 to 41 hr.</td>
<td>H-J</td>
<td>41. Terminal 68</td>
</tr>
<tr>
<td>100</td>
<td>Acute, mild, short</td>
<td>Day 6</td>
<td>H-J</td>
<td>123</td>
</tr>
<tr>
<td>101</td>
<td>Acute, mild, short</td>
<td>Day 3</td>
<td>H-J</td>
<td>94</td>
</tr>
<tr>
<td>102</td>
<td>Continuous, severe</td>
<td>Birth to 4 hr.</td>
<td>H-J</td>
<td>112, 74</td>
</tr>
<tr>
<td>103</td>
<td>Acute, severe short</td>
<td>Day 4</td>
<td>H-J</td>
<td>43</td>
</tr>
</tbody>
</table>

The number of the case is that allocated to the pregnancy. As a number of these failed to result in the birth of a live child the case numbers exceed 100, although only 90 infants have been studied.
<table>
<thead>
<tr>
<th>Time</th>
<th>Blood Sugar Level (mg. %)</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hr.</td>
<td>39</td>
<td>Good</td>
</tr>
<tr>
<td>7 hr.</td>
<td>44</td>
<td>Slight improvement</td>
</tr>
<tr>
<td>1/4 hr.</td>
<td>-</td>
<td>Improving death</td>
</tr>
<tr>
<td>26 hr.</td>
<td>73</td>
<td>Good</td>
</tr>
</tbody>
</table>

**Twin 1 (Case 90a)**

**Twin 2 (Case 90b)**
a fall occurred which was less than 50 per cent. of the birth level and in the centre of the middle section and one is in the lowest section.

Only 10 of the 54 infants represented on this graph were symptomatic in the first few hours when the trough of hypoglycaemia is normally attained. Three of the 10 died (Case 18 at 3 days. Case 32 at 11 hours and Case 40 at 4 hours) and none of them feature in the top section; two are in the middle section and there is one in the lowest. In two of the 10 symptomatic infants (Cases 3 and 6) the respiratory difficulties were undoubtedly the result of inhaling orally administered glucose. One other infant (Case 37) who is represented in the top section was apnoeic for some minutes after his initial cry, but he was perfectly normal at the time when his lowest blood sugar level was recorded. One (Case 69) had no significant fall in the blood sugar level (62 to 48 mg.%) while another (Case 46) showed a rise from 53 mg.% to 62 mg.%. One (Case 1) falls clearly into the topmost section and the last of the 10 (Case 19) also does so but the initial level of 522 mg.% certainly does not represent accurately the birth level of blood sugar as there were some minutes of delay in obtaining the specimen and the infant had been given 2 g. of glucose into the umbilical vein on delivery. Of those 10 infants, therefore, who were symptomatic when the maximum fall in blood sugar was to be expected, only three fall into the topmost section and of these one was asymptomatic at the most hypoglycaemic point,
point, while in another the sugar level at birth did not represent the true fact. There are 17 infants in the top-most section of the segment, so that at least 15 of these were asymptomatic at the time-interval during which the blood sugar of these infants is normally at its lowest. The symptoms presented beyond the first few hours in the remaining 44 infants bear no relationship to the change in blood sugar immediately after birth and occurred at a time when the sugar level had become stabilized.

In the series of 90 live born infants there have been eight neonatal deaths. With one exception these have been among the lighter infants. Very adequate cause for it has been found in seven at autopsy and in the eighth (Case 40, whose blood sugar rose from birth) the clinical and pathological picture was of anoxia, although its cause was not determined. The important pathological findings have been given in Table 2 (Page 37) and in addition the pancreas of each baby was found to have very definite hyperplasia of the islets of Langerhans. In Cases 18, 35, 40, 84, 90b and 98, either serial blood sugar levels or one preceding death are available and in none was hypoglycaemia present. Case 9 was a preventable death from neonatal pneumonia on Day 9, and Case 32 (whose blood sugar underwent a minimal fall) presented signs of respiratory embarrassment immediately after birth and went on to die of pulmonary hyaline membrane at 11 hours.

Of the 90 infants born, 82 survived the newborn period.
One of these (Case 30) died suddenly at home at the age of 1 month. His neonatal course in hospital was quite uneventful. The blood sugar fell from a birth level of 94 mg.\% to 72 mg.\% at 1 hour and 50 mg.\% at 3 hours from which point it rose steadily. Death was sudden and unexpected. His doctor heard a cardiac murmur for the first time just before the baby died and on this evidence alone certified death as having been due to congenital disease of the heart. There was no autopsy. Another infant (Case 3), whose neonatal course was complicated by inhalational incidents, but whose blood sugar was never abnormal, developed very severe meningococcal meningitis complicated by cerebral venous thrombosis at 2 months and suffers from secondary amentia.

Of the remaining 80, all but five (three of whom have emigrated) have been traced and their present health assessed. Of the 75 children, 71 have been examined personally; three have been examined by other physicians; and information was supplied about the remaining case by a children's officer.

From these various sources it can be said that 71 of the children are apparently normal in intelligence and behaviour. One (Case 42) was in hospital from 1953 - 1956 with Perthe's disease of the hip. The physician there thought that at 5 years of age the child was a little backward, but it has not been possible to see her personally to assess how much of her retardation may be attributed to prolonged institutional care. She now attends an ordinary school. She certainly had a normal neonatal course and was not hypoglycaemic at any /
any point. Two children are known to be mentally defective, one being a mongol and the other is the surviving dizygous twin (Case 90a). The latter infant weighed only 1021 g. at birth, and although he had a rather low blood sugar level initially, it rose spontaneously and he was in good condition in the newborn period. He also suffers from retrolental fibroplasia.

Finally, Case 63 is a small boy who is undoubtedly dull, but whose home background is very bad. The mother was a prostitute, she was very unstable emotionally and she did not care for her children. She died while attempting to induce the miscarriage of a further pregnancy when the patient was only a few months old. The father, who is an unstable and violent man and whose intelligence may be subnormal, married again, but with no advantage to the family. The child has grown up unloved, without proper care and was backward and dirty when last seen at the age of 4 years. Although his blood sugar level did in fact fall by over 50% in the first hour of life, and although it remained below 30 mg.% on days two and three, he was quite asymptomatic throughout the neonatal period. Case 75, whose blood sugar fell by more than 75% in the first hour, and in whom it was 20 mg.% on day two, and in whom the level did not exceed 40 mg.% until day five, is at the same age a very normal little girl. It seems much more likely that the backwardness in Cases 90a and 63 is the result of factors other than the hypoglycaemia.

An unsuccessful attempt was made to determine the influence /
influence of hypoglycaemia upon respiratory function. Information about this is available on Page 56.

**SUMMARY**

No relationship exists between the development of a morbid neonatal course and the blood sugar level at the time or the extent and rapidity of the fall in the level. It is shown also that there is no relationship between the degree of hypoglycaemia or the gradient of the change in levels and abnormal incidents later in the first two weeks of life. It is probable that there is no relationship between the blood sugar changes and subnormal intelligence in later childhood.

The administration of glucose may be dangerous and at the least it may serve to postpone the establishment of the correct diagnosis in abnormal infants.
STUDY 7

THE INFLUENCE OF HYPOGLYCAEMIA UPON
RESPIRATORY FUNCTION

Intention

The intention of this study is to determine the influence of hypoglycaemia upon respiratory function and particularly upon the respiratory effort.

Plan of the investigation

The plan was to develop apparatus which would collect accurately all of the expired air of infants born to diabetic women over various equal time-intervals during the first few hours of life and so to measure simultaneous changes in the ventilation rate and in the blood sugar level. These were to be compared with the same measurements on the third day of life. Because of the rigid fixation of the infant and his inaccessibility for blood-samples if he were enclosed in an infant plethysmograph, this method was excluded.

The collection of expired air through a low-resistance valve into a small light-weight plastic Douglas bag was selected. This method involved the accurate fitting of a face-mask to the baby. The development of this apparatus will now be described.

Low-resistance valves

The valve allowed the infant to inspire from the atmosphere but to expire only into the collecting system. Resistance had to be as low as possible without reducing the valve's efficiency.
Valve A (Figure 45). This valve was made for this study by the University Department of Physiology at the suggestion of Dr. R. Passmore and with the agreement of Professor D. Whitteridge. It is based upon a valve used in experimental work by Dr. Roger Bannister. The valves, which were light flaps of Perspex, were housed in a brass Y-tube, the diverging limbs of which were used for inspiration and expiration respectively. The Perspex flaps each lay on the oblique mouth of smaller brass tubes which were fitted very closely into the limbs of the Y tube. In this way one valve permitted the entry of environmental air, but prevented the escape of expired air, whereas the other allowed the escape of expired air into the bag but would not permit its re-entry into the baby's mask with the next inspiration. The resistance was the weight of the little Perspex flap and the closing force was gravity. In practice the valve was not entirely efficient and it was abandoned in favour of valve B.

Valve B (Figure 46). This valve, of German manufacture, was already in Dr. Passmore's possession. It was made of a light transparent plastic, T-shaped and incorporating two hair-spring-loaded ingress and egress valves made of thin plastic plates. The valves were efficient and could be operated by the respiration of a rat.

The Douglas Bag.

No suitable bag existed for the purpose of this sort of experiment /
LOW RESISTANCE VALVE A.

VALVE A

To and From Baby

To Douglas Bag

Brass Cartridge Valves

From Atmosphere

Brass Cartridge Valve

Hinge

Perspex Flap Valve
Figure 46

LOW RESISTANCE VALVE B.
Figure 47

POLYTHENE DOUGLAS BAG

20 litre capacity
experiment and the material from which the standard Douglas bag is made is so thick and heavy that it would offer too much resistance to a baby's expiration even if the bag itself could be reduced to a capacity of 20 litres. Advice was obtained from Dr. G. Pugh of the successful 1953 British expedition to Mount Everest as it was known that he had sampled the expired air of the climbers and it seemed impossible that they had carried orthodox Douglas bags. They had in fact been made of a light-weight rubberised material and the firm concerned agreed to make a number of small bags for this experiment. A delay of some months would have occurred, however, and enquiries were therefore made about the use of polythene sheeting, a substance of which the author has had previous experience (Farquhar & Lewis, 1948). The opinion of Dr. John E. Cotes who has extensive experience of collecting expired air samples at The Pneumoconiosis Research Unit, (Cardiff) was obtained at Dr. Pugh's suggestion. He believed that bags could be made by heat-sealing sheets of polythene 2/1000ths. of an inch thick. These would not allow the escape of gas through the minute punctures he had found in other plastic materials and the permeability to carbon dioxide 

\[13 \times 10^{-6} \text{ millilitres at N.T.P. passing through one centi-metre cube per second at a pressure difference of one centi-metre of mercury at } 25^\circ \text{C} \]  

would be negligible unless the gas were being stored in the bag for more than one hour. The bags which had a cubic capacity of 20 litres when filled, were /
were made to my pattern by Visqueen Ltd., 94 Tewin Road, Welwyn Garden City, Herts. The fabrication of bags of orthodox design was a little difficult, however, and doubt was expressed about the ability of the point at which the two internal gussets meet to take the strain when the bag was nearly full. The bag was, therefore, redesigned and manufactured with external gussets. (Figure 47) It could still be pressed flat to expel all air before and after use and there was much less danger of a burst seal. A polythene tube containing 2 per cent. carbon black was bonded into the bag to allow the easy connection of it to the rest of the apparatus. The carbon particles were encased in polythene so that absorption of carbon dioxide was not possible.

The Mask.

Standard anaesthetic masks proved to be quite useless. A fit which was close enough to prevent the loss of expired air and contamination of the expired air with atmospheric air proved to be impossible. A U.S.A.A.F. oxygen mask was therefore adapted for the purpose. It was free from valves, but had two short rubber tubes leading from it. One of these was clamped and the other was connected to the low-resistance valve B. The mask was applied inverted to the baby's face so that his chin fitted into the narrow angle and the broad base and the sides of the mask fitted snugly across his forehead and over his cheeks. The soft "rolled-in" edge of the mask helped it to fit gently.
An efficient harness was made from one inch wide elastic with a thick pad of sorbo rubber to fit behind the baby's head.

**Assembly of apparatus**

The mask was fitted with the valve and this was connected by a short piece of rubber tubing to a two-way ground stop-cock. The latter was held lightly on a retort stand and clamp and it was connected directly to the Douglas bag. By means of the stop-cock the baby could be made to breathe either into the room or into the bag. The distance from the infant to the bag was as short as possible and the diameter of the collecting system approximated closely throughout its length to the diameter of the newborn infant's trachea. It was never less and it was little more.

**Making the observations**

The infant was transferred to the heated premature room as soon as respiration was established and he was placed in a shallow plastic basinette. The mask was fitted closely and connected to the collecting system. He was allowed to breathe from and into the room for a few minutes until respiration was normal. The stop-cock was then turned quickly and his expired air was thus directed into the Douglas bag. After exactly ten minutes the stop-cock was turned and the tube leading into the bag was clamped simultaneously.

The infant was released and the bag was taken at once to
to the Department of Physiology where the necessary gas samples were taken and the total volume of the collection was measured. The observations were repeated when possible at the age of 3 hours (when the blood sugar would probably be low) and again at 3 days before feeding was begun.

RESULTS

Only 4 infants were studied before the development of difficulties in the technique brought the study to an end. The results are given in Table 18.

The first patient was studied at the age of 3 days only. So far as these observations went they confirmed that the ventilation rate did not decrease from the first to the third hour when hypoglycaemia was developing. Dr. Passmore was impressed by the greater consistency among these results from newborn infants than he usually found among adults. He accepted the results obtained from Case 100 as being a true record. The ventilation rates and oxygen consumptions were very constant and the Respiratory Quotient altered in the expected way. The third day record of Case 98 may have been correct but he thought that the high ventilation rate in Case 99 may have been the result of embarrassment caused by the mask. The other results from this case were reasonably good. The collection obtained at three hours from Case 101 may have been contaminated with air.

Further Experience

Further experience with Cases 102 to 104 showed clearly that /
### Table 18

**Results of Respiration Studies on Offspring of Diabetic Women**

<table>
<thead>
<tr>
<th>Case</th>
<th>Ventilation rate litres / minute</th>
<th>O2 consumption ccs / minute</th>
<th>Respiratory quotient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>birth</td>
<td>3 hours</td>
<td>3 days</td>
</tr>
<tr>
<td>98</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>99</td>
<td>1.16 1.27 1.46</td>
<td>19.3 16.9 17.7</td>
<td>0.86 1.05 0.77</td>
</tr>
<tr>
<td>100</td>
<td>0.63 0.59 0.52</td>
<td>17.9 17.4 18.7</td>
<td>0.98 0.82 0.64</td>
</tr>
<tr>
<td>101</td>
<td>0.52 0.74 0.84</td>
<td>20.4 13.9 31.3</td>
<td>0.79 0.90 0.73</td>
</tr>
</tbody>
</table>
that the mask was by no means a universal good fit and that it was poor in some cases. Efforts to improve the seal with wool which had been impregnated with petroleum jelly seemed to embarrass the baby probably as a result of pressure below the chin which was the point at which leakage was most common.

No other suitable mask existed and an attempt was made to have a number of masks manufactured which would fit accurately to babies of different weight. As a first step the author prepared a number of death-masks of newborn babies.

**Technique of making death-masks.** A large bowl was filled with melted medicinal paraffin wax of the type used by physiotherapists. The dead infant's head was shaved and his nostrils were plugged with cotton wool. The head was then lowered face-first into the wax to a point just in front of the ears. The wax was then allowed to cool and solidify and the head was gently eased free. Plaster-of-Paris was then run into the wax impression and allowed to set. The wax was then reheated gently and the plaster death mask was removed.

**Failure.** The masks were then sent to a manufacturer who had expressed interest. The following reply was obtained. "The problem raises two factors which must be mentioned prior to any experimental work by us. One is the question of development charge, which will be considerable, owing to the necessity of obtaining new moulds which are likely to be modified /
modified many times prior to a final design being approved. It seems in this connection that an expense of at least £100 can be envisaged". The second "factor" was that the manufacturer could not supply the author direct, but only through a retailer whose profit would be additional. The opinion of another medical instrument firm was similar.

By this time the clinical analysis of the influence of hypoglycaemia (Study 7) had been made and further expense of this magnitude did not seem justifiable. The study was abandoned with reluctance.

**SUMMARY**

Apparatus was designed for the collection of expired air from newborn infants so that the ventilation rate could be determined at various blood sugar levels.

The study was limited by the lack of air-tight masks and it was abandoned. The few results obtained suggest that the ventilation rate is not significantly lower at 3 hours than it is just after birth.
STUDY 8

THE EOSINOPHIL LEVELS OF NORMAL NEWBORN INFANTS

Intention

The intention of this study is to determine the normal absolute eosinophil levels of newborn infants during the first ten days of life so that they might be compared with those of babies born to diabetic mothers.

Method

The group of babies is that which has been described in Study 4. (Page 158). The blood specimens were taken within one minute of the blood sugar samples and the eosinophils were counted using the technique modified by Smart (1950) from Randolph's method (see Appendix IV).

RESULTS

The group collectively described.

The means, the ranges, the standard deviations and the coefficients of variation for each time-unit are given in Table 19.

TABLE /
### TABLE 19

**SERIAL READINGS OF EOSINOPHIL LEVELS IN NORMAL FULL-TERM NEWBORN INFANTS.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Eosinophils (cells/c.mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hours</td>
</tr>
<tr>
<td></td>
<td>Birth</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Days</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>
Figure 48

SERIAL EOSINOPHIL LEVELS
IN 32 NORMAL FULL TERM NEWBORN INFANTS

x = males
o = females
The first six hours.

In the immediate birth period it may be seen from the time-trend diagram (Figure 48) that in the group as a whole the mean circulating eosinophils fell by 156 during the first three hours of life and then rose by 27 cells/c.mm. in the next three hours, a considerably smaller increase.

Second to tenth days.

In this period the group average value of the eosinophil levels decreased from 390 cells/c.mm on the third day to 259 cells/c.mm. on the tenth, but this fall took place largely from day three to four.

The mean values, as in Study 4 cannot be taken as adequate descriptions and in this study particularly the scatter of values around the group mean at any time-unit was great. This can be seen both from the time-trend diagrams, which illustrate also the daily scatter of the actual observations, and from the coefficients of variation in Table 19. The scatter of values around the group mean was very much greater however than for the blood sugar, the coefficient of variation starting above 60 per cent. and fluctuating widely about 40 per cent. even towards the tenth day.

Although the scatter of actual values on individual days decreased slightly, suggesting stabilisation, the actual scatter of increments of individual infants from day to day did not decrease. (see Appendix, V, Table 52).

Individual eosinophil patterns.
INDIVIDUAL SERIAL EOSINOPHIL LEVELS IN 32 NORMAL NEWBORN INFANTS
# TABLE 20

## INDIVIDUAL PATTERNS OF THE EOSINOPHIL LEVEL IN 32 NORMAL INFANTS

<table>
<thead>
<tr>
<th>Hours</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Birth 3 6</td>
</tr>
<tr>
<td>A</td>
<td>70 86 108</td>
</tr>
<tr>
<td>B</td>
<td>219 203 148</td>
</tr>
<tr>
<td>C</td>
<td>400 316 381</td>
</tr>
<tr>
<td>D</td>
<td>894 600 711</td>
</tr>
<tr>
<td>E</td>
<td>289 216 225</td>
</tr>
<tr>
<td>F</td>
<td>231 161 195</td>
</tr>
<tr>
<td>G</td>
<td>655 591 617</td>
</tr>
<tr>
<td>H</td>
<td>202 177 188</td>
</tr>
<tr>
<td>I</td>
<td>373 295 228</td>
</tr>
<tr>
<td>J</td>
<td>164 156 153</td>
</tr>
<tr>
<td>K</td>
<td>444 313 353</td>
</tr>
<tr>
<td>L</td>
<td>161 177 216</td>
</tr>
<tr>
<td>M</td>
<td>1,011 - 753</td>
</tr>
<tr>
<td>N</td>
<td>238 272 317</td>
</tr>
<tr>
<td>O</td>
<td>806 850 723</td>
</tr>
<tr>
<td>P</td>
<td>961 - 794</td>
</tr>
<tr>
<td>Q</td>
<td>147 208 161</td>
</tr>
<tr>
<td>R</td>
<td>619 520 505</td>
</tr>
<tr>
<td>S</td>
<td>197 206 242</td>
</tr>
<tr>
<td>T</td>
<td>1,005 839 634</td>
</tr>
<tr>
<td>U</td>
<td>392 161 106</td>
</tr>
<tr>
<td>V</td>
<td>286 148 119</td>
</tr>
<tr>
<td>W</td>
<td>288 139 109</td>
</tr>
<tr>
<td>X</td>
<td>420 244 33</td>
</tr>
<tr>
<td>Y</td>
<td>373 292 445</td>
</tr>
<tr>
<td>Z</td>
<td>461 217 330</td>
</tr>
<tr>
<td>a</td>
<td>409 227 203</td>
</tr>
<tr>
<td>b</td>
<td>1,153 498 617</td>
</tr>
<tr>
<td>c</td>
<td>603 272 253</td>
</tr>
<tr>
<td>d</td>
<td>431 208 275</td>
</tr>
<tr>
<td>e</td>
<td>256 106 197</td>
</tr>
<tr>
<td>f</td>
<td>316 317 266</td>
</tr>
</tbody>
</table>
Individual eosinophil patterns.

A study of Figure 49 and Table 20 shows that 6 of 32 babies (18.72%) responded with a variable rise in the eosinophil count over the first six hours and that in 11 infants the eosinophils increased in number from the third to the sixth hour after an initial fall after birth.

Although the group means for eosinophils tended to fall, the very wide scatter of daily readings reflected great individual variations from day to day. These are apparent on the small individual graphs in Figure 49, from which it is clear that there is no consistent pattern of eosinophil behaviour for all normal infants and that although there is a general downward trend in the majority, many obvious exceptions exist.

Seven infants show a fairly progressive fall in eosinophils from birth, in nine there is a continuous upward trend, in 11 the values fluctuate widely from day to day and in 5 progressive decrease in the eosinophil count follows an initial steep rise from the first to the third day. The figures reached at that point in this latter type are so high that they dominate the mean for the group as a whole, with the result that it appears from the arithmetic mean as if the eosinophil levels of newborn infants rise from birth to the third day and then fall.

COMMENT

Several previous studies of the numbers of circulating eosinophils /
### TABLE 21

**EOSINOPHIL RANGE IN NORMAL NEWBORN INFANTS**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Days 3-5</th>
<th>Days 6-8</th>
<th>Days 8-10</th>
<th>Days 9-11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Forkner (1929)</strong></td>
<td>0-895 (429)</td>
<td>168-1110 (600)</td>
<td>160-727 (411)</td>
<td></td>
<td>205-873 (417)</td>
<td></td>
</tr>
<tr>
<td><strong>Klein and Hanson (1950)</strong></td>
<td>78-988 (359±47)</td>
<td>75-1100 (420±43)</td>
<td></td>
<td>63-483 (268±42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean values in brackets.
eosinophils in newborn infants have been made (Table 21). The means in both these series appear to rise in the first few days of life and then to fall progressively. Burrell (1953) recorded graphically the mean of eosinophil counts in full-term infants and this appeared to rise from birth to one week and then to become stable. The behaviour of the mean in the present study corresponds to that described by Forkner (1929) and by Klein and Hanson (1950), but it shows that an increase of eosinophils in the first three days followed by a progressive fall does not occur consistently in the normal baby.

SUMMARY

Serial eosinophil levels have been determined in 32 normal newborn infants. Wide variations exist in the group at any time-unit, and from day to day in individuals within the group. Although the group mean reflects a trend toward rising eosinophil counts in the first 2-3 days and falling levels thereafter, such a pattern does not exist consistently in the normal baby.
STUDY 9

THE EOSINOPHIL LEVELS OF INFANTS BORN TO DIABETIC WOMEN

Intention

The intention of this study is to determine the absolute eosinophil levels of infants born to diabetic women and to find if these suggest increased adrenocortical activity at birth and adrenal insufficiency during the next few days.

Method

The group of babies is that which has been described in Study 5 (Page 171). The blood specimens were taken within one minute of the blood sugar samples and the eosinophils were counted using the technique modified by Smart (1950) from Randolph's method (see Appendix IV).

RESULTS

The First Six Hours. A spontaneous decrease in the number of circulating eosinophils from birth to the sixth hour was observed in every infant of the abnormal group (Table 22) with the exception of Case 59 in which after an initial fall the number increased by the sixth hour to a figure which just exceeded the birth level. Table 23 shows that the percentage decrease from birth to six hours was usually considerably greater in the infants of the abnormal group than in the control series, almost 90% of individuals in the /
### Table 22

**Individual Patterns of the Eosinophil Level in 17 Infants Born to Diabetic Women**

<table>
<thead>
<tr>
<th>No.</th>
<th>Birth</th>
<th>3</th>
<th>6</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>125</td>
<td>92</td>
<td>133</td>
<td>227</td>
<td>264</td>
<td>306</td>
<td>198</td>
<td>242</td>
<td>194</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>1,108</td>
<td>583</td>
<td>572</td>
<td>269</td>
<td>290</td>
<td>466</td>
<td>744</td>
<td>599</td>
<td>422</td>
<td>422</td>
<td>473</td>
<td>428</td>
</tr>
<tr>
<td>63</td>
<td>450</td>
<td>186</td>
<td>83</td>
<td>11</td>
<td>42</td>
<td>188</td>
<td>272</td>
<td>197</td>
<td>233</td>
<td>81</td>
<td>164</td>
<td>220</td>
</tr>
<tr>
<td>64</td>
<td>391</td>
<td>155</td>
<td>108</td>
<td>55</td>
<td>59</td>
<td>159</td>
<td>209</td>
<td>533</td>
<td>373</td>
<td>364</td>
<td>370</td>
<td>128</td>
</tr>
<tr>
<td>65</td>
<td>238</td>
<td>144</td>
<td>33</td>
<td>25</td>
<td>36</td>
<td>128</td>
<td>138</td>
<td>180</td>
<td>39</td>
<td>105</td>
<td>128</td>
<td>108</td>
</tr>
<tr>
<td>69</td>
<td>1,940</td>
<td>952</td>
<td>475</td>
<td>488</td>
<td>1,203</td>
<td>620</td>
<td>581</td>
<td>206</td>
<td>763</td>
<td>522</td>
<td>441</td>
<td>234</td>
</tr>
<tr>
<td>70</td>
<td>388</td>
<td>223</td>
<td>175</td>
<td>56</td>
<td>141</td>
<td>452</td>
<td>509</td>
<td>297</td>
<td>281</td>
<td>222</td>
<td>155</td>
<td>97</td>
</tr>
<tr>
<td>71</td>
<td>756</td>
<td>439</td>
<td>370</td>
<td>123</td>
<td>320</td>
<td>411</td>
<td>695</td>
<td>816</td>
<td>884</td>
<td>569</td>
<td>300</td>
<td>464</td>
</tr>
<tr>
<td>72</td>
<td>1,000</td>
<td>681</td>
<td>209</td>
<td>61</td>
<td>505</td>
<td>616</td>
<td>839</td>
<td>920</td>
<td>628</td>
<td>616</td>
<td>708</td>
<td>630</td>
</tr>
<tr>
<td>73</td>
<td>817</td>
<td>372</td>
<td>269</td>
<td>245</td>
<td>455</td>
<td>344</td>
<td>214</td>
<td>161</td>
<td>142</td>
<td>89</td>
<td>203</td>
<td>166</td>
</tr>
<tr>
<td>74</td>
<td>467</td>
<td>309</td>
<td>264</td>
<td>202</td>
<td>372</td>
<td>738</td>
<td>855</td>
<td>672</td>
<td>667</td>
<td>802</td>
<td>391</td>
<td>602</td>
</tr>
<tr>
<td>75</td>
<td>523</td>
<td>453</td>
<td>183</td>
<td>156</td>
<td>219</td>
<td>772</td>
<td>616</td>
<td>684</td>
<td>553</td>
<td>473</td>
<td>386</td>
<td>320</td>
</tr>
<tr>
<td>83</td>
<td>127</td>
<td>78</td>
<td>42</td>
<td>53</td>
<td>148</td>
<td>163</td>
<td>388</td>
<td>375</td>
<td>280</td>
<td>236</td>
<td>202</td>
<td>156</td>
</tr>
<tr>
<td>84</td>
<td>142</td>
<td>72</td>
<td>80</td>
<td>47</td>
<td>55</td>
<td>158</td>
<td>23</td>
<td>130</td>
<td>103</td>
<td>200</td>
<td>358</td>
<td>206</td>
</tr>
<tr>
<td>85a</td>
<td>378</td>
<td>277</td>
<td>134</td>
<td>47</td>
<td>55</td>
<td>158</td>
<td>23</td>
<td>130</td>
<td>103</td>
<td>200</td>
<td>358</td>
<td>206</td>
</tr>
<tr>
<td>85b</td>
<td>233</td>
<td>103</td>
<td>25</td>
<td>47</td>
<td>55</td>
<td>158</td>
<td>23</td>
<td>130</td>
<td>103</td>
<td>200</td>
<td>358</td>
<td>206</td>
</tr>
<tr>
<td>88</td>
<td>966</td>
<td>752</td>
<td>638</td>
<td>92</td>
<td>58</td>
<td>70</td>
<td>256</td>
<td>222</td>
<td>191</td>
<td>827</td>
<td>809</td>
<td>745</td>
</tr>
</tbody>
</table>
TABLE 23  
Frequency Distribution of Spontaneous Eosinophil Changes in Normal and Abnormal Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Time Interval</th>
<th>Percentage of Infants Showing Increase in Absolute Eosinophils</th>
<th>Percentage of Total Group Showing Varying Percentage Decrements in Absolute Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Infants</td>
<td>Birth to 6 hr.</td>
<td>18.75</td>
<td>0-9  10-19  20-29  30-39  40-49  50-59  60-69  70-79  80-89  90-99</td>
</tr>
<tr>
<td>(Total 32)</td>
<td></td>
<td></td>
<td>12.5  15.6  18.75  9.4  6.25  9.4  3.1  3.1  -  3.1</td>
</tr>
<tr>
<td>Normal Infants</td>
<td>Birth to 3 or 6 hr. (lowest) eosinophil figure</td>
<td>18.75</td>
<td>0-9  10-19  20-29  30-39  40-49  50-59  60-69  70-79  80-89  90-99</td>
</tr>
<tr>
<td>(Total 32)</td>
<td></td>
<td></td>
<td>3.1  18.75  9.4  15.6  3.1  21.9  3.1  3.1  -  3.1</td>
</tr>
<tr>
<td>Abnormal Infants</td>
<td>Birth to 6 hr.</td>
<td>5.9</td>
<td>0-9  10-19  20-29  30-39  40-49  50-59  60-69  70-79  80-89  90-99</td>
</tr>
<tr>
<td>(Total 17)</td>
<td></td>
<td></td>
<td>5.9  17.6  11.8  23.6  17.6  17.6  -  -  -  -</td>
</tr>
</tbody>
</table>
the former as compared with only 25% of those in the latter producing decreases greater than 40% of the birth level. Alternatively, if the maximum eosinophil decrements within the first six hours are compared, then the eosinopenic responses in the abnormal group are still seen to be the greater.

Second to Tenth Days: Several patterns of eosinophil movement were observed in this group. Cases 60, 64, 70, 71, 72, 74, 75 and 83 all showed a rise from the second day, a peak occurring between days 4 and 7 (pattern A1). A less obvious rise to the same point was observed in Cases 63 and 65 (pattern A2). In Cases 84 (a) and 88 a similar rise occurred, but the peak was not reached until days 9 and 8 respectively (pattern A3). A curious high early peak on the third day was followed by a lower second peak on the seventh day in Case 69 (pattern B). Insignificant daily variation (pattern C) was seen in Cases 59 and 85 (b) and in Case 73 a steady fall in the eosinophil count took place from the third day (pattern D).

The mean curve (Figure 50) reflects the above facts in that a rapid fall occurred in the first six hours, was followed by a rise to the fifth day and then by a slight decline.

Correlation of Eosinophil Count with Clinical Behaviour in Infants of Diabetic Women. In the 17 infants in whom frequent eosinophil values were determined five showed dyspnoea or cyanotic attacks at some stage and of /
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Birth Weight (g)</th>
<th>Eosinophil Pattern</th>
<th>Clinical incident</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>3,742</td>
<td>C</td>
<td>No incident</td>
</tr>
<tr>
<td>60</td>
<td>2,835</td>
<td>A1</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>63</td>
<td>4,132</td>
<td>A2</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>64</td>
<td>5,032</td>
<td>A1</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>65</td>
<td>2,019</td>
<td>A2</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>69</td>
<td>3,820</td>
<td>B</td>
<td>Prolonged respiratory distress until day 4.</td>
</tr>
<tr>
<td>70</td>
<td>3,728</td>
<td>B</td>
<td>No incident</td>
</tr>
<tr>
<td>71</td>
<td>3,615</td>
<td>A1</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>72</td>
<td>3,232</td>
<td>A1</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>73</td>
<td>3,097</td>
<td>D</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>74</td>
<td>3,402</td>
<td>A1</td>
<td>Brief cyanotic attack on day 5</td>
</tr>
<tr>
<td>75</td>
<td>3,707</td>
<td>A1</td>
<td>No incident</td>
</tr>
<tr>
<td>83</td>
<td>2,693</td>
<td>A1</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>84</td>
<td>1,701</td>
<td>Continuous fall</td>
<td>Death at 16 hours. (terminal count 34/c.mm.)</td>
</tr>
<tr>
<td>85(a)</td>
<td>2,438</td>
<td>A3</td>
<td>Brief cyanotic attacks on days 3, 6 and 8</td>
</tr>
<tr>
<td>85(b)</td>
<td>2,495</td>
<td>C</td>
<td>No incident</td>
</tr>
<tr>
<td>88</td>
<td>2,445</td>
<td>A3</td>
<td>Brief cyanotic attack at fifth hour.</td>
</tr>
</tbody>
</table>

A.1 Rise from day 2. Peak day 4-7
A.2 Less obvious peak day 4-7
A.3 Later peak (day 8-9)
B Two peaks, days 3 and 7
C Insignificant daily variation
D Steady fall from day 3
Figure 50

SERIAL EOSINOPHIL LEVELS OF 17
NEWBORN INFANTS OF DIABETIC WOMEN

SERIAL EOSINOPHIL LEVELS OF 17 NEWBORN INFANTS OF DIABETIC WOMEN

*(1940)*
of these one baby died at the age of 16 hours. It may be seen, however, from Table 24, that there was no correlation whatsoever between any particular eosinophil pattern or change and the clinical disturbances.

**COMMENT**

Serial observations upon the absolute eosinophil counts of babies born to diabetic women show that significant reductions in levels follow birth in each case and that these are greater and more consistently present than are the reductions which are achieved by the normal infants of non-diabetic women. No relationship has been found between the eosinophil levels or the pattern of eosinophil movement and the clinical behaviour of the baby.

The eosinopenic response to being born occurs in both normal babies and those of diabetic women. The eosinophil level is high in both group at birth, and indeed it rarely reaches the same level again. These findings suggest either that there is little glucocorticoid activity in the foetus before birth or that the eosinopenic mechanism does not function until after delivery. The immediate post-natal eosinopenia, the rise which follows it, and the secondary fall are features of the alarm reaction.
THE ADRENAL CORTEX OF THE NEWBORN.

The structure of the cortex

The possible relationship of post-natal adrenal changes to the blood sugar and eosinophil levels.

Theories relating to the normal control of the neonatal blood sugar level.

The adrenal glands of the newborn are relatively much larger than at any other age. The literature describing their weight and structure is the subject of a detailed study by Tähkkä (1951). Their size is due almost entirely to the large cortex which has a light-coloured, narrow exterior and a wide, dark inner zone.

The foetal zone. This inner layer of cortical cells has been named the 'foetal cortex' by Elliot & Armour (1911). It has been called the "X-zone" by Gruenwald (1946) and the "Androgenic zone" by Grollman (1936). Careful morphological studies led Blackman (1946) to conclude it corresponded in many ways to the reticular cells of the adult gland and the term "foetal reticular zone" was proposed. It accounts for 85 per cent. of the entire neonatal cortex (Swinyard, 1943). The embryology of the gland has been studied by Uotila (1940) who observed primary and secondary proliferative phases which presumably give rise to the foetal and definitive zones respectively.

The definitive zone. The definitive or permanent zone remains small in amount, compared to the foetal zone, until birth /
birth when proliferation begins. During the last ten weeks of gestation there is a gradual increase in the thickness of the permanent cortex (Keene & Hewer 1927), but at term it accounts for about one fifth only of the width of the whole cortex.

**Involution of the foetal zone.**

The size of the foetal cortex is no more remarkable than its dramatic involution after birth. This occurs irrespective of gestational age or foetal weight and can be related only to separation from the mother. According to McNeil (1947) the foetal zone has disappeared by the end of the third week but Benner (1940) has found microscopic traces of it at two months and a residual connective tissue capsule which disappears finally at the age of 2 to 3 years. This connective tissue may occupy 15.9 per cent. of the gland at one year (Swinyard, 1943). The process of involution may begin, on occasion, before birth according to Benner (1940) and Benirschke, Bloch, & Hertig (1956).

**The function of the foetal zone.**

The function of the foetal zone is still obscure, but its appearance in pathological conditions has provided a possible clue. Hyperplasia has been reported frequently in female pseudohermaphrodites (Broster, Allen, Vines, Patterson, Greenwood, Marrian & Butler, 1938); (Wilkins, 1949), (Zuelzer & Blum, 1949); (Wilkins, 1950); (Harris & Scowen, 1951); and in macrogenitosomia praecox (Wilkins, 1949 as above); and Wilkins /
The observation of a hyperplastic foetal cortex in a case of macrogenitosomia praecox led Grollman (1936) to call this layer the "androgenic zone", but in a later study (Gersh & Grollman, 1939) he recorded his failure to extract steroid hormones with an androgenic property from the foetal cortex of "normal" human newborns and foetuses.

Because of the androgenic extract obtained by Wilkins et al. (1940) from a single case of adrenal hyperplasia, the higher 17-Ketosteroids reported by Puck, Sievert, Meinecke, (1953) & Gardner & Walton (1954) in the bloods of male and female foetuses when compared with maternal blood, the greater content of 17-Ketosteroids in newborn urine diminishing during the first few days of life (Read, Venning & Ripstein, 1950) and the masculinisation of female infants at birth in adrenal hyperplasia, a biochemical analysis of a large number of immature adrenal glands obtained from foetuses at therapeutic abortion was undertaken by Benirschke, Bloch, & Hertig (1956a). The abortions were undertaken for the treatment of such general diseases as cardiac decompensation, tuberculosis and cancer and none of the mothers had given birth previously to infants with the adrenogenital syndrome or other conditions affecting the adrenal glands. They were able to show that the foetal cortex contained weak androgenic steroids and a sodium-retaining factor. The concentration of these steroids was higher in smaller foetuses and it was approximately equal in males and females. This finding agrees with the original suggestion by /
by Grollman (1936) that the foetal cortex is "androgenic".

The function of the definitive zone.

In some pathological conditions of the newborn the definitive cortex (the zonae glomerulosa and fasciculata) have been reduced in amount (Zuelzer & Blem, 1949) and (Wilkins et al 1940) and such babies had frequently suffered from severe electrolyte imbalance of Addisonian type (Blackman, 1946, and Zuelzer & Blum, 1949). According to Staemmler (1953a and 1953b) the adrenal of the young foetus contains no 17-hydroxycorticosterone, but this appears after the fifth month of gestation and then increases gradually. This finding has been confirmed by Benirschke, Bloch & Hertig (1956a). It seems likely that these steroids are produced by the definitive zone but the results of analysis of the microdissected zones are not yet available.

The development of the foetal cortex.

Just as a clue to the function of the cortex has been provided by pathological conditions, so some idea of its development has been deduced from observations made by Benirschke (1956b) on anencephalic foetuses. The anencephalic baby (and some hydrocephalic, acardiac and amorphous foetuses) has very small adrenal glands. The glands, however, develop normally until about the twentieth week of gestation, after which they gradually regress until they are very small or even invisible to the naked eye. Where foetal hydrocephaly develops in late pregnancy, adrenal involution may then take place. These observations strongly suggest that the foetal
Foetal cortex is stimulated initially by a maternal secretion but that from about the twentieth week a foetal mechanism is necessary for its maintenance and that this involves the pituitary and possibly the hypothalamus and neurohypophysis.

Occasionally, however, the anterior pituitary of such babies is present and yet adrenal involution has occurred. This suggests that the pituitary can only release a foetal pituitary adrenocorticotrophic substance if stimulated to do so by something akin to the ACTH - release substance of the neurohypophysis.

The high ACTH production in the adrenogenital syndrome and the 17-Ketosteroid excretion pattern after corticotrophin indicated that there is some influence of corticotrophin on the foetal or reticular zones. The accumulated evidence provided by Lanman (1953), suggests that corticotrophin is not essential for the maintenance of the foetal zone in extra-uterine life and its administration will not prevent its involution.

The X-zone of the mouse foetal adrenal is similar in structure to the human one. According to Jones (1949), degeneration of the X-zone in hypophysectomised mice can be prevented by the administration of gonadotrophin thought to contain luteinising hormone (LH). Corticotrophin and follicle stimulating hormone (FSH) failed to maintain it and so did human chorionic gonadotrophic (HCG). These experiments have been confirmed by Botella-Llusia & Nogales (1953). Human chorionic gonadotrophin (principally luteinising in effect) /
effect) will also produce a significant rise in the urinary
17-Ketosteroid excretion of surgically castrated women,
(Botella-Illusia & Nogales, 1953; and Borell, 1954).
Benirschke suggests that the high maternal HCG levels of the
first trimester are responsible for the growth of the foetal
cortex, but that as these levels fall the foetal pituitary
secretion of interstitial cell stimulating hormone (I.C.S.H.),
which is identical with L.H., maintains it. The stimulus
to I.C.S.H. production is considered to be maternal oestrogens
(Markee, Sawyer & Hollinshead, 1948) and these steroids in-
crease greatly during the second half of pregnancy. Some
support for this is provided by the observations of Chang &
Witschi, (1955) that the adrenal hyperplasia induced by the
administration of oestrogens to larval frogs occurs only in
non-hypophysectomised animals. With the withdrawal of
oestrogens at birth, the secretion of I.C.S.H. falls and the
foetal X-zone involutes.

The development of the permanent cortex.

Benirschke suggests that the permanent cortex grows
after birth only as the foetal production of corticotrophin
is released from the inhibition of high pregnancy levels of
maternal corticosteroids. The definitive zone (permanent
cortex) does grow slowly during the last trimester of preg-
nancy when the maternal corticosteroid production is increas-
ing and 17-hydroxycorticosterone has been demonstrated in
the foetal gland. This would suggest that the growth of
the /
the permanent cortex is only partly inhibited by a maternal secretion and that it is functional in prenatal life. The histological studies of Langley (1955) indicate that the definitive cortex is responsive at birth to disease and injury.

**The Control of Carbohydrate Metabolism**

The elucidation of carbohydrate control in the mature organism is incomplete, but the present knowledge of it has been stated by Long (1952) and Talbot, Sobel, McArthur and Crawford (1952). From these reviews of a very great deal of animal and human investigation it is apparent that the glucocorticoids (sometimes known as the sugar-fat-nitrogen hormone or S,F,N.) play an important part in maintaining the blood sugar level. Pituitary Growth Hormone is diabetogenic because it retards the oxidation of glucose in the tissues, but it may be seen from Figure 51 that the glucocorticoids also accelerate the production of glucose from non-carbohydrate sources (fat and protein) while retarding its oxidation in the tissues. Deficiency of this hormone results in hypoglycaemia, increased tolerance of glucose and sensitivity to insulin, while an increased production leads to directly opposite conditions. The glucocorticoids are produced by the adrenal cortex as a result of stimulation by pituitary corticotrophin, and this accounts for the diabetogenic effects of therapeutic corticotrophin, for the decreased sugar intolerance of Cushing's syndrome and for the hypoglycaemia of Addison's disease.

Insulin /
FACTORS INFLUENCING CONTROL OF CARBOHYDRATE METABOLISM

Figure 51

DIETARY CHO  SFN  ADRENALINE

BLOOD GLUCOSE

SFN  TISSUE OXIDATION  INSULIN

SFN  EOSINOPHILS
SFN  EOSINOPHILS
Insulin antagonizes the glucocorticoids by stimulating glycogenesis and by the conversion of glucose into fat and protein. It is now believed that the pancreatic beta cells respond not to a pancreatropic pituitary hormone, but simply to the blood sugar level and this, should it be raised, may increase insulin production and then exhaust it. In short, it appears that the homeostatic mechanism by which the blood glucose is maintained at a given level is largely an interplay between the pituitary-adrenal axis and the pancreas, the liver being both fuel reserve and furnace while the hormones form the thermostat (Soskin, 1941).

The rather low blood sugar levels of the newborn infant, and the even lower ones reached if his mother is diabetic, may, therefore, be related in some way to the remarkable changes which take place simultaneously in the neonatal adrenal gland.

The Blood Sugar and Eosinophil Levels

The mean blood sugar level of a group of babies falls during the first few days and then rises slowly. The mean eosinophil level of a group of babies rises during the first few days and then slowly falls. The fact that operative procedures, cold, haemorrhage and other stimuli result in eosinopenia has been recognized for some time and Selye (1949) included this as part of the alarm reaction. Hills, Forsham and Finch (1945) demonstrated that corticotrophin and compound F produced a decrease in the numbers of circulating eosinophils and /
and have shown that the stimuli required to reproduce it are stress conditions, while Thorn, Forsham, Prunty and Hills (1948) made it clear that the adrenal cortex was essential if eosinolysis was to occur and that the corticosteroids were responsible for it. Although the dramatic post-natal changes in the adrenal gland concern cells which appear to be more concerned with the production of androgens, and the control of sodium in earlier foetal life than with the secretion of adult corticosteroids, it is clear that clucocorticoids are also in production at term and that secretion is likely to be influenced by separation from the mother.

Reduced secretion in the first week (either because secretion has been suppressed before, or because the previous stimulus has been withdrawn) and increasing secretion thereafter might explain the blood sugar and eosinophil changes, the increased glucose tolerance of the first week as compared with the second (Svensgaard, 1931-32), the poor responsiveness of the adrenal and the low excretion of corticosteroids in the first week (Venning, 1945; Klein, 1950, 1951; Talbot, Zygmuntowicz, Wood & Christo, 1951) and the rising levels in the second week (Klein, Fortunato, & Papadatos, 1954).

The possible relationship between a lack of corticotrophin in the newborn and neonatal hypoglycaemia occurred to Klein and Hanson (1950) and to Talbot et al (1952) who, discussing low corticoid excretion in the first week of life state - /
'It remains to be determined whether the tendency of infants to have relative eosinophilia, to develop hypoglycaemia and to show involution of the foetal zone of their adrenal cortices during the neonatal period, is significantly related to the foregoing'.

**Intention**

This study was made to determine whether serial parallel investigations of glucose and eosinophil levels in capillary blood showed that these move simultaneously in opposite directions. If such were shown to be the case then each might be associated with adrenocortical changes.

**Method**

Two samples of blood were taken within one minute from each baby of the group described in Study 4. The blood sugar of the first sample was determined in duplicate and the eosinophils were counted in the second sample. The blood sugar and eosinophil results are recorded in Studies 4 & 8. The simultaneous readings of sugar and eosinophil levels made possible this study of their movement relative to one another and to the age of the baby.

**RESULTS**

Of the 32 infants in the series, 18 chanced to be females. When the means of the blood sugar and eosinophil levels are superimposed (Figure 52) the two features (excluding the first few hours) do appear to move simultan-
Figure 52

SERIAL BLOOD SUGAR AND EOSINOPHIL LEVELS OF 32 NORMAL FULL TERM NEWBORN INFANTS

- males
- females
- mean of male and female groups
in opposite directions. Furthermore, the male infants have a lower mean blood sugar value, but a higher mean eosinophil count than the female infants.

The blood sugar eosinophil readings were submitted, however, to statistical analysis, not only of average figures for each feature, but also of the concomitant trend of the two features in each individual child; this was done not only for the actual readings at each age, but for the day-to-day changes in readings throughout the study. The methods of analysis are described in Appendix V.

The group described collectively.

At each day. The average values for blood sugar readings and eosinophil counts were studied in various ways. The standard deviations and coefficients of variation were calculated for each feature for each time unit (Tables 49, 50).

Taking the immediate birth period first it may be seen from the time-trend diagrams (Figures 41, 48) and from Tables 49, 50 that the mean blood sugar level for the group as a whole fell rapidly during the first two hours of life and that this was arrested before a similar period of time had elapsed: that is, the average blood sugar for the group fell by 11.2 mg. in the first two hours, by 1.1 mg. in the following two hours and by 0.1 mg. only in the next two hours. Similarly in the group as a whole the mean of circulating eosinophils fell by 156 during the first three hours of life and then rose by 27 cells/c.mm. in the next three hours, a considerably smaller increase. /
In the next period, from the second to tenth days, the mean blood sugar level for the group as a whole increased steadily from 65.5 mg.% on the second, to 82.7 mg.% on the ninth and 91.3 mg.% on the tenth day. Over the same period the group average value of the eosinophil levels decreased from 390 cells/c.mm on the third day to 259 cells/c.mm on the tenth, but this fall took place largely from day three to four.

Mean values cannot be taken as adequate descriptions and in this series particularly the scatter of values around the group mean at any time unit for both blood sugars and eosinophils was great. This can be seen both from the time-trend diagrams, which illustrate also the daily scatter of the actual observations, and from the coefficients of variation in Tables 49. In the blood sugar the coefficient of variation ( = S.D./mean expressed as a percentage) rose from 19% to 29% in the first hour and settled with some fluctuations thereafter to 12%. This is a high coefficient of variation. For eosinophils the scatter of values around the group mean was very much greater, the coefficient of variation starting above 60% and fluctuating widely above 40% even towards the tenth day.

Day-to-day Mean Increments. Although the scatter of actual values on individual days decreased slightly suggesting stabilization, the actual scatter of increments of individual /
individual infants from day to day did not increase.

**Components of the Group**

*Time-units.* Although the group mean for blood sugar tended to rise daily from the third day and over the same interval the group mean for eosinophils tended to fall; this was not accepted as reflecting the behaviour of individuals within the group. So great was the daily scatter of readings, particularly for eosinophil values, that more detailed analysis of this behaviour was considered essential, for many individuals within the group could have had rising eosinophils even though the group mean fell slightly.

The component 'paired readings' of blood sugar and eosinophil counts for each child at each time unit to some extent explain this wide scatter. The relationship existing between the blood sugar and eosinophils for each infant on each day was found from the correlations (see Appendix) and is also illustrated in the scatter diagrams (Figures 53 to 55).

It is clear from these that the eosinophil levels were not lower in those infants who had higher blood sugars. On some days the visual impression appears to indicate that those infants with higher sugar values tended to have higher eosinophil levels. On most days even this visual impression is absent.

*Increments.* The calculation of the correlation coefficients in fact shows that there was no relationship whatever between the changes in blood sugar and the changes in eosinophils;
Figure 53

THE RELATIONSHIP BETWEEN THE BLOOD SUGAR AND EOSINOPHIL LEVELS OF NORMAL NEWBORN INFANTS DURING DAYS 1 TO 4

![Graphs showing the relationship between blood sugar and eosinophil levels for birth, day 2, day 3, and day 4.](image)
THE RELATIONSHIP BETWEEN THE BLOOD SUGAR AND EOSINOPHIL LEVELS OF NORMAL NEWBORN INFANTS DURING DAYS 5 TO 8

Figure 54

DAY 5

1000

EOSINOPHILS
C. min.
500

DAY 6

1000

EOSINOPHILS
C. min.
500

DAY 7

1000

EOSINOPHILS
C. min.
500

DAY 8

1000

EOSINOPHILS
C. min.
500

BLOOD SUGAR mg%
THE RELATIONSHIP BETWEEN THE BLOOD SUGAR AND EOSINOPHIL LEVELS OF NORMAL NEWBORN INFANTS DURING DAYS 9 AND 10
eosinophils; on some days there was a small positive correlation and on others a negative, as detailed in Appendix V.

The Individual Child

Though there was no relationship between the two features on any day or between one day and the next, it might still be possible for each child to have falling eosinophils and rising blood sugars, each having its own cycle, and the phase in any individual not necessarily corresponding in time with the same phase in another individual. Graphs were therefore drawn for each individual showing the changes in both features (Figure 56). It then became apparent that the following patterns of movement (illustrated in Figure 57) existed for individuals within the group: A, blood sugar and eosinophil movement fairly consistently in opposite directions; B, an upward trend for both blood sugar and eosinophils; C, level blood sugar trend and downward trend for eosinophils; D, no eosinophil trend while blood sugars increased; E, blood sugar increased, eosinophils decreased but not simultaneously or consistently in opposite directions. In five individuals of the 32 in the group, the day-to-day graphs of the two features formed a pattern of opposite movement of type A, in nine both features rose as in B, in two the blood sugar was level and the eosinophils decreased as in C, in 11 there was no trend for eosinophils although the blood sugars increased as in D, and in five the blood sugars increased and the eosinophils decreased as in E.
SERIAL BLOOD SUGAR AND EOSINOPHIL LEVELS IN 32 INDIVIDUAL NORMAL NEWBORN INFANTS
Figure 57

MOVEMENT PATTERNS OF THE BLOOD SUGAR AND EOSINOPHILS

OF NORMAL NEWBORN INFANTS DURING THE FIRST TEN DAYS OF LIFE

[Graphs showing movement patterns of blood sugar and eosinophils over the first ten days of life]
Five infants only of the 32 studied produced a pattern of simultaneous movement in opposite directions. The largest single group of individuals, 11, had widely varying eosinophil levels from day to day which conformed to no pattern at all but were associated with rising blood sugar values. The majority of infants showed an upward trend of blood sugars, and, although the eosinophil pattern was more erratic, six infants had particularly high levels at birth and another five such very high levels on the third day that they dominated the means. This helps to explain why a study of the means alone gives the impression of increasing blood sugar and decreasing eosinophils.

It is clear from this individual analysis that simultaneous movement in opposite directions did not often occur.

COMMENT

A number of theories, mostly relating to the function of the liver, have been elaborated to explain the hypoglycaemia of newborn infants and these have been reviewed by Smith (1951) and by Pedersen (1952). van Creveld (1929), investigating the blood glucose levels of premature infants, suggested that hepatic immaturity was responsible, for with progressive maturation the levels rise. That the liver is immature in its function in both premature and in the majority of full-term infants has been shown in a variety of ways and more recently by Mollison (1948) but why it should be responsible /
responsible for hypoglycaemia is far from plain. It is true that the lowest post-natal levels correspond roughly to the days of weight loss and of minimal calorie intake but the newborn infant is born with an adequate glycogen store in the liver which is built up during the last trimester (Windle, 1940). This means that the low blood sugar levels are not due initially to lack of glycogen as suggested by van Creveld (1929) when he spoke of glucose from the placenta by-passing the foetal liver via the ductus venosus. Ward (1953) suggested that the glycogen was used quite quickly in starvation, but the cases studied were few and the duration of pregnancy and birth weights very varied.

Because of hepatic immaturity it has been suggested that normal glycogenolysis does not result from adrenalin but Desmond, Hild & Gast (1950) have shown that the blood sugar level does rise when adrenalin is injected at any time from birth, but the curve is flatter during the first few days than later. A prompt response to adrenalin has also been observed by Cornblath et al (1956, 1957). The fact that chromaffin tissue at this age, however, is secreting mainly non-adrenaline (West, Shepherd & Hunter, 1951) and (West, Shepherd, Hunter & Macgregor, 1953) which has less effect upon the blood sugar level may be of some importance.

The possibility of the foetal pancreas producing an excess amount of insulin has been raised and there is controversy as to whether or not functional over-activity exists. Nakamura (1924) described an excess of islet cells in foetuses and /
and newborn infants, while Fisher and Scott (1934) found pancreatic insulin levels in the newborn calf higher than in the adult animal. Kohler (1932) and Ketteringham and Austin (1939) applied this to human infants and ascribed the hypoglycaemic levels to true insulin hypersecretion.

Winter (1933) opposed the suggestion of excessive insulin on the grounds that the post-natal blood sugar was rising at a time when the pancreas was unchanged but this assumes that the function of a normal endocrine gland is necessarily reflected in the histology of those who die. White (1949) discarded the idea of hyperinsulinism as the mechanism of hypoglycaemia in the infants of diabetics because in her view such a process should inevitably be continuous and should eventually produce a zero value. Such an argument would also apply to the normal were hyperinsulinism a fact and were no other mechanism to intervene. Hartmann and Jaudon (1937) believed the cause to be relative hyperinsulinism, without necessarily hyperplastic beta cells, there being incomplete development of opposing mechanisms; while Wachter (1949) speaks of an absolute hypersensitivity to insulin in the first few days of life. The latter found that adrenalin was capable of producing a normal rise at this age, but if insulin were previously injected then no such rise occurred, a phenomenon confined to this age group. No explanation of the hypersensitivity was offered.

Soskin (1941) and Soskin and Levine (1946) believed the fasting blood sugar at any age to be identical with the hepatic /
hepatic threshold for glucose; above the threshold liver glycogenesis occurs and below it there is liver glycogenolysis. The hepatic threshold in turn is determined by hormonal activity, insulin lowering and anterior pituitary hormones producing a rise. The low blood sugar levels of the first few days of life are not likely to be the result of hyperinsulinism because hypoglycaemia is normally followed by decreased stimulation of the pancreatic islets and decreased insulin production. The low levels must depend upon a mechanism which is pre-set by intrauterine conditions and which the body readjusts over a period of some days. Pedersen (1952) has suggested that the blood sugar level on the first day of life in normal infants and in the offspring of diabetic women is explicable on this basis of hepatic threshold. The maternal blood sugar level determines the foetal level and, as a result, the foetal output of insulin. The latter is responsible for the foetal liver threshold so that the higher the maternal level the lower the foetal threshold and the lower the glucose levels in the first 24 hours. Similarly low maternal levels result in a low foetal output of insulin, a high foetal liver threshold and higher levels on the first day of extra-uterine existence.

Such a theory has much to commend it, but it disregards the continued low blood sugar on the second and third days of life and the important changes in an organ, the adrenal cortex, which is intimately associated with the control of the blood sugar. The foetal adrenal gland certainly secretes /
Figure 58

INDIVIDUAL SERIAL BLOOD SUGAR AND EOSINOPHIL LEVELS OF 16 NEWBORN INFANTS OF DIABETIC WOMEN

SERIAL BLOOD SUGAR AND EOSINOPHIL LEVELS IN 16 NEWBORN INFANTS OF DIABETIC WOMEN
Figure 59

ARITHMETIC MEANS OF SERIAL BLOOD SUGAR AND EOSINOPHIL LEVELS OF 17 NEWBORN INFANTS OF DIABETIC WOMEN
secretes glucocorticoids in increasing, if small, quantities during the last ten weeks of intra-uterine life and it opposes the insulin mechanism. A temporary fall in production for any reason (e.g. the withdrawal of maternal corticotrophin or the sequel of an "alarm reaction") might result in a lowering of the blood sugar. The activity of the definitive adrenal cortex and the hepatic glucose threshold both increase after the first few days and the blood sugar rises consequentially. If the diabetic mother is hyperglycaemic in pregnancy and if she has stimulated the foetal secretion of glucocorticoids excessively then, according to the above hypotheses, a more profound and possibly longer post-natal hypoglycaemic phase may be expected. The present study, however, fails to provide evidence of a relationship between the blood sugar and adrenocortical function. Similarly comparison of the fasting blood sugar and eosinophil levels in the infants of diabetic women (Studies 5 and 9) shows that simultaneous movements of these features in opposite directions does not (Figure 58) occur although comparison of the group means (Figure 59) suggests that some such relationship might exist.

CONCLUSION

The group average blood sugar and eosinophil levels in Studies 5 and 9 and in 6 and 10 appear to move in opposite directions.

This suggested the possibility that temporary post-natal hypoadrenocorticism might play some part in maintaining the /
the low blood sugar levels of the newborn.

Other methods of examination of the values have shown that simultaneous movement of these two features in opposite directions did not take place in individual babies. The circulating eosinophils, whose day-to-day fluctuations are so great that their mean values have little meaning, are an unreliable index of adrenocortical function at this age.