MATERNAL HYPERGLYCAEMIA AND FOETAL HYPERINSULINISM IN DIABETIC PREGNANCY

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THE babies born to diabetic women, and to those women whose diabetes declares itself only in later life, are usually heavier than average for their gestational age, and their overall length may be greater. They have a pronounced tendency to develop brief neonatal hypoglycaemia and a considerable increase both in pancreatic islet cell area and in the insulin-secreting response to injected glucose. Under ideal conditions and in large series they have a perinatal mortality rate which may be four times that for babies of normal women, and which even in good hospitals may be six or seven times greater than normal (Farquhar, 1958a).

This paper summarizes the evidence for the existence of these physical abnormalities and speculates on their cause.

The Physical Abnormalities

Weight

Since Bennewitz (1828) first recorded the enormous still-born foetus of a woman who was recognizably diabetic only in pregnancy, indisputable evidence for the excessive birth weight of such infants has been presented. It was described by Fischer (1935), and in the experience of White and Hunt (1943) the average weight of normal babies at any gestational age is exceeded by four-fifths of these infants. Similar findings have been reported from large series studied by Miller, Hurwitz and Kuder (1944), Peel and Oakley (1950), Warren and Le Compte (1952), Cardell (1953), Pedersen (1954), Farquhar (1959) and Gellis and Hsia (1959). The increased weight is clearly a function of the diabetic environment in which the foetus develops, as the babies of diabetic fathers do not differ discernibly at birth from those of non-diabetic men (Babbott, Rubin and Ginsburg, 1958).

The infants have often been described as oedematous (Miller, Johnson and Durlacher, 1944; Given, Douglas and Tolstoi, 1950; White, 1952; and Gellis, 1954). Many authors believed that this

implied such retention of water that it made a significant contribution to the excessive birth weight, and that in shedding it as urine the infants lost much more than the usual amount of weight during the first week of life. The fact that Cardell (1953a) found little oedema in his autopsy series could be explained by the infants having shed their fluid before death, and the first real challenge to the popular 'waterlogged baby' story came when we surprised ourselves by finding that in the Edinburgh series the babies had *not* lost significantly more weight than control infants during the first week of life when they were matched as closely as possible for several relevant factors, including the route of delivery (Farquhar and Sklaroff, 1958). Osler, in Copenhagen, studied the total body water and the extracellular water of such babies and of a normal group. He was able to show that the infants of diabetic mothers have significantly less total and extracellular water, although they have no reduction in intracellular water, and he suggested that these findings are in keeping with foetal obesity and the possible binding of water in cells by increased glycogen formation (Osler, 1960a). He then compared the subcutaneous fat layer of such babies with that of normal full-term infants and with control babies of the same maturity born to non-diabetic women, using measurement of skin-fold thickness and radiological measurement of the subcutaneous tissue of the lower leg and chest. He showed that subcutaneous fat was increased in the diabetic series by from 38 to 46% compared with normal infants and by 50% compared with controls (Osler, 1960b).

Only one direct chemical analysis of the cadaver of a typical infant of a diabetic woman has been published so far (Fee and Weil, 1960). This baby suffered from idiopathic respiratory distress and died at 21 hours. Fat was found to be moderately increased for an infant of comparable size and markedly increased on the basis of gestation when compared with figures given by Widdowson and Spray (1951). Similarly the body water-to-protein ratio corresponded more with gestational age than with body size and the relationship between sodium, chloride and potassium suggested that

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there was no increase in extracellular fluid, but a slight increase in intracellular water. These authors have now completed the direct examination of eight further cadavers and of a number of babies of non-diabetic mothers. Their results will be published later, but, although their calculations are as yet incomplete, they are likely to confirm their original finding, and the body fat of infants of diabetic women seems to be increased certainly from the 34th week of gestation (Fee and Weil, 1962).

The recent development of commercial techniques for finding the lean meat content of animal and bird carcasses by determining their natural radioactive potassium-40 content (Kulwich, Feinstein, Golumbic, Hiner, Seymour and Kaufman, 1961) opens up a possible new way of calculating the muscle mass contribution to total weight in live infants of diabetic and non-diabetic women.

Length

Length is a one-dimensional measurement and any variation from the normal is likely to be less impressive than in the case of body weight, but the earlier reporters of foetal gigantism in diabetic pregnancy suspected an increase in body length as well as in weight, a fact of considerable interest in view of experimental work on the production of animal diabetes with pituitary growth hormone.

Actual length was said by Warren and Le Compte (1952) to exceed that calculated in more than half the babies in their series, and Cardell (1953a) confirmed that the infants in his were longer than normal controls of the same gestational age, and that this increase was proportionate to weight. No comment was passed on length by Driscoll, Benirschke and Curtis (1960), but in any case their observations, as well as those of Warren and Le Compte and of Cardell, refer to autopsy examinations, and the birth weight, and so possibly also the birth length, of perinatal deaths may not be representative of these characteristics for the group as a whole (Farquhar, 1962).

In Pedersen's series (1954) the infants of diabetic mothers were found as a group to exceed in total length by an average of 1.5 cm. the babies of non-diabetic 36- to 38-week pregnancies. Routine but rather inexact measurements of crown-heel length in the earlier Edinburgh series indicated at least this order of difference (Farquhar, 1958b). Gellis and Hsia (1959) did not discuss length. Osler and Pedersen (1960), however, confirmed Pedersen's earlier observation and stated that the infants were no longer than babies of comparable weight or, as Cardell had said, the infants were large but proportionate. They also showed that the radiological bone age of infants of diabetic mothers does not correspond to their length and

FIG. 1.—Crown-heel lengths of babies born to diabetic mothers in Boston (Mass.) and Edinburgh.

weight, but to their gestational age or even less. Radiological measurements of bone, muscle and fat widths are feasible from quite early in childhood (Stuart, Hill and Shaw, 1940; Maresh, 1961), but personal attempts at such in newborn infants in Boston were so full of possible error that they were abandoned. Careful measurements of crown-heel lengths were made by measuring-board on a further series of infants of diabetic mothers at the Boston Lying-in Hospital, Massachusetts, and the Simpson Memorial Maternity Pavilion, Edinburgh. (Crown-heel length was used rather than crown-rump to allow comparison with previous studies.) The calculation of gestational age according to the date of onset of the woman's last menstrual period is notoriously imperfect, but is probably as good as any other method available. The results are given in Fig. 1, where the normal mean curve has been calculated from Ellis (1951) and is probably acceptable for both cities. The vertical lines intersecting the curve indicate ± 1 cm. from the mean, and the graph very strongly suggests that infants of diabetic mothers in Boston and Edinburgh are as a group appreciably longer than controls. Each infant of a diabetic woman was carefully re-measured about the fifth day of life when weight loss was greatest, and it may be seen from Fig. 2 that increases and decreases in measurement were small and that they were probably the result of positional change. Thus there is evidence that newborn infants of diabetic mothers are not only obese, but they are longer than controls, and this probably results in part from increased skeletal growth.

Hypoglycemia

The fact that the newborn infants of most diabetic women develop a brief period of hypo-

FIG. 2.—Frequency distribution of changes in crown-heel lengths of infants born to diabetic mothers (Boston, Mass., and Edinburgh).

FIG. 3.—Arithmetic means of the blood sugar levels in a group of normal infants and in a group of infants of diabetic women.

glycaemia during the first few hours of life and that on average this is more pronounced than in babies of non-diabetic women has probably been proved beyond all reasonable doubt and is illustrated in Fig. 3 (Farquhar, 1956a). Later work, particularly that of Hallman, Furuholm, Harri and Puranen (1956), who used a so-called 'true glucose' method, has shown that the neonatal blood glucose level may be even lower than was previously suggested by older techniques, but this probably holds true equally for infants of diabetic and non-diabetic mothers. This is certainly the personal impression gained from current, as yet unpublished, work using a modification of the glucose-oxidase technique of Huggett and Nixon (1957).

Pancreatic Islet Area

Unusual size of the pancreatic islets of Langerhans in babies of diabetic mothers has been recognized by many histologists since the early descriptions of Dubreuil and Anderodias (1920) and Wiener (1924). Many of these references are given by Pedersen (1952) and Farquhar (1958a). The islets vary in size appreciably, not only from one pancreas to another, but from field to field within the same pancreas, and doubt has existed among pathologists as to whether the total islet cell volume of such glands would prove abnormal if

FIG. 4.—Relative areas of pancreatic islets in newborns of normal and diabetic mothers.

they were matched properly for duration of pregnancy. Ogilvie (1958) is in no doubt about the quite remarkable size of such islets, and if the extensive experimental observations of Topping (1947) be applied to such a belief, then an increased islet cell volume may be assumed from his conclusion that 'if in a section of pancreas we find a number of islets which is relatively greater than normal we can—in spite of the fact that the very large and the largest islets are only a relatively small part of the islet tissue—draw the conclusion that the total volume of islet tissue is larger than normal'. But there are also two separate studies of actual islet area. Cardell (1953b) found that the islets of infants of diabetic mothers formed from 1.8 to 9.9% of total pancreatic tissue compared with a normal neonatal range of from 0.7 to 2.6%, while Woolf and Jackson (1957) found the means of the two groups to be 6.5 and 1.3% respectively. Thus, in relation to the size of the pancreas, the dead newborn infants of diabetic women seem to have roughly four times more islet tissue than the normal (Fig. 4), although another really large, careful study may be desirable. Unfortunately, the Boston group have gone no further so far than to state that 81% of 57 infants examined by them showed appreciable islet hyperplasia (Driscoll and others, 1960).

Although histological knowledge of the islets of foetus and newborn is fairly recent (Ferner, 1958; Robb, 1961), several careful studies report that in babies of diabetic mothers the beta cells commonly form much more than the normal 50% of total neonatal islet cells, so that islet hypertrophy is

FIG. 5.—The position of the catheter in relation to the venous drainage of the pancreas.

achieved by beta cell hyperplasia (Hultquist, Lindgren and Dalgaard, 1946; Cardell, 1953b; Woolf and Jackson, 1957; Driscoll and others, 1960). This finding implies an increased capacity to secrete insulin (Farquhar, 1959).

Insulin-secreting Capacity

The capacity of the islet beta cells of the newborn infant of the diabetic woman to respond to the normal physiological stimulus (i.e. a rise in the level of blood glucose) has been tested recently by determining both the speed with which an intravenous glucose load is removed from circulation and the plasma-insulin activity of venous blood collected close to the point of insulin discharge (Fig. 5) immediately before and again five minutes after the injection of glucose (Baird and Farquhar, 1962).

The experiment can be criticized on such grounds as the admitted inability to provide an entirely satisfactory control group or even on the rat-diaphragm technique of assay, but the results are quite clear and they suggest that the pancreas of these babies during the first few hours of life responds more actively to a rise in blood glucose than does the pancreas of the normal infant. The experiment also excludes the possibility that the high plasma-insulin activity produced in the baby is accounted for by the transfer of exogenous or endogenous insulin from the mother.

Possible Causes of Increased Insulin Secretion

Pedersen believes that the maternal blood sugar level determines the foetal one, that there is little lag between the two, and that at birth the baby's blood glucose falls to a point decided by the average prenatal glycaemia. He suggests that the hyperglycaemia of maternal diabetes, or pre-diabetes, promotes foetal hyperglycaemia, and that this so stimulates the foetal pancreatic beta cells that abnormal amounts of insulin are secreted which, in the presence of copious glucose, promotes foetal obesity. The positive correlation of islet cell area and birth weight (Cardell, 1953b) is in keeping with this thesis.

Foetal obesity is also accompanied by increased foetal length, and animal experiment strongly suggests that this may also result from increased insulin in the presence of abundant food (Farquhar, 1956b), so that the phenomenon of the sleek, fat and proportionately long baby of a diabetic mother may be explicable on hyperglycaemia and increased insulin activity alone. Among the possible known causes of hyperinsulinism which require consideration, the most important are maternal hyperglycaemia, pituitary growth hormone, hyperadrenocorticism and the insulin antagonist which has been so intensively investigated by Vallance-Owen.

Hyperglycaemia

Islet cell hyperplasia has been produced by maintaining hyperglycaemia in guinea-pigs (Woerner, 1938), dogs (Houssay, Foglia, Smyth, Riether and Houssay, 1942), cats (Dohan and Lukens, 1948) and rats (Tejning, 1947; Hultquist, 1948; Wissler, Findley and Frazier, 1949). In Hultquist's experiments the tissue was taken from the offspring of rats who had been pancreatectomized in pregnancy. Hyperglycaemia has been doubted as the cause of increased foetal weight because of the well-known gigantism of babies born to women who only became frankly diabetic many years afterward and who were not recorded to have glycosuria in pregnancy. Both Hagbard (1958) and Hagen (1961) have claimed, however, that women who bear large infants have higher than normal fasting blood sugars and some decrease in glucose tolerance. This finding may not be shared by everyone, but such decreased glucose tolerance as the prediabetic woman may have in pregnancy can be balanced by the increased foetal use of glucose, so that the maternal level may not rise to the renal threshold unless the glucose load is so suddenly imposed that her level rises faster than the mechanism for maternal-foetal equilibration permits.

The 'hyperglycaemia hypothesis' is borne out

FIG. 6.—Patterns of family birth weight in prediabetic and diabetic pregnancy.

within certain limits by the experiences first of Pedersen (1952) and Pedersen and Brandstrup (1956), and later of Oakley (1961), who claimed that the average birth weight of such infants could be reduced to within the normal range by prolonged very strict control of the maternal glycaemia throughout each 24 hours for much of the pregnancy.

Many people believe that during the pre-diabetic years maternal glucose tolerance may be progressively impaired with each pregnancy until clinical diabetes appears. Were this so, then a gradually mounting mean maternal blood sugar in each pregnancy could be expected, with the consequent birth of heavier and heavier babies up to the point where diabetes is recognized and the maternal hyperglycaemia is controlled. But in practice there are important exceptions to this pattern.

Some examples of prediabetic family birth weights may be seen in Fig. 6. Some women bear infants of steadily increasing weight, others are remarkably consistent over many years, while with some the trend is steadily downward, and with yet others there is no trend at all (Farquhar, 1962). Were no other changing factor involved than these, then differing patterns could be explained only by such variables as appetite and activity or, less conspicuously perhaps, on a genetic basis (Pyke, 1960).

Pituitary Growth Hormone

The experiments of Young (1953, 1961) suggest that pituitary growth hormone (PGH) may play a part in causing diabetes mellitus. The administration of purified PGH to pancreatectomized and hypophysectomized baboons causes a rise in blood sugar and the appearance of ketosis (Gillman,

Gilbert, Epstein and Allan, 1958). Similarly hypophysectomized human diabetics develop a pronounced rise in blood glucose and ketosis when given purified human growth hormone (Luft, Ikkos, Gemzell and Olivecrona, 1958; Raben, 1959; Hernberg, 1960).

Using an immunological method for measuring this hormone, Ehrlich and Randle (1961) found it increased in the majority of obese diabetics and in diabetics with retinopathy, but less so or not at all in other diabetics. They suggest that increased maternal PGH may be responsible for the large size of the foetus in diabetic pregnancy. This possibility was discussed by Osler and Pedersen (1960) because they believed foetal obesity to be inconsistent with it, the hormone having fat-mobilizing and protein-sparing effects. But Ehrlich and Randle point out that fat mobilization can be suppressed if the animal or human has free access to liberal amounts of glucose or food (Salter and Best, 1953; Raben and Hollenberg, 1960).

Of some interest are the observations that PGH is strongly lactogenic (Chadwick, Folley and Gemzell, 1961; Lyons, Li and Johnson, 1961), because as a group diabetic women lactate rather poorly (Farquhar, 1959). There are individual exceptions to this rule, and a variety of discouraging factors exist, among which the physician or obstetrician may sometimes be numbered. Excessive lactation in prediabetic pregnancy has been suspected by Jackson (1952), in whose experience lactation failed as overt diabetes appeared. But if excessive PGH is directly responsible for foetal overgrowth in diabetic pregnancy, and if it is truly lactogenic, then failures of maternal lactation would surely be less usual, and there might be foetal breast enlargement and secretion even in the immature newborn, a development which is rare.

Adrenal Glucocorticoids

The puffy features, plethora and oedematous appearance of the babies at birth led to their being described as 'Cushingoid' by Jackson (1955) among others. Unusual hirsutism has been noted by Eklund, Hjelt and Lumme (1960) and Driscoll and others (1960). Adrenal glucocorticoids can be diabetogenic to normal human subjects, may exaggerate the carbohydrate disorder of diabetic ones, have been reported as increased in diabetes mellitus, have caused foetal gigantism and intra-uterine death when given to pregnant animals, and can promote pancreatic islet hypertrophy (Farquhar, 1956b). Increased corticosteroids have been described in the amniotic fluid, the blood or the urine of babies of diabetic mothers by Hoet and Lukens (1954), Björklund and Jensen (1955), Farquhar (1956b), Klein and Taylor (1960) and

Lloyd (1961), but not in the careful blood study made by Migeon, Nicolopoulos and Cornblath (1960), nor in the amniotic fluid study by Baird and Bush (1960).

The recently established findings that such infants are obese and are without increased total body water, extracellular water or salt indicate that any increase in corticosteroids (maternal or fœtal) which they possess is unlikely to be great or prolonged and is not the principal cause of their beta-cell hyperplasia and obesity. This does not exclude the possibility that corticosteroids are active in some other way.

Insulin Antagonist

The existence of an insulin antagonist in normal human subjects was described by Vallance-Owen and Hurlock (1954). Such an excess of this antagonist was found in the plasma of hyperglycæmic diabetics that it could inhibit the action of added insulin (Vallance-Owen, Hurlock and Please, 1955). It opposes insulin activity in muscle, *but not lipogenesis* (Pyke and Please, 1957). It is found in the albumin fraction of plasma (Vallance-Owen, Dennes and Campbell, 1958a), is probably of low molecular weight and may be a polypeptide (Vallance-Owen and Lilley, 1961a). Its action is believed by Vallance-Owen, Dennes and Campbell (1958b) to depend upon the pituitary, but Lowy, Blanshard and Phear (1961) think it may be independent of it. It would seem to be dependent upon adrenal corticosteroids (Vallance-Owen and Lilley, 1961a). High levels of antagonist have been found in the plasma of obese diabetics and prediabetics (Vallance-Owen and Lilley, 1961b), and it has been found in the plasma of young untreated ketotic diabetics (Steinke, Taylor and Renold, 1961).

Such findings are in keeping with those of Maclean and Ogilvie (1959) that diabetes in the young may be accompanied by initial islet hyperplasia, and that it may occur in some patients who have a normal quantity of islet tissue. Thus the antagonist may result in increased secretion of insulin which is unblocked or at least less restricted in lipogenesis than it is in glucose utilization in muscle. The child or adult becomes obese and later may develop diabetes, even although islet tissue may not decline for some years. The low molecular weight of the antagonist makes possible its transfer across the placenta from prediabetic or diabetic mother to the baby (Vallance-Owen and Lilley, 1961b), where it would oppose the secretion of fœtal beta cells, so causing fœtal obesity and possibly a true acceleration of linear growth if the action of insulin on skeletal growth is uninfluenced by it.

Variable Activity of PGH and the Antagonist in Relation to Fœtal Morphology

Both human growth hormone, as a pituitary product, and the antagonist, whose action is dependent upon the pituitary and adrenal cortex, are probably subject to variations in their amount and activity, and this could explain not only spontaneous changes in diabetic control, but also the variable pattern of fœtal weight in prediabetic or diabetic pregnancy (Fig. 6).

If increased length for gestational age results directly from the action of PGH (unmediated by insulin), then the maintenance of maternal normoglycæmia by strict control in pregnancy should result in the birth of long babies of normal birth weight, whereas if increased length results from increased insulin secretion promoted by hyperglycæmia or the antagonist, then such strict control may be followed by the birth of infants whose weight and length are normal for gestation. Further comparison of accurately measured fœtal lengths and weights is required and the results should be related to the standard of carbohydrate control in individual patients.

Perinatal Mortality

The experiences of Pedersen (1952) and of Oakley (1961) show that strict control of the pregnant diabetic's blood glucose, and all the extra care that goes with that, results not only in babies of more normal appearance and birth weight, but also in significant reduction of perinatal mortality in viable pregnancies. This may suggest that the 'hyperglycæmia hypothesis' may also explain the high incidence of fœtal death.

The Time of Death

Until now appreciably more than half the fœtal deaths which have been reported in most large series have occurred *in utero*, and it is important that the pædiatrician, who may never see the macerated still-births, recognizes this when considering the possible causes of neonatal disturbance or death. Thus intrauterine death may be independent of the jungle of abnormal findings described in the live newborn, among which are congenital malformation, hypoglycæmia, hypopotassæmia, hyperpotassæmia, hypocalcæmia, hypoadrenocorticism, hyperadrenocorticism, hypotension, pulmonary hyaline membrane, metabolic and respiratory acidosis and hyperbilirubinæmia. One or other of these may be productive of symptoms or even of death, but the fundamental abnormality predates their development.

Autopsy Findings

The post-mortem examination of still-born infants of diabetic women seldom reveals any ex-

FIG. 7.—Examples of high foetal survival rate at high birth weight in prediabetic and diabetic pregnancy.

planation for death other than signs of intrauterine anoxia. Neonatal deaths may show similar changes, and pulmonary hyaline membrane is commonly present. Congenital malformations have not contributed to neonatal mortality in the Edinburgh series, and Cardell (1953a) found significant malformations just as commonly in babies of non-diabetic women. In this respect these two studies are quite different from the Boston one, where an increased incidence of serious congenital abnormalities is reported (White, 1952; Driscoll and others, 1960). Personal experience of the Boston series, however, suggested that, even with this increased incidence, less than 20% of the deaths could be explained by lethal malformations. Similarly, although the occurrence of renal vein thrombosis (Takeuchi and Benirschke, 1961) is interesting, it is extremely rare.

The Role of Obesity

Osler and Pedersen (1960) have suggested that obesity may restrict neonatal respiration and that breakdown of excessive glycogen may so release water that circulatory difficulty results. This may possibly contribute to the embarrassment of an already abnormal infant, but experience in this series suggests that, if the safe birth of the larger babies can be assured, then they may make entirely satisfactory progress. In Fig. 7 examples are given of several families of such larger babies, only one member of whom died, and all the others were quite normal in all respects. Indeed, the process of growing heavier and longer because of the stimulus of extra glucose and insulin seems so physiological that it provides a poor explanation for death, and the babies seem to conform to the principle so clearly enunciated by McCance (1959) and

McCance and Widdowson (1961) that growth has protective properties.

Mortality and Birth Weight

In the large Boston series, perinatal foetal mortality is higher among those diabetic mothers who suffer from nephropathy, and their babies are significantly smaller than are those of women whose diabetes is unassociated with such a gross renal lesion (Oppé, Hsia and Gellis, 1957). But irrespective of whether the mothers in the Edinburgh series suffered from this complication or not, still birth, idiopathic respiratory distress and neonatal death (Fig. 8) have all been much commoner among babies of less than 3 kg. birth weight than in heavier infants, even when consideration is given only to those of 36 weeks' gestation or more (Farquhar, 1959, 1962). The perinatal mortality is also greater in the smaller babies in the Birmingham series (Malins, 1962). Thus this experience accords with that of Brandstrup, Osler and Pedersen (1961), who found a 'middle-cut' of babies within their series who were of a gestational age and birth weight in which mortality was low. The Edinburgh series suggests further that it is much safer to be above this optimum weight range than it is to be below it, and this conflicts with the notion that simple intrauterine over-nutrition is the harmful factor.

Mortality in Families

A study of the mortality pattern of families born to diabetic women varies widely (Fig. 9) from those in which all the babies survive to those in which all die, and in the 108 families of this series 57 mothers have produced 185 babies without loss, whereas the other 51 mothers have produced 203 babies with a mortality of 38% (Farquhar, 1962).

The Influence of Control

Although the standard of both diabetic control and obstetrical supervision very materially affects the prognosis for foetal survival (Farquhar, 1959, 1962), just as the strictness of carbohydrate control alone may alter the prognosis for circulatory health in pure pancreatic diabetes (Duncan, MacFarlane and Robson, 1958), it is equally clear from this study that some women without nephropathy and with optimal care may have a dismal record of foetal loss and that others may be entirely successful, although their supervision and co-operation do not differ. Furthermore, even if diabetic control is of the very high, almost unique, standard achieved by Pedersen and his colleagues in Copenhagen, where the mothers are maintained virtually normoglycaemic for many weeks until delivery, the viable foetal mortality over a number of years

FIG. 8.—Maturity, birth weight and survival of infants of diabetic women.

does not fall below 120 per 1,000 (Brandstrup and others, 1961). This figure is three or four times greater than that for non-diabetic pregnancies. Thus it would seem certain that some factor other than control of the blood glucose level contributes toward intrauterine death and to those biochemical or clinical abnormalities which may appear in the live-born.

Idiopathic Respiratory Distress Syndrome

The idiopathic respiratory distress syndrome (IRDS) is seen commonly in newborn infants of diabetic mothers, and pulmonary hyaline membrane is found in from 25 to 75% of the neonatal deaths. In the 95 neonatal deaths described by Driscoll and others (1960), membrane formation of some degree was recognized in 75%, it was diffusely present in the lungs of 57%, it was the major autopsy lesion in 51%, and it existed presumably

in other distressed infants who survived. The authors found the lesion to be identical with that seen in babies of non-diabetic women. The extensive literature about this very important neonatal problem has been comprehensively reviewed by James (1959) and by Gregg and Bernstein (1961). Whatever may be the aetiological importance of such deficiencies as those of the surface-active mucopolysaccharide material described by Avery and Mead (1959), which facilitates lung expansion, or of the plasminogen-plasmin system (Quie and Wannamaker, 1960) which promotes the lysis of exuded fibrin, all that is known of clinical factors common to the two susceptible groups (prematurely born babies and infants of diabetic mothers) is that both are immature, that both are likely to have experienced intrauterine oxygen-lack of dangerous duration, and that Cæsarean section may have a provocative

FIG. 9.—Patterns of viable foetal mortality in the families of diabetic women.

effect. Infants who are more mature may survive hypoxia and neonatal asphyxia without developing distress, and those who are less mature may survive undistressed if the cause of their premature delivery does not involve intrauterine hypoxia. A period of insufficient placental exchange before birth seems to form the foundation upon which immaturity of such enzyme systems as these just quoted and the normal post-natal adjustments of circulation and of fluid compartments build further mechanical and metabolic abnormalities with resultant hyaline membrane formation. Progressive degrees of placental disruption were accompanied by diminishing concentrations of hexosamine (mucopolysaccharide) in the lungs of foetuses and newborns in the study by Crawford and Mitchell (1962). This may reflect falling concentrations of the surface-active material of Avery and Mead (1959), but no correlation was established between concentrations and the occurrence of neonatal respiratory distress. The authors indicate, however, that the series may be too small and that autopsy analyses do not necessarily mirror the 'live' situation. It is also interesting to recall in this connection that the incidence both of IRDS and of neonatal death in this series is higher in infants of less than 3,000 g. birth weight, and that Gruenwald (1960) has shown that the surface-active material in lung is uniformly present in babies who weigh 3,000 g. or more. This is again inconsistent with the belief that babies who have been fattened and forced in growth with glucose and insulin should have an increased incidence of respiratory distress and neonatal death.

The present evidence fits the hypothesis that neonatal disturbance and mortality result from pre-natal under-nutrition and impaired exchange of oxygen and carbon dioxide caused by placental insufficiency and that their rarer occurrence in obese infants may be due either to difficult and therefore anoxic birth or to late failure of a placenta upon the efficient performance of which a macrosomatic infant depends. Once respiratory distress has developed, however, the conditions which prevail in babies of diabetic women may increase the difficulty. A study of the various large autopsy series already quoted will show that there is no good evidence for the existence of increased glycogen in these infants. They are known to raise their blood sugars at an unstated time after birth in response to adrenalin (Reardon, 1958), but the better documented study of Cornblath, Nicolopoulos, Ganzon, Levin, Gordon and Gordon (1961) has shown not only that spontaneously born infants of diabetic mothers have a hyperglycaemic response to glucagon which is similar to that provoked in those born by the same route to non-diabetic women, but that those delivered by Caesarean section require a ten-fold increase in glucagon dosage to achieve the same result, while Cornblath gained the impression that infants with distress were less responsive to the hormone than were asymptomatic babies. Although the histological studies may imply simply that the excessive glycogen was used before the infants died, it could be a point against the simple maternal-hyperglycaemia-foetal hyperinsulinism hypothesis and in favour of activity of the maternal insulin antagonist within the foetus. Furthermore, the need of these distressed infants to use their fat, of which they have more than their share, for energy may require that they obtain more oxygen than the metabolism of glycogen would need at a time when pulmonary exchange is inadequate and releases more water than would glycogen at a time when the circulation is already embarrassed.

The Placenta and Micro-circulation in Diabetes

Although the ratio of foetal to placental weight is similar in deaths and survivors and does not differ from that in non-diabetic pregnancy, placental structure and function have attracted much interest in diabetes, and the possibility of premature placental ageing and consequent insufficiency resulting in foetal starvation and anoxia, often slowly but sometimes abruptly, has been discussed (Farquhar, 1959).

The hormonal replacement therapy used by the Joslin Clinic to correct a suspected imbalance arising out of placental insufficiency has failed to meet with universal acclaim and it certainly fails to prevent foetal death or idiopathic respiratory

distress. Calcification of the maternal pelvic vessels, reported in Boston (White, 1952), is rarely found in Edinburgh and so provides no explanation for the foetal mortality in this series.* The extensive extra-medullary erythropoiesis which exists at birth, the considerable normoblastæmia and raised hæmoglobin have been ascribed to intra-uterine hypoxia (Miller, Johnson and Durlacher, 1944; Given and others, 1950; Berglund and Zetterström, 1954). Reduced availability of oxygen to the foetus was demonstrated in diabetic pregnancy by MacKay (1957) and the normal myometrial blood flow found by Brudenell, Miles and Coleman (1961) cannot exclude possible poor transfer of oxygen and nutrients across the placenta.

Earlier histological studies of the placenta in diabetes were unrevealing except for an unconfirmed suggestion of abnormal stromal œdema made by MacKay (1952). More recently Burstein, Soule and Blumenthal (1957) have found that, unlike those of either normal or hypertensive-toxæmic groups, the placenta of about one-third of diabetic women show marked endarteritic lesions of vessels which may progress to vascular obliteration or thrombosis and true infarct formation. But whatever the larger vessels of maternal origin may show, general recognition is now given to the early widespread involvement of the venules, capillaries and arterioles throughout the body in this condition (Colwell, 1960). This may be seen in the small vessels of the bulbar conjunctiva if good equipment is used (Ditzel, White and Duckers, 1954; Ditzel, 1956; Ditzel and Moinat, 1957; Bech, Hansen, Lorentzen and Lundbaek, 1960; Ditzel, Beaven and Renold, 1960; Landau and Davis, 1960; Farquhar, 1962). Electron microscope studies of diabetic kidney have shown that thickening of the basement membrane up to ten times normal may exist in all glomeruli (Farquhar, Hopper and Moon, 1959). Earlier lesions take the form of small deposits of hyaline in close relation to the basement membrane and between the cell membranes of adjacent endothelial cells. These deposits expand and isolate endothelial cytoplasm until the capillary lumen is obliterated. Sabour (1961), Sabour, Nagy El Mahallawy and Abou-El-Naga (1961) and MacDonald (1962) have confirmed these findings in renal biopsy material from young Edinburgh patients with recent onset diabetes and have shown that the abnormalities are probably almost or entirely coincidental with the onset of the metabolic disturbance. Simultaneous studies of conjunctival

and nail-bed vessels by Landau and Davis (1960) have revealed what has been called the basic diabetic lesion, capillary congestion on the venous side, severe capillary narrowing and conjunctival micropools. Light- and electron-microscope studies of toe and finger pulp capillaries from diabetics by Aagenaes and Moe (1961) revealed a peri-endothelial PAS-positive material in many specimens. This abnormality was particularly pronounced in those patients whose disease had begun before the age of 40 and where retinopathy and nephropathy were present. In the worst cases the PAS-positive layer was more than ten times thicker than the normal basement membrane.

The delicate micro-vessels in the foetal placental villi by means of which supply and excretion are maintained are exposed to a continuous high-pressure flow of diabetic blood. It seems reasonable to expect that as part of an organ which may age prematurely even in apparently normal pregnancy, and more commonly in toxæmia, these micro-vessels may undergo the same sort of subtle change which electron-microscopy has revealed in capillaries elsewhere, and which could interfere with foetal nutrition and excretion and even with survival.

Plasma Protein Abnormalities

(a) *In the Diabetic Mother.* The literature on protein, lipoprotein and protein-bound carbohydrate abnormalities in the serum of diabetic patients has been extensively reviewed by Éjarque, Marble and Tuller (1959), and they make it clear that these protein fractions can be abnormal before clinical evidence of vascular complications appears. In their own study of sera from young diabetics they have found decreased albumin, increased α_2 -globulin, raised β - and reduced α -lipoproteins and increased α_2 -glycoproteins, particularly in the presence of vascular complications. Ditzel and Moinat (1957) have shown that in diabetic pregnancy great increases in maternal β -lipoprotein and α_2 -glycoprotein fractions are also possible during the last trimester in association with changes in the small vessels of the bulbar conjunctiva, but they were unable to relate these findings to the outcome of pregnancy.

The abnormal serum lipoprotein component, pre- β -lipid (p- β -l), which is known to occur in patients with clinical coronary artery disease, has been studied in diabetic pregnancy by Vernet and Smith (1961). Whatever its relationship to the development of vascular complications, it was found to increase in successful diabetic pregnancies from the 25th week, to be considerably elevated at term and to fall rapidly after delivery. In unsuccessful diabetic pregnancies, however, the p- β -l was found to be slightly raised even before

* Such differences between various centres are probably real. The Joslin Clinic must attract previously unsuccessful cases from all over the United States.

FIG. 10.—Changes in serum lipid and lipoprotein lipid concentrations during the first week of life in infants of diabetic mothers and in normal infants.

the 25th week and to increase through the last trimester to a very high level in the first two weeks' post-partum. This abnormality is not associated with poor diabetic control and, although the study failed to establish a relationship between p-p-l levels and recognizable vascular lesions, this does not exclude the existence of subtle but important changes in the placenta.

(b) *In the Newborn Infants of Diabetic Women.* We have been unable to distinguish much variation of cholesterol, phospholipid, α -, β - or γ -lipoprotein levels from normal values in cord blood in a series of 11 asymptomatic babies of diabetic mothers (Fig. 10), although the mean pattern in venous blood varied from the normal (as determined by Rafstedt and Swahn, 1954) during the first week (Lloyd, 1961).

Elevation of certain glycoprotein fractions has been recognized in adults with clinical signs of degenerative vascular disease, and the serum of newborn infants of diabetic women has been studied by Sirek, Sirek and Liebel (1961), who determined the hexose, hexosamine and sialic acid contents of the carbohydrate moiety conjugated with serum proteins (glycoproteins). All these constituents were found to be significantly elevated

in infants whose mothers had no signs of degenerative vascular disease, had uneventful pregnancies uncomplicated by ketoacidosis or hypoglycaemia and had glycoprotein values similar to the pregnant non-diabetic woman at term. As in our own series, the babies who were studied ran normal neonatal courses and the raised levels were attributed to rapid tissue growth in macrosomic infants.

Possible Inherited Abnormality of Foetal Tissue

The PAS-positive material found in intimate relationship with capillary endothelium in diabetes may be the extracellular product of neighbouring cells which are inherently abnormal in this condition or else the response of normal cells to an abnormal milieu. Thus foetal and foetal placental tissue affected by an inherited metabolic disorder, probably in mucopolysaccharide metabolism, could respond to some diabetogenic factor in the maternal blood with lesions capable of interfering with placental function. In this respect it is worth noting that, although the work of Ditzel and others (1954) has not yet been confirmed, they described a variety of 'diabetic' changes in the microcirculation of the bulbar conjunctiva in from one-quarter to almost one-half of young asymptomatic

children of diabetic mothers and established a positive correlation between the degree of these vascular changes and prediabetic glucose tolerance tests. Although purely speculative, this hypothesis that foetal tissue which is inherently abnormal itself may respond in a dangerous way to the diabetic milieu has the merit of explaining the inconsistencies of foetal mortality in a population most of whom are presumably diabetic for a similar if not identical cause, whether this be the existence of the insulin antagonist or an excess of human growth hormone with or without the participation of adrenal corticosteroids. And as all these factors may cross the placenta, perhaps we should submit the capillaries of these infants to electron-microscopy if the placental villi present too great a problem for this technique.

Management

In the light of these factual and speculative considerations brief comment may be made on management of the diabetic woman and her newborn child.

Diabetic Control

The diabetic should be maintained as nearly normoglycæmic as possible and ketone-free during the last two months of pregnancy. Pedersen (1952) aimed at very careful supervision for about 20 weeks prior to delivery and during the latter half of this time the woman was in hospital. Insulin is adjusted by him according to blood sugar determinations carried out four times daily. This standard of control is exceptional elsewhere, but the evidence strongly suggests that it should be our aim. And with this the foetal mortality can be reduced to a figure below which it seems impossible to lower it by carbohydrate control alone

Avoidance of Drugs Toxic to the Fœtus

The great majority of diabetic women must have dietary control and insulin during pregnancy. But a woman may also have drugs which affect carbohydrate metabolism, which relieve anxiety, which deal with urinary infection, which effect diuresis or lower blood pressure, which are designed to correct anæmia, and so forth. The possible teratogenic effects of tolbutamide and its relatives (De Meyer, 1961) are currently under discussion, but there are many other harmful things which the pregnant diabetic may be given (*Lancet*, 1961, 1962), and nowhere does a greater need exist for the closest co-operation between general practitioner, consultant physician, obstetrician, pædiatrist and others on prescribing and record-keeping.

Obstetric Care

Ante-natal care must be regular and for the last six weeks or more will be in hospital. Toxæmia, hypertension, hydramnios and other complications of pregnancy which significantly alter diabetic perinatal mortality must be recognized early and dealt with suitably.

The time and method of delivery will be influenced by parity, by past obstetric history, by the existence of pregnancy complications and by the growth of the fœtus. Where history and examination indicate maternal good health, excellent control and successful foetal growth as estimated roughly by size and possibly by X-ray, then the nearer the obstetrician may approach toward planning vaginal delivery at term. The majority of clinics are likely to permit this only where the past obstetric history is excellent, and they are likely to undertake premature induction of labour or abdominal delivery at about 37 weeks for all others. On the other hand, a poor past obstetric history, the presence either of factors likely to impair placental function or of such an indication of placental insufficiency as failure of foetal growth, are all indications for early delivery by means which will avoid as far as is possible intra-partum anoxia. The exact timing of this between 35 and 37 weeks is a skill developed by long obstetrical experience. The practice of permitting placental transfusion of the infant by delaying clamping of the cord should be observed with care. Personal experience no more than suggests that some infants of diabetic mothers, possibly those who have been hypoxic and who have a raised hæmatocrit, may be distressed by this extra load.

Care of the Newborn

The principles of management are those for all newborn infants and include gentle warm handling, the assurance of a clear airway and the early oxygenation of the baby, using such modern methods as are indicated. We have not found that any advantage follows emptying the baby's stomach at birth (Farquhar, 1959), but experience suggests that the average volume of gastric contents at birth may vary widely in different hospitals and possibly with control and the technique of delivery.*

The baby should then be kept under very close observation for some days. The Edinburgh practice is to place the nude infant in an 'Isolette' at an environmental temperature of from 85 to 90°F.,

* I should like to say in passing that we can never be quite certain that personal observations and practices are applicable everywhere else, e.g. the urine volume of infants of diabetic mothers in Edinburgh during the first 24 hours is only a fraction of what it is in two American centres, and this seems to depend upon the volumes of intravenous fluid given to mothers in the hours before delivery.

depending on birth weight, where he is watched continuously by a personal nurse for about four days and certainly until 24 to 48 hours of feeding have been accomplished without incident. Environmental temperature may be reduced gradually if the baby is well established or showing signs of being too hot, and after four days he is transferred to a cot. Oxygen is not given as a routine except in the minutes following delivery.

Hypoglycæmia

An earlier study, in which the literature up until that time was reviewed, failed to show that the subnormal blood sugar levels achieved by these infants were productive of symptoms, and on this evidence the common practice of giving glucose from birth by one or other route was discontinued (Farquhar, 1956a). Although the evidence on which this policy was based has been criticized by Cornblath and others (1961) largely on the grounds of the blood sugar method then available, we have not as yet altered the practice of allowing the hypoglycaemia to correct itself spontaneously during the first few hours. Thus we give neither glucose nor a glycogenolytic agent, such as glucagon. During the recent study by Baird and Farquhar (1962) very low levels of blood glucose, determined by an enzyme technique, were found in quite asymptomatic babies, and an extensive personal series being conducted at present by the same method has shown that asymptomatic levels below 20 mg./100 ml. are common and that they can be unproductive of symptoms below 10 mg./100 ml. Experience, however, has also confirmed the finding of Cornblath, Odell and Levin (1959) that occasionally the newborn babies of non-diabetic mothers can be symptomatic as a result of prolonged hypoglycaemia and that they can be relieved by raising the blood glucose. This is a complicated problem which requires further clarification, but perhaps the very low levels achieved by infants of diabetic mothers in *this* series may be too brief to provoke a clinical response. And yet the possible need of these babies to burn fat and protein in the presence of poor pulmonary exchange may indicate a need for glucose even where a normal blood glucose exists.

Idiopathic Respiratory Distress Syndrome

Water and detergent aerosols were shown by Hsia, Peterson and Gellis (1957) not to influence the respiratory distress of these babies. There are certainly other measures now available, and time is likely to show that one or other of them is much more effective. The intravenous correction of acidosis by sodium and of tissue breakdown and rising potassium levels by glucose (monitored by studies of blood pH, PCO_2 and oxygen saturation)

is now being practised by many people in addition to Usher (1959), and opinion varies from conservatism to enthusiasm, with the latter gaining ground.

Feeding

Practice during the past 15 years with regard to feeding has swung from starting within minutes of delivery to delaying until the fourth or fifth day. The evidence now suggests that there is merit in starting careful oral feeding at from 24 to 48 hours of age, dependent upon the baby's condition. Some may practise intravenous feeding within hours of the baby's birth if they are convinced by the findings of Carrington, Shuman and Reardon (1957) and Reardon (1958). The Boston Lying-in Hospital study published by Rudolph, Hubbell, Drorbaugh, Cherry, Auld and Smith (1959) and by Hubbell, Drorbaugh, Rudolph, Auld, Cherry and Smith (1961), in which cases were allocated at random to early and late feeding groups, has failed to confirm Reardon's claim that early feeding reduces mortality and, indeed, more deaths occurred in the 'early feeders' than in the 'late', although this result did not achieve statistical significance in view of the relatively small number of deaths involved. The principal difference between the two groups lay in the significantly higher level of unconjugated bilirubin in the 'late feeders', but exchange transfusion for an idiopathic rise of unconjugated bilirubin of 20 mg./100 ml. has been necessary only once in the Edinburgh series. When feeding is introduced early the baby must be under continuous observation so that inhalational accidents may be treated with immediate efficiency.

Infection

The incidence of staphylococcal infection has been variable in this series over the years. They may be a little more susceptible, but then they have often been handled a great deal, exposed to a high environmental temperature and submitted to dehydration. They should be examined carefully at least once daily for any abnormality and particularly for infection at all sites, including the lungs, whether or not there has been so-called idiopathic respiratory distress.

Summary

(1) Babies of diabetic mothers are fatter, longer and more likely to become hypoglycaemic than those of normal mothers. Their pancreatic histology suggests increased beta-cell activity and direct evidence exists of increased capacity to secrete insulin.

(2) These findings are in keeping with the maternal hyperglycaemia-fœtal hyperinsulinism hypothesis.

(3) Possible reasons for maternal hyperglycemia are reviewed, including abnormal Human Growth Hormone and corticosteroid activity and also the existence of an Insulin Antagonist.

(4) The hypothesis does not explain easily the high perinatal mortality.

(5) Placental function may become inadequate in some pregnancies, possibly because the organ's short-lived micro-circulation becomes involved in the general small vessel changes of diabetes mellitus. This might be more likely where placental cells inherit the basic diabetic abnormality.

(6) The management of diabetic pregnancy and the newborn infant is briefly reviewed.

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