

# Maternal Prediabetes as a Cause of the Unexplained Stillbirth

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Before becoming overtly diabetic, women may betray their prediabetic state by producing stillbirths and over-large babies. We found the stillbirth rate in prediabetic women in the Cape of Good Hope to be 14 per cent, rising to 29 per cent in the five-year period directly preceding diabetes.<sup>1</sup> It is to be expected, then, that a number of stillbirths for which the pathologist can find no good cause may actually be related to latent or prediabetes in the mother. In a preliminary investigation into the glucose tolerance of mothers with babies of various birth weights, eighteen mothers whose last pregnancies had produced unexplained stillbirths were included. Seven of these were found to be mildly but definitely diabetic. Five others had slightly abnormal tolerance curves, with high figures for the two or two and a half hour reading.<sup>1</sup> We gave reasons for considering such curves to be "prediabetic" in type. After being followed up for three years or more all these five mothers became plainly diabetic.<sup>2</sup>

## LARGE PANCREATIC ISLETS

Diabetes or prediabetes in the mother may be suspected or even assumed by the finding of enlarged islets of Langerhans on examination of the pancreas of the stillborn infant. It has long been known that the infant of the diabetic mother has large islets,<sup>3,4</sup> and it has more recently been suggested that islet hypertrophy may be present in the infant of a mother who is not at the time diabetic but who becomes so later.<sup>5</sup> We have been able to confirm this. Pancreases from 109 autopsies\* which had been performed in this medical school have been examined. Suitable stained sections were projected onto paper of uniform weight and thickness, tracings of the islets were made (figure 1), cut out and weighed. (Method described in detail elsewhere.)<sup>6</sup> In pancreases of stillborn infants in which there was no Rh incom-

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\*These autopsies included the stillborn infants and also those who died within forty-eight hours of birth.

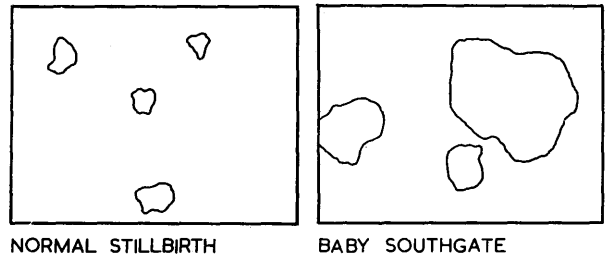


FIG. 1. a. Typical tracing of projected islets of Langerhans in case of a stillbirth with a normal mother (left).  
b. Tracing in case of a stillbirth with prediabetic mother (becoming diabetic four years later).

patibility and whose mothers were not known diabetics, the mean islet area of eighty-eight unselected cases was 2.13 per cent (standard deviation 1.7 per cent). Three proved cases of erythroblastosis fetalis had islet areas of over 5 per cent and in three infants of known diabetic mothers the figure was 6.5 to 7.4 per cent (figure 2).

Eighteen additional cases were indexed in the histological files as showing islet hypertrophy. These were also re-examined and the islet areas were assessed.

Large islet area was shown to be unrelated to fetal

## MEAN ISLET AREAS OF STILLBIRTHS

|                         |   |       |
|-------------------------|---|-------|
| CONTROLS                | □ | 1.3 % |
| DIABETIC MOTHERS        | □ | 6.5 % |
| PRE-DIABETIC MOTHERS    | □ | 7.5 % |
| ERYTHROBLASTOTIC BABIES | □ | 7.1 % |

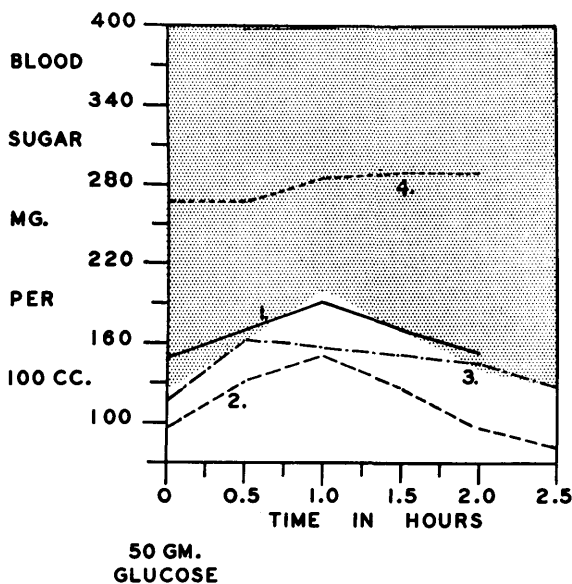
**NOTE:** SQUARES INDICATE RELATIVE SIZES ONLY

FIG. 2. The 1.3 per cent for "controls" islets is the mean figure for islet area in stillbirths for which there was an obvious cause of death which was neither erythroblastosis nor maternal diabetes.

body weight or to length of gestation.<sup>6</sup> The problem then was to assess its relationship to carbohydrate tolerance in the mother. After elimination of the three cases of erythroblastosis and the three infants born to known diabetics, there were eighteen with islet areas above 5.5 per cent. (The figure of 5.5 per cent was chosen because this was twice the standard deviation above the mean of 2.13 per cent.) We were able to trace the mothers of twelve of these infants and have performed glucose tolerance tests on them, in some cases on several occasions. Five of these women who, during the pregnancies which produced these abnormal babies, showed no evidence of impaired carbohydrate tolerance, have since become overt diabetics. Five other women had abnormal curves of the type we associate with prediabetes, either in the last trimester of pregnancy or in the immediate postpartum period. On follow-up, two of these five have become more plainly diabetic (figures 3 and 4).

The final two of these twelve mothers had normal tolerance curves on three separate occasions, but in each there was collateral evidence of prediabetes. One had a diabetic mother, uncle and aunt, and had had multiple

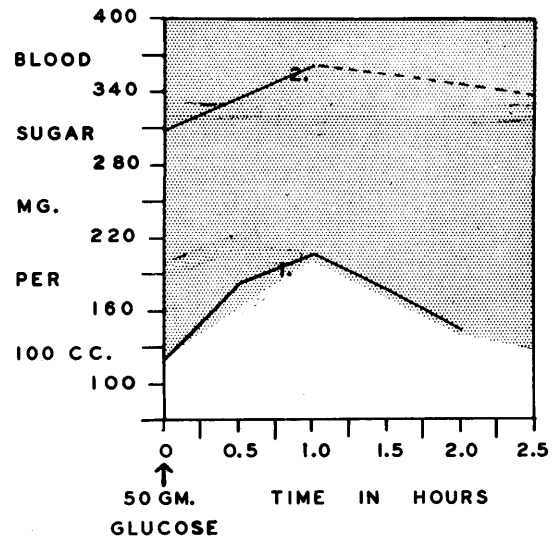
W.S. NO. 304



- 1.- 1953 - 8 MONTHS PREGNANT
- 2.- 1953 - 8 DAYS POST-PARTUM
- 3.- 1954 - 2 MONTHS AFTER LAST BABY
- 4.- 1956

FIG. 3. Glucose tolerance curves on W.S.  
 (1) Eight months pregnant.  
 (2) Eighth day after large stillbirth which had hypertrophied islets (13.5 per cent of total pancreas).  
 (3) One year later, following a live 13-lb. baby.  
 (4) Three years later, aged thirty-eight.

D.R. NO. 314 AGE 43  
 1953 - SECOND STILLBORN INFANT - ENLARGED PANCREATIC ISLETS.



- 1.- 5 TH. POSTPARTUM DAY - 1953
- 2.- 2 YEARS LATER

FIG. 4. Glucose tolerance curves in D.R.  
 (1) On fifth postpartum day after delivery of stillborn infant with large pancreatic islets (12.5 per cent of total pancreas); curve is possibly just diabetic.  
 (2) Two years later; patient aged forty-three.

stillbirths, while the stillborn child of the second\* weighed 14½ lb. We have evidence, therefore, that all twelve mothers of the stillborns with large islets were prediabetic.

We were able to obtain for follow-up seven of the eighty-three mothers of stillborn infants with normal islet area, and all of these had completely normal glucose tolerance curves. Since the expected incidence of diabetes mellitus in the childbearing population is approximately 2.5 per 1,000,<sup>7</sup> we believe that the incidence of impaired carbohydrate tolerance among the mothers of infants with islet hypertrophy is far too high to be coincidental, and that the results justify the estimation of islet area as a diagnostic tool.

#### THE UNEXPLAINED STILLBIRTH

Among the stillbirths with large islets the pathological cause of death was listed as pneumonia in four, multiple congenital defects in three, cerebral hemorrhage in two, hyaline membrane in one. In eight cases no satisfactory pathological cause of death could be found. We believe

\*This patient has recently become overtly diabetic, with symptoms.

TABLE 1

Length of prediabetic period. An over-all stillbirth rate of 14 per cent in women before becoming diabetic, rising to 29 per cent in the five-year period immediately before.

| Years Before Diabetes | Total Babies | Babies Over 10 lb. Per Cent | Stillbirths. Per Cent |
|-----------------------|--------------|-----------------------------|-----------------------|
| 0-4                   | 35           | 54                          | 29                    |
| 5-9                   | 55           | 44                          | 13                    |
| 10-14                 | 61           | 23                          | 23                    |
| 15-19                 | 92           | 28                          | 13                    |
| 20-29                 | 102          | 35                          | 8                     |
| Over 30               | 43           | 26                          | 9.3                   |
| Whole series          | 398          | 33                          | 14                    |
| Control series        | 439          | 4.6                         | 5                     |

that the examination of the islets of Langerhans supplies the answer (or at least takes us back one stage further and gives us a clinical correlation). Enlargement of the islets (sometimes rather "continents") of Langerhans, with known maternal diabetes and Rh incompatibility excluded, appears to indicate prediabetes in the mother. Even in cases where a pathological diagnosis has been made, prediabetes may still be the important factor which predisposed to the condition found (e.g., in hyaline membrane disease).

The discovery of such islets and the consequent diagnosis of prediabetes in the mother is not purely a matter of academic satisfaction, but, like the finding of Rh incompatibility, may indicate how to obtain a live baby from the mother's next pregnancy. Such mothers should be treated as though they were established diabetics from the point of view of their confinements, with premature induction of labor and special care of the newborn infant.

SUMMARY

Women in their prediabetic years frequently produce stillborn infants. It is to be expected, therefore, that some unexplained stillbirths may be related to maternal prediabetes. We purport to show that a presumptive diagnosis of prediabetes in the mother may be made from the finding of hypertrophied islets of Langerhans in the stillborn pancreas, provided erythroblastosis can be excluded. In eight cases in our series we have been able to offer this explanation of the cause of an unexplained stillbirth, while in several others the maternal

prediabetic state probably played a part in predisposing to the pathological condition which was found.

SUMMARIO IN INTERLINGUA

*Prediabete Materne Como Causa De Alteremente Non-Explicate Nascentia Morte*

Feminas frequentemente parturi morte-natos durante lor annos prediabetic. Ergo il pare plausibile cercar un relation inter "inexplicate" nascentias morte e prediabete materne. Nostre objectivo es monstrar que un diagnose de presumption de prediabete in le matre pote esser facite super le base del constatacion de hypertrophiate insulas de Langerhans in le pancreas del morte-nato, providite que erythroblastosis pote esser excludite. In octo casos in nostre serie il esseva possibile citar iste constatacion pro explicar un "inexplicate" nascentia morte, durante que in plure altere casos le stato prediabetic del matre esseva probabilemente un factor in predisponer le organismo al condition pathologic que esseva trovate.

ACKNOWLEDGMENT

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