Prognosis for Babies Born to Diabetic Mothers in Edinburgh

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The physical features and perinatal hazards of infants of diabetic mothers are well known. There are fewer reports, however, about the later progress of surviving children, though the experience of this hospital and university department has been published (Farquhar, 1959, 1965). The outcome of all viable pregnancies at the Simpson Memorial Maternity Pavilion between 1948 and 1966 is reviewed here with regard to perinatal mortality, congenital malformations, other important health problems, the growth of survivors, and the occurrence of clinical diabetes mellitus.

Population Studied

The group of 329 babies studied comprised all babies of 28 weeks' gestation or more born dead or alive to diabetic mothers at this hospital between the years 1948 and 1966 inclusive.* No baby was excluded even if fetal death had already occurred when the mother made her first contact with the hospital. The diagnosis of maternal diabetes was always made by the physician-in-charge of pregnant diabetic women at the Royal Infirmary of Edinburgh. Each woman had glucosuria and clearly abnormal glucose tolerance. Most women were insulin-dependent (Table I).

All babies who survived the newborn period have been followed and regularly re-examined.

Perinatal Fetal Loss

The perinatal loss rate for the series is 20.9% and the breakdown by stillbirths and neonatal deaths is shown in Table II. In the entire series 30 of the 40 stillbirths took place before the start of labour and 4 were anencephalic.

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*It should be understood abroad that the National Health Service, which began in 1948, ensures that the diabetic mothers are an unselected group as all treatment is free and the Royal Infirmary Clinic draws from a wide geographical area and from all economic levels of society.

Fetal loss has changed little in the insulin-treated group since 1958 when care passed from one obstetrician to another (Fig. 1), a small decrease in stillbirths being offset by a small rise in neonatal deaths. The further analysis of these deaths according to possible cause will be published later, but the failure to improve fetal survival is disappointing in view of the considerable effort which has been made.

Follow-up

All children who survived the first 4 weeks of life are contacted at intervals of from 1 to 3 years, and the present report refers to a follow-up conducted in 1966-67.

The success of this follow-up is shown in Table III and the geographical distribution is given in Table IV. In previous similar examinations children in this series have been examined in Aden, Cyprus, and Zambia. Where children died, the necropsy report was obtained, or, in a few where no

TABLE I
Prenatal Treatment of Diabetes in 329 Mothers

Insulin and diet	293 (89%)
Oral hypoglycaemic drugs ..	7 (2%)
Diet alone	29 (9%)

TABLE II
Outcome of 329 Diabetic Pregnancies

Infants of Diabetic Mothers	Treatment of Maternal Diabetes			Total
	Insulin	Diet Only	Drugs	
Stillbirths	38	2	0	40
Neonatal deaths ..	26	3	0	29
Survived first month ..	229	24	7	260
Total series	293	29	7	329

TABLE III
Success of Follow-up

Treatment of Mother	No. of Children	% Examined
Insulin	229	98
Diet only	24	96
Drugs	7	100
Total	260	98

TABLE IV
Geographical Distribution of
Surviving Infants of Diabetic Mothers in 1966

Area	No.
City of Edinburgh	86
South-eastern Scotland	120
Rest of Scotland	17
England and Wales	19
Africa	1
Australia	1
Canada	2
Europe	2
New Zealand	2
United States	1
Total	251

necropsy was performed, the death certificate was scrutinized.

A description of the methods by which these children were traced may be obtained from the author on request.

Malformations

Malformations have been assiduously sought in the living and in the dead. Necropsies were performed in the Regional Paediatric Pathology Department by Dr. Agnes Macgregor (until 1960) or by Dr. A. D. Bain, or under their personal supervision by a very small number of assistant paediatric pathologists. Most of the survivors have been examined at intervals by the author to a maximum of 18 years. The remainder have been examined remote from Edinburgh by paediatricians or physicians who were specifically asked to look for congenital malformations.

Perinatal deaths. Necropsy was not performed in 4 of the 69 babies. None of the 4 had any malformation on inspection or clinical examination. All macerated fetuses (28) were necropsied with care. Of the 40 stillbirths, 4 were anencephalic, and of 9 neonatal deaths 1 had a very large meningoencephalocele. No other malformations were detected before or after death, and in particular there were no cardiac malformations.

FIG. 1.—Perinatal mortality in insulin-treated diabetic pregnancy, subdivided into stillbirths and neonatal deaths and into the periods 1948-57 and 1958-66.

Later deaths. Of 260 babies who survived the first four weeks of life, 4 died later. One died at 5 weeks of age: no malformation had been found at birth and the baby was well on discharge from the Simpson Pavilion until the day of death. This was unexpected and quick: the family doctor arrived moments before the infant died and heard a soft heart murmur; he certified death as being due to congenital heart disease, but no necropsy was performed. Other causes are at least equally possible.

Of the 3 others, 1 died at 7 years of purulent meningitis, 1 was killed at 5 years in a road accident, and 1 developed Hodgkin's disease and died at 15 years. None had any detectable malformation.

Survivors. The malformations (Table V) range from a lethal deformity to a slight cosmetic disability. Trivialities such as small naevi on unexposed areas were disregarded. Detection was by history and by clinical examination. Laboratory aids and x-ray diagnosis were undertaken only if there was clinical indication.

The incidence of such malformations in the various groups and over-all is shown in Table VI.

Other Abnormalities or Notable Illnesses

Table VII lists other abnormalities. The bilateral pes cavus was not apparent in early life. There are also 6 children who, without malformation, are intellectually subnormal (Table VIII).

Later Growth

Paired values for naked weight and standing height are available for 231 children and are shown in Fig. 2, 3, 4, and 5 on simplified forms of the growth

TABLE V
*Classified List of Malformations
In 329 Infants of Diabetic Mothers*

Malformation	No.
<i>Central Nervous System</i>	
Anencephaly (born dead)	4
Encephalomeningocele (neonatal death)	1
Congenital diplegia	1 + 1?
Bilateral spastic hemiplegia (BW 1300 g.) (see also Educational Subnormality Group)	1
<i>Skeletal System</i>	
Sacral agenesis	1
Thoracic hemivertebrae, accidental finding, no disability	1
Fused cervical vertebrae (C 1,2), no disability	1
Lumbo-sacral spondylolysis, congenital?	1
Extra thumb; removed; no disability	1
Extra thumb + cleft lip and palate (sibs)	2*
Bilateral pes cavus	1
<i>Genito-urinary System</i>	
Absent left kidney and ureter (neonatal death)	1
Slight unilateral hydronephrosis, non-progressive over 10 years	1
Bilateral double ureter	1
<i>Gastro-intestinal System</i>	
Tracheo-oesophageal fistula	1
Inguinal herniae	2
<i>Cardiovascular System</i>	
Persistent ductus arteriosus (operation)	1
Systolic murmur only at 6 mth. (In addition, one baby died suddenly at 5 weeks and was said to have a terminal heart murmur; no necropsy, see text)	1*
<i>Eyes</i>	
Dermoid cyst	1
Cataracts	1
<i>Others</i>	
Lymphangioma	1
Fused central incisor teeth	1

*Maternal diabetes treated with diet only. All others on insulin.

charts of Tanner, Whitehouse, and Takaishi (1966). The weights and heights are distributed fairly evenly over the normal range, but an excess of both boys and girls (9 and 13 respectively) falls below the 3rd centile for height, whereas only 1 boy and 4 girls lie above the 97th centile. Weight, on the other hand, is distributed unusually on the graph, only in that there are more than the expected

TABLE VI
Incidence of all Types of Malformation

Infants of Diabetic Mothers	Percentage of Malformations in Each Subgroup				Group as a Whole
	Treatment of Maternal Diabetes				
	Insulin	Diet Only	Drugs		
Stillbirths	10.5	0	0	10.0	
Neonatal deaths	7.7	0	0	7.0	
Survivors	8.7	12.5	0	8.8	
Total series	8.9	10.3	0	7.9	

TABLE VII
Other Abnormalities in 329 Infants
of Diabetic Mothers*

Abnormalities	No.
Retrolental fibroplasia, partial	2
Osteochondritis	2
Communicating, acquired, hydrocephalus	1
Possible early Huntington's chorea (very strong family history)	1
Bilateral pes cavus (gradual development; neurological opinion—'one of hereditary ataxias')	1
Deafness, causing discharge from Army (one other is classified with malformations as he has hemivertebrae) —his deafness is unilateral; another is grouped with educationally subnormal)	1
Recurrent ketotic hypoglycaemia	1
Diabetes mellitus	2

*The mothers of all the children in this group were treated with diet and insulin.

number of abnormal values lying fairly equally below (11) and above (13) the normal range. Table IX suggests that there is an excess of short boys and girls, and that these boys in particular may be heavier than expected.

The possibility of abnormal weight in later childhood has been further explored by calculating a 'weight-to-height index' for each child. Using the same charts, the weight (W) and the height (H) of each child have been expressed as a percentage of the 50th centile for age and sex. Thus, a child who is on the 50th centile for each has a W/H index of $1.0 \left(\frac{100}{100} \right)$. The greater the weight in relation to height, therefore, the more will the index exceed

TABLE VIII
Educational Subnormality in 329 Infants
of Diabetic Mothers*

Child Number	
33/41	IQ 54; birthweight 3267 g.
45/56	IQ 35; birthweight 2835 g.; possible chicken-pox encephalitis.
52/66	IQ 56-66; birthweight 4132 g.; parents of low intelligence
70/93a	IQ less than 50; birthweight 1021 g.
123/172	IQ 66; birthweight 3345 g.; bilateral nerve deafness and ataxia
222/330	DQ about 70; birthweight 2920 g.; very extensive cellulitis and pyoarthritis in newborn period

Note: There are also two severely defective children in the group of CNS malformations. Three other children in the 'normal group' are dull but manage at a normal school.

*The mothers of all the children in this group were treated with diet and insulin.

FIG. 2.—Standing heights of 117 surviving boys born to diabetic mothers (modified Tanner et al. chart, 1966).

FIG. 3.—Standing heights of 113 surviving girls of diabetic mothers (modified Tanner et al. chart, 1966).

FIG. 4.—Weights of 118 surviving boys born to diabetic mothers (modified Tanner et al. chart, 1966).

FIG. 5.—Weights of 114 surviving girls of diabetic mothers (modified Tanner et al. chart, 1966).

unity (e.g. $\frac{125}{75} = 1.67$), whereas the lower the weight in relation to height, the lower the index will be (e.g. $\frac{75}{125} = 0.6$).

Individual indices for boys and girls are shown in Fig. 6. Only 10 children have an index of unity, and other horizontal lines indicate 1.25 and 0.75. Fig. 7 shows the much greater frequency of indices exceeding rather than falling short of unity. It also shows that children with indices of 1.25 or more make up 22% of all whose indices exceed unity, whereas children with indices of 0.75 or less make up only 2.5% of those with indices below unity. Excessive weight is almost 10 times commoner than unusually low weight.

These numbers are distributed by sex according to age-groups in Fig. 8, and indices in excess of unity are commoner at each age-group studied. When particular attention is paid to those with abnormally high or low indices, it becomes clear that there are so few very low ones that they do not merit further study. If the scatter of W/H indices simply implies that few children conform to the vital statistics of the 'standard' boy or girl at any age, and that most of them are heavier or lighter than the standard in relation to height, then the indices should be evenly distributed above and below unity. But this is clearly not the case for surviving children of diabetic mothers who are commonly

FIG. 7.—The frequency distribution of 'W/H Indices' of surviving children. Note preponderance of children relatively heavy for their height.

too heavy and only infrequently too light in relation to the standard of 1.0.

The number of children in each age-group with an index of 1.25 or more has been expressed as a percentage of all the children in the same age-groups, and the results are shown in Fig. 9. Excessive weight relative to height in these children increases progressively from birth to adolescence until it affects almost 1 in 4. Girls are affected more commonly than boys, but this difference between the sexes narrows between 15 and 18 years of age.

Development of Diabetes

The chemical diagnosis of diabetes by methods more sophisticated than urine analysis (with or without a prior oral load of glucose) has not been

FIG. 6.—'W/H Indices' (see text) at various ages of surviving children of diabetic mothers.

FIG. 8.—'W/H Indices' of surviving children (boys and girls shown separately) distributed according to age-groups.

FIG. 9.—Surviving children with 'W/H Indices' of 1.25 or more as a percentage of all those in this series at each age-group and by sex.

attempted in this large group of asymptomatic children. Two diabetic children have emerged and were diagnosed by history, clinical examination, and conventional tests. At least two other children now have a diabetic older brother or sister.

Summary of Progress of Survivors

The progress of those children who survived the first month of life is summarized in Table X.

Discussion

Fetal loss. The inclusion in this series of all diabetic pregnancies of at least 28 weeks' duration, whether the mothers had attended for regular obstetric and diabetic care or not, partly explains the high perinatal fetal loss rate of 20.9 per 100. This figure has changed very little with time in spite of advances in paediatric care, though it is governed, of course, by many factors which may also have altered for better or worse over this period. As in other series, it is possible to select a large group of mothers whose antenatal care was good and whose babies survived.

The previous observations (Farquhar, 1959, 1962a), that more than half of the mothers had no

fetal loss, that the smaller rather than the larger babies are primarily at risk, and that the best care cannot always prevent mortality, are still true. And yet there is no doubt that poor diabetic control and poor antenatal supervision correlate closely with perinatal loss. A detailed analysis of factors influencing fetal loss in this series will be published.

Congenital malformations.

Does the incidence or the type of malformation differ in infants of normal and of diabetic mothers? This subject has been reviewed by Hagbard (1961), Pedersen, Tygstrup, and Pedersen (1964), Farquhar (1965), and Pedersen (1967). Earlier studies (Rubin and Murphy, 1958) suggested that the incidence of malformations differed little in infants

TABLE X

Summary of Results for 260
Babies who Survived First Month
Maximum follow-up period 18 years

TABLE IX

Percentages of Boys and Girls whose Measurements Lie Above 97th or Below 3rd Centiles for Age

	Height		Weight	
	Above 97th	Below 3rd	Above 97th	Below 3rd
Boys ..	0.9	7.7	6.0	1.7
Girls ..	3.5	11.5	5.2	7.9

Infants of Diabetic Mothers	Treatment of Maternal Diabetes			Total
	Insulin	Diet only	Drugs	
Untraced ..	4	1	0	5
Later deaths ..	4	0	0	4
Diabetes mellitus ..	2	0	0	2
Congenital abnormality ..	20	3	0	23
Educational subnormality ..	5	1	0	6
Other abnormalities ..	9	0	0	9
Normal ..	185	19	7	211
Total ..	229	24	7	260

of normal and of diabetic mothers. This was certainly not the opinion of White (1959) who claimed an incidence of 80% in infants of diabetic women in contrast to an expected incidence of 1.8% in the population. The repetition of this statement in successive editions of the late Dr. Joslin's textbook emphasizes the author's belief in it. In a previous study here (Farquhar, 1965), infants of diabetic mothers were matched with a simultaneous control series, and both groups were examined by the author using the same criteria of 'significant abnormality'. No striking difference in incidence was found, though the nature of the defects differed a little and those in the diabetic group were more serious. So far as can be found, this was, until recently, the only study in which diabetic and normal groups were matched in this way. Another control study has now been reported from London (Watson, 1968).

Pedersen (1967) concludes that there is now general agreement that significant congenital malformations occur more frequently in infants of diabetic mothers, and present a major problem in diabetic pregnancy, and his data and his review of the literature have convinced Jackson (1967). Though it has been impossible to continue the controlled series in Edinburgh, it has been possible to examine all children of diabetic mothers at birth, throughout life, and at necropsy. The different experience of Boston and Copenhagen on the one hand and of Edinburgh on the other is obvious.

Perinatal deaths. Malformations killed 1.5% of babies in the Edinburgh series and 2.0% in the Copenhagen one (Pedersen *et al.*, 1964). Dr. Mølsted Pedersen has provided details of all malformations in the Danish series, and this makes possible a more detailed comparison.

The Edinburgh series includes a baby of 2 kg. who, as a newborn, survived an operation for oesophageal atresia and tracheo-oesophageal fistula. Had she died, then the Edinburgh mortality from malformations would be 1.8%. Similarly, that in Copenhagen would have been reduced to 1.6% had one baby with a diaphragmatic hernia and 2 with neonatal volvulus been saved. This means that the figures for 'lethal' malformations, based as they are on small numbers, differ little and depend to some extent on successful treatment of the infant.

Malformations of the *central nervous system* killed 1.5% of babies in the Edinburgh series and 1.2% in the Copenhagen one, but they differ in type. Hydrocephalus or meningocele or both caused the deaths of 0.3% (a meningoencephalocele) in Edinburgh and 0.7% in Copenhagen. Anence-

phaly killed 1.2% in Edinburgh and 0.5% in Copenhagen (12 and 5 per 1000 respectively). These are high figures. The incidence of these severe CNS malformations in Britain (for diabetic and non-diabetic pregnancies) ranges from 1 per 1000 births in south-east England, to 2 or 3 times this figure in most of Scotland and 4 per 1000 in Ireland (*Brit. med. J.*, 1968). In Sweden, where the population resembles that in Denmark, the general incidence is lower, 0.54 per 1000 births (McKeown and Record, 1960).

In both Edinburgh and Copenhagen, therefore, the incidence of anencephaly is much higher in the diabetic than in all pregnancies, though the usual greater incidence in a Scottish than in a Danish population persists. The Boston (U.S.A.) series of necropsies on infants of diabetic mothers, described by Driscoll, Benirschke, and Curtis (1960), however, does not include a single anencephalic fetus, and this is surprising in view of the proportion of Irish (Celtic) people there. Anencephaly is in fact a common cause of perinatal death in Boston (Naggon and MacMahon, 1967). Perhaps anencephalic babies were not necropsied in the Boston Lying-in Hospital series, and thus escaped inclusion in the report.

The Edinburgh series of necropsies had not a single serious congenital malformation of the heart, but these were found in 23.5% of necropsies in Copenhagen and 14.7% in Boston. Similarly, Cardell (1953) found one supernumerary valve cusp in his series of 25 necropsies in London in what was obviously a most meticulous search. A recent study of 'Potential Diabetes' in Belfast by Hadden and Harley (1967) reported 4 times as many CNS malformations as cardiac ones in the perinatal deaths. The apparent national differences in the incidence of lethal congenital heart malformations in babies of diabetic mothers may be due in part to the incidence of necropsy examination in the published series (94% of the Edinburgh deaths were examined in this way) or they may represent a true difference among all births in these communities. Thus, Forfar and Nelson (1969), in a report about to be published, calculate that the incidence of all congenital heart malformations, whether lethal or not and whether the mother is diabetic or not, is no more than half of that reported from the United States by McIntosh *et al.* (1954).

In summary, the incidence of lethal congenital malformations may be higher in diabetic than in non-diabetic pregnancy, but the Danish and Edinburgh series differ less than was thought. The Boston series may be a selected one and, if so, it cannot be compared with the others. The

common type of malformation may differ between series and this may depend on racial or environmental factors.

Survivors. Figures for the incidence of malformations provided by different authors from different communities at different times may all be criticized and cannot be compared with certainty. The practical problems of personally comparing the incidence in surviving children of normal and diabetic mothers became too great for this author, and the present report is, therefore, confined to an examination of the types of abnormality found. Only one case of congenital heart disease (persistent ductus arteriosus) has been proved in 329 viable births and, in the previous study, there was one case of coarctation of the aorta in the control group. Even if congenital heart disease is accepted as the cause of death in the 5-week-old infant already mentioned, the incidence is very low. White's statement (1959) from Boston that congenital anomalies continue to exact their toll in the age period 2 weeks to 12 months, and that for the most part these are cardiac, is untrue of Edinburgh.

Passarge and Lenz (1966), describing agenesis of the sacrum and coccyx and malformations of the lower extremities in what they call the syndrome of caudal regression, estimate that it may occur in 1% of infants of diabetic mothers. Pedersen (1967) also found severe osseous malformations of the limbs, especially of the femora, in about 1% of the Copenhagen series. The Edinburgh series does contain one case of sacral agenesis and a further case of asymptomatic lumbosacral spondylolysis, on the congenital or acquired origin of which an experienced orthopaedic surgeon declined to pronounce judgement.

Of the 260 children who survived the first month of life, excluding those who died for non-congenital reasons, the important problems have been one sacral agenesis, one patent ductus arteriosus (successful ligation), one tracheo-oesophageal fistula (successful repair), sibs with cleft lip and palate (probably genetic, repaired), one congenital cataract (successful surgery), and one abdominal lymphangioma (successful surgery). The surviving genito-urinary abnormalities have presented no problem. To these must be added the children with cerebral palsy (one of whom was of very low birthweight) and those who are educationally subnormal. These may represent a small excess over the usual incidence.

Why should there be a difference? The commoner occurrence in some studies of certain types of

malformation (e.g. caudal regression syndrome) in children of diabetic mothers than in children of normal mothers is apparent. The experience of Boston, Copenhagen, and Edinburgh with regard to congenital heart disease certainly differs, and yet American, Danish, and Scottish diabetes mellitus is indistinguishable. Why then should such differences occur? Are they real or artificial? It is important to know this, and as Edinburgh seems to be out of step, particularly with the Scandinavian and American studies, the local situation is re-examined.

(a) THE CERTAINTY OF THE MOTHER HAVING DIABETES.

All the mothers in this series were diabetic, 9 out of 10 required insulin and the others needed dietary control with or without a sulphonylurea. Every case in which the diagnosis was in the slightest doubt has been discarded.

(b) THE SIZE OF THE SERIES.

Pedersen (1967) infers that the lower incidence, and presumably the altered type of malformations in the Edinburgh series can be explained by its containing fewer than 100 cases. But he refers to the series in 1959 and not to the publication of 1965 (almost 200 cases) when the situation was similar. The present series of over 300 shows no obvious change in pattern, and it has the possible merit of having been collected since 1948, i.e. during a period of greatly improved social conditions and free modern medical care. The Copenhagen series dates from 1928 and the Boston one from 1940. The possible risks from teratogenic drugs have, of course, increased more recently.

(c) THE ADEQUACY OF THE NECROPSIES.

All perinatal deaths are reported and the necropsy rate is 94%. The remaining bodies showed no external abnormality. This is stressed because some centres may dispose of anencephalic fetuses without necropsy, or they may operate some other form of selection which excludes or emphasizes important pathology.

The pathologists are paediatric pathologists of international standing. They have had a long and particular interest in the stillborn fetus and the neonatal death and in malformations. They were aware of the importance of excluding congenital anomalies in these babies, and they were of the opinion that congenital malformations of the heart would not escape detection even in macerated fetuses.

(d) THE ADEQUACY OF THE FOLLOW-UP EXAMINATION.

The over-all follow-up rate of 98% is very high in relation to general experience (Small, 1967) and was highest in the insulin- and drug-treated groups. Of these about 85% were examined by the author

(and had been examined at intervals of 2 or 3 years all their lives). The great majority of the remainder were examined by specially briefed senior paediatricians. Laboratory and radiological investigations were not undertaken without a positive clinical lead. It would be pointless, for example, to examine each child by excretion urography without resorting again to the same technique in properly matched controls. It is believed that clinical examination was of an adequate standard.

On the basis of this reappraisal of the Edinburgh study it is probably fair to conclude that, whatever the truth may be about the incidence of malformations in the world as a whole, differences do exist in the frequency of certain anomalies, and this is most strikingly true of the heart.

There is no evidence that variation in incidence and quality can be related to the use of drugs in the complex situation of early diabetic pregnancy. The theory that stricter carbohydrate control in other centres might lead to an improved fetal survival rate but to a high incidence of hypoglycaemia and of consequent congenital malformations seems to be unlikely. This is sad because it is an attractive idea. The enormous meningo-encephalocele in this series occurred in the baby of a young girl who had two severe hypoglycaemic comas during the first 12 weeks of the pregnancy. Pedersen *et al.* (1964) conclude, however, that hypoglycaemia is not important.

On the other hand, Pedersen relates the occurrence of congenital anomalies to the existence of diabetic vascular complications in the mother, and shows, in the Copenhagen series, that the incidence of serious malformation rises as vascular complications advance. Were this true, it could explain the difference between this series and Pedersen's, because the Edinburgh series contains very few women with advanced vasculopathy. Therapeutic abortion and maternal sterilization have made this a rarity, and certainly in the past 12 years there have been no pregnant diabetics in White's groups E or F at the Simpson Memorial Maternity Pavilion. Strangely enough, the only case of sacral agenesis was born in 1950: this mother had been an insulin-treated diabetic since 1946 when she was 18 years old. She had one further healthy baby in 1966. She has commonly defaulted from the diabetic clinic. In 1964 she was specifically examined for vascular changes. She had no proteinuria, her blood pressure was 120/70 mm. Hg, and her creatinine clearance was normal. She had very little change in the optic lens and the retinal background was graded I. This position was unchanged in 1966, so that 16 years after bearing the only

severe skeletal anomaly in the whole series this woman remains remarkably free from vascular degeneration.

Fetal malformation could not be correlated with diabetic severity in the Boston series according to Driscoll *et al.* (1960), and Pedersen (1967) is forced to conclude that 'geographical differences have to be contemplated too'. Certainly the other controlled study from Britain (Watson, 1968) claims no significant difference in congenital malformations in the diabetic and control groups. Thus, the incidence may vary from centre to centre, and so may the nature of the malformations and their association with hypoglycaemia and vascular degeneration.

The problem may be approached from two directions. The first is to discover the incidence of maternal diabetes mellitus in a large series of children showing specific malformation, and this has indicated that diabetes can somehow be related to these. The other is to examine, as here, large series of children born to diabetic and normal women, and this is obviously going to take much longer to establish proof. I agree with Pedersen (1967) that no recorded series may be large enough at present to settle the matter in this way. Most diabetes mellitus is assumed to result from the same chemical pathology in most countries. If this is so, then variations in congenital anomalies must surely be explained by the actions of physicians and obstetricians (e.g. treatment of diabetes and preventing pregnancy in advanced diabetes) or possibly by genetic factors (e.g. race and consanguineous marriage).

Later growth. The study of height and weight in children born in Edinburgh to diabetic mothers was undertaken to discover if fetal overgrowth is continued into childhood and if there might be a group, within the group, whose unusual growth performance might suggest the operation of diabetic inheritance long before the carbohydrate disorder becomes apparent. It was, of course, inspired by the claim of White, Koshy, and Duckers (1953) that this might be so. In 1959 the Edinburgh survivors showed no clear relation between birthweight and later height or weight, and in 1965 children of normal and of diabetic mothers differed little in height, but there was just a suggestion that a few older girls of diabetic mothers might be overweight.

White's statistical reporting (1959) is difficult to follow, but she claims both excessive height and weight in survivors, more so in boys than in girls. From Australia, Breidahl (1966) reports that 7% of survivors are above the 90th centile for height,

but 21% exceed it for weight. He interprets these data as being in agreement with White's, though his evidence for statural overgrowth is unconvincing; they seem to suggest a tendency to excessive weight. In Sweden, Hagbard (1961) found that survivors at a mean age of about 5 years were smaller but heavier than average, and this fits the Edinburgh experience. The present study shows in the first place that almost 1 in 10 of surviving children falls below the 3rd centile for height, whereas only 1 in 50 falls above the 97th. In the second place, and this is more striking, excessive weight is very much commoner than poor weight for height, and is true of every fourth or fifth survivor by late adolescence, with a slightly higher incidence in girls. This represents an interesting return by some to the obesity which affects almost all infants of diabetic mothers at birth.

Diabetes in children of diabetic mothers.

According to White (1959), 9 of every 100 children in the Boston study are already diabetic by the age of adolescence, and a further 14 are borderline diabetics, with diagnostic impairment of glucose tolerance. This high figure is unequalled in other recorded series. White does not declare how many of the children in her study also had diabetic fathers, and this information may be important, though only 4 of every 100 children born to diabetic mates had developed clinical diabetes in the study of Cooke *et al.* (1966). Nor does White say if she followed a consecutive series of cases. Her patients were drawn from the Boston area, but she does not tell us how many of them declined examination. The series could, therefore, represent a group in which those with diabetes or with a strong family history might enter the follow-up, while others, less anxious, did not. In contrast, Harris (1950) suggested that 1·4 per 100 might become diabetic by the age of 40 years. In Sweden Hagbard (1961) found 1 diabetic child aged 12 years in 514, giving an incidence of 0·19 per 100. In Australia Breidahl (1966) reported 1 diabetic in 200 such children or 0·5 per 100. Neither of these series seem to have involved personal follow-up of an unbroken sequence of children.

The present study, with only one known mating of diabetic parents, includes 2 diabetic children in 260 or 0·77 per 100. This figure is a long way short of the Boston one, but it is already approaching Harris's predicted incidence at an age when only about 0·035 per 100 Scottish children are diabetic in the general population (Farquhar, 1962b). This suggests that the incidence of diabetes in children of diabetic mothers is 22 times greater than

in the general child population. The final incidence is obviously quite unknown and there is little chance of keeping this group intact for much longer.

The incidence of potential diabetes among the perinatal deaths is unknown. There are the pancreases in which islet hypertrophy is recognized and in which increased insulin secretion is assumed. Perhaps the fetus who carries the full genetic message of diabetes is more vulnerable in the diabetic environment, but this suggestion is purely speculative.

Growth and prediction of diabetes. White (1959) suggested the existence of a positive correlation between accelerated growth and clinical diabetes or chemical prediabetes. This thought inspired the present growth study in the hope that body size and shape might prove to have predictive value. In spite of the unusual growth pattern described above in this series our experience conflicts with this. In the first place the physical deviation from normality in Edinburgh is toward excessive body weight for height and, possibly, toward short stature. In the second place neither of the two Edinburgh diabetic children, described below, fully fits the hypothesis.

The girl who has become diabetic weighed 2551 g. when born at 37 weeks' gestation. Her mother was 24 years old at that time, had been diabetic for 5 years, and had been treated with insulin since she was diagnosed. One year before becoming diabetic the child was below the 3rd centile for height, but she was also below the 3rd centile for weight and was distinctly thin rather than obese. She had been similarly tiny for age at 2 years when her large persistent ductus arteriosus was recognized and successfully treated. Her 'W/H Index' in 1966 was 0·79 so that she was not only short but also thin.

The male diabetic, however, weighed 3827 g. when born at 36 weeks' gestation. His mother was 22 years old when he was born, had been diabetic for 13 years, and had been treated with insulin since she was diagnosed. Five months before the boy's diabetes was diagnosed he was above average height and weight (near to the 75th centile for each) and he was not obese. His 'W/H Index' in 1966, was 1·09.

None of the children with 'W/H Indices' of 1·25 or more has become diabetic so far.

None of the short and/or plump children in this study has been submitted to chemical tests, other than urine analysis, primarily because the main value of this consecutive series is its completeness, and this might be lost if children or parents were

frightened by such investigations. If a convincing diagnostic test for prediabetes emerges it may be applied. The divergent physical patterns of these two established diabetics cast doubt on the merit of laboratory study of particular body types in this series.

Summary

Edinburgh experience is described of 329 consecutive deliveries in diabetic women, 90% of whom required treatment with diet and insulin. The high perinatal fetal mortality of 20.9% in this unselected series includes a high proportion of deaths which occurred before the start of labour, sometimes in women who had failed to seek antenatal care.

98% of all survivors have been examined at intervals for up to 18 years.

A necropsy rate of 94% was achieved by two paediatric pathologists. Lethal malformations were present in 1.5% of all births compared with 2.1% in Copenhagen and 2.2% in Boston. These affected the central nervous system in Edinburgh, but the heart was much more affected in the other two centres.

The incidence of significant malformations was 7.9% in the whole series and 8.8% in all who survived the first month. This figure may be higher than in a normal population but further comparison with a simultaneous control series was impossible.

Not only the incidence but perhaps the type of malformation may vary in different communities. This may result in part from genetic factors, but other possible causes exist.

Maternal diabetic vasculopathy is thought to correlate with the occurrence of congenital malformations in Copenhagen. Pregnancy associated with diabetic degenerative disease is rare in Edinburgh, and this could account for differences in incidence and quality. Such a correlation, however, does not exist in Boston, and the only Edinburgh mother who produced a child with sacral agenesis was still free from obvious degenerative disease 16 years later.

Symptomatic hypoglycaemia during early pregnancy does not correlate with the production of malformed babies in Copenhagen, but it does exemplify the kind of fetal insult which could be commoner in one centre than in another. No conclusive evidence exists to implicate this or any other iatrogenic factor.

The present weights and heights of most surviving children fall within the normal distribution of weight and height for age and sex. There are,

however, more children than expected whose heights fall below the 3rd centile.

A weight-to-height index has been calculated for each child, and an index of 1.25 or more is taken to represent excessive weight for height. High indices are common and low indices are uncommon. The incidence of high indices increases progressively with age and is greater in girls than in boys.

The incidence so far of juvenile clinical diabetes among survivors is 0.77 per 100, which is already 22 times greater than in the general population under 16 years of age. Neither of the two cases recorded has a high weight-to-height index: one is short and thin, the other is of average build.

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