DIABETIC EMBRYOPATHY*

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The diabetic mother frequently gives birth to a foetus with several peculiarities. A high proportion of her infants are over-weight, often over 10 lb., and this increase in weight is made up of several components. The babies are both over-long and over-fat; they are oedematous and characteristically lose a pound or so of fluid weight during the first few days of life. Their internal organs are large; in particular there is cardio- and hepato-megaly. They may have an expanded erythron, with widespread haematopoiesis and a high haemoglobin content in their blood. Their general appearance of fat, flabby, rubicund weakness may closely resemble the picture of Cushing's syndrome.

These babies, and also those which escape being overlarge, behave as if they were feeble, undersized, premature infants; they have difficulty in breathing and sucking, and easily regurgitate fluids into their lungs. They are susceptible to birth trauma, infection, and hyaline membrane disease, so that they may die within the first few days of life unless specially protected. Although their blood-sugar levels may be very low soon after birth, this is probably of no significance, since a normal baby may likewise have extreme hypoglycaemia without any symptoms from it.

Foetuses of diabetic mothers probably show an increased incidence of major congenital anomalies, some of which, such as anencephaly and ectopia cordis, may be incompatible with life. Quite apart from such anomalies, of course, a number of foetuses are not born alive. They die about the 36th week or earlier and are delivered in a macerated state, or they die nearer term and are delivered in a better state of preservation. Although these stillbirths are near or even at full term, they are distinguished by active hepatic haematopoeisis, similar to that seen in premature and erythroblastotic infants. Luteal cysts may be found in the ovaries. Warren and Le Compte,[1] and Cardell,[2] in particular, have described the pathological features of these infants in more detail, but I think the most interesting abnormalities reside in the pancreas. Almost invariably the islets of Langerhans in these pancreases are large, and occupy an excessive part of the whole organ. Both cellular hyperplasia and cellular hypertrophy are present. Further than this, there is an increased proportion of beta cells in the islets. In the normal newborn infant the alpha cells comprise 60 - 70% of islet tissue—the figure is reversed in the infant of the diabetic mother. The sections we have examined appear, moreover, to show an unusual degree of granularity in the beta cells which, following Wrenshall and Hartroft,[3] may indicate an excess of insulin content. In fact, if we take all these items together it looks as if the pancreas of the diabetic's infant may contain up to 30 times the normal amount of insulin.

This abnormal condition of the embryo, or 'embryopathy', as it has rather unfortunately been called, owes its existence to some abnormality in the diabetic mother, since it is not seen in the infants of diabetic fathers. Certainly we have found,[4] and it has been confirmed by Pirart,[5]

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that the birth weights of the infants of diabetic fathers are larger on the whole than those of non-diabetics, but this increase in birth weight is not nearly so striking as in the infants of diabetic mothers, and there is no increase whatever in the stillbirth rate in the progeny of diabetic fathers.

Now what types of diabetic are liable to such an embryopathy? Here we come across some discrepancies. In most centres of the world the same type of baby has been found to be produced by the severe, insulin-requiring, growth-onset diabetic, by the mild, diet-controlled diabetic, and even by the prediabetic several years before she shows any obvious metabolic carbohydrate disorder. In Boston[6] and Brussels,[5] apparently, the tendency for foetal loss to occur in the mild diabetic and in the prediabetic is very much less, and the data from these cities seem to be unimpeachable. In Cape Town we found evidence that the tendency to produce stillbirths and large babies extends back indefinitely into the past obstetric life of the diabetic woman, in her prediabetic phase.

In fact, in our experience all the above-described features of the diabetic's infant apply with equal force to the infant of the prediabetic. It was Van Beek[7] who first emphasized that the enlarged islets of Langerhans were to be found in the stillbirths of women who only later became diabetic. We have amply confirmed this.[8] The mean percentages of islet tissue in stillborn pancreases in control stillbirths was 1·3% by our method, while it was around 7% in erythroblastotics, in children of diabetic mothers and in children of prediabetic mothers. It is extraordinary that once again this similarity is seen between erythroblastosis and diabetes. We know of no other cause for such enlarged islets in the stillborn infant. In fact, the finding of enlarged islets in a stillborn which is not erythroblastotic and whose mother is not an overt diabetic, is the best possible indication of prediabetes in the mother. Our results illustrate this: Pancreases from 109 autopsies on stillbirths were specially examined and their islet contents estimated; 18 were found in which the proportion of islet tissue was over 5·5%. Of the 18 relevant mothers, 12 were traced for follow-up; 5 were found to have become diabetic, 5 gave slightly abnormal glucose tolerance curves, of whom 2 are now plainly diabetic, and in the other 2 there was strong collateral genetic and obstetrical evidence of prediabetes. Thus we believe all 12 mothers to have been prediabetic when they gave rise to the stillborn infants with large islets of Langerhans.

Looked at from another angle, these findings may provide a pointer in hitherto unexplained stillbirths, since the finding of large islets will indicate that maternal diabetes or prediabetes has played a part in the foetal death.[9]

These excursions into the realms of prediabetes may help us in our search for the cause of this strange embryopathy. It is certainly most unlikely that maternal hyperglycaemia can play any part, since many prediabetics show normal blood-sugar levels during pregnancy, and yet produce abnormal infants.[10] A sensitivity to, or excessive production of, growth hormone or glucocorticoids in the diabetic pregnancy has been suggested and, although Professor Hoet[11] has made some interesting experiments the results of which favour the participation of glucocorticoids in this syndrome, the evidence is as yet not very good in favour of either. Although the plasma-cortisol level rises during all pregnancies, the levels observed are no higher in the diabetics. We have not found any tendency for women who are in the early stages of acromegaly or Cushing's syndrome to produce large babies or stillbirths, and this is surely strong evidence against either growth hormone or corticoids being the sole cause of the embryopathy.[10] The large pancreatic islets suggest an excessive stimulation of this tissue. Is the infant's own insulin, acting as a 'growth hormone', itself in fact the stimulus to the excessive size? And what is the connection with the large islets in erythroblastosis?

Turning finally to the prevention and management of the embryopathy, Professor Hoet[12] and Dr. Wilkerson[13] believe that insulin given to the prediabetic during pregnancy, even when her blood sugar is normal, may be effective in preventing some of the features of the embryopathy. And yet in the established diabetic, the very best possible control of the mother's diabetes will reduce the incidence of abnormal babies only partially. To obtain a live child it appears to be even more important to induce labour early if the foetus is judged to be large enough, and to manage the baby exactly as though it were truly a premature infant. Before this can be done, of course, it is necessary to make a diagnosis of maternal diabetes or prediabetes, and I am sure that a number of babies may be saved if the latter diagnosis is suspected and the suspicion is acted upon.

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