Dominant Inheritance Diabetes Mellitus

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Tattersall (1974) reported three families showing dominant inheritance of diabetes mellitus, and Fajans and Conn (1960) drew attention to the occasional occurrence of mild 'maturity onset type' diabetes in the young. By combining their information, Tattersall and Fajans (1975) outlined the characteristic features of this group of diabetic patients — absence of acute diabetic symptoms, mild or absent ketonuria, stabilisation of the young on oral therapy, lack of progression of the glucose intolerance, absence of complications over many years, involvement of three generations and of 50 per cent of the children of each generation. The family reported here (Fig. 1) fulfils these criteria.

C. B., female aged 17 years, was found to have a symptomless glycosuria on routine testing. No family history of diabetes was known. However, a 50 g glucose tolerance test showed that she was diabetic (Table 1). In August 1965 her diabetes was initially controlled by a 2,000 calorie diet and 20 units of insulin zinc suspension. Two months later insulin was replaced by chlorpropamide, 100 mg b.d., and the dose was later reduced to 100 mg daily. She remained well and had no glycosuria. In 1966 she became pregnant and in her 36th week was admitted to hospital with pre-eclamptic toxaemia. There was no glycosuria but a trace of ketonuria. She was delivered by Caesarean section of a 7 lb 6 oz baby. Three days later glycosuria was noted and for five days she received soluble insulin, 10 units b.d.; thereafter chlorpropamide 200 mg/day was restarted and her diabetes remained controlled. In August 1968 she was again delivered by Caesarean section of a 6 lb 9 oz male child. Following the pregnancy, the 2,000 calorie diet and chlorpropamide 100 mg daily were continued. She has not been seen since but her general practitioner reports (1974) that she is well, her treatment is unchanged, her diabetes is well controlled and she has no complications.

Subsequent to the demonstration of diabetes mellitus in C.B., a 50 g glucose tolerance test was done on the remaining members of the family. All were symptom-free and of average weight. The mother and brother had a normal curve but the father (H. B.) and two younger sisters (D. B. and J. B.) showed abnormal curves (Table 1). The four children had all been of normal weight at birth (6\(\frac{1}{2}\), 7\(\frac{1}{2}\),
The family tree of the ‘B’ family: the diabetic members are indicated by solid circles.

Table 1. Results of the first 50 g glucose tolerance tests done on the diabetic members of the B family. The levels are expressed in mg/100 ml.

|       | C. B. | H. B. | D. B. | J. B. | M. B. |
|-------|-------|-------|-------|-------|-------|
| Fasting | 148   | 112   | 100   | 178   | 86    |
| ½ hr    | 205   | 146   | 317   | 260   | 130   |
| 1 hr    | 240   | 210   | 338   | 310   | 172   |
| 1½ hr   | 250   | 223   | 314   | 310   | 180   |
| 2 hr    | 242   | 268   | 256   | —     | 200   |
| 2½ hr   | 177   | 213   | 187   | 105   | 138   |

6½ and 7 lb). The father’s mother (M. B.), aged 70 years, had a slightly abnormal glucose tolerance test. Her husband had been dead for many years but had not suffered from diabetes.

The diabetes of H. B. (45 years) was rapidly stabilised in September 1965 on a 2,000 calorie diet and 250 mg of chlorpropamide. He has remained on this régime ever since and has been well controlled, showing no glycosuria and having a blood sugar level within the normal range. His weight has increased by 12 lb. He has no diabetic complications.
D. B. (16 years) had glycosuria and ketonuria in September 1965. A 2,000 calorie diet was started. After three injections of 10 units of soluble insulin over 36 hours, her urine became sugar- and acetone-free. Insulin was discontinued and she was maintained on diet alone. On this régime she remained well and showed no glycosuria apart from a brief spell in November 1966, when she had an upper respiratory infection. In 1969 she became pregnant and showed evidence of a lowered renal threshold for glucose. At 30 weeks she was admitted with pre-eclamptic toxaemia and a week later went into labour spontaneously, being delivered of a 5 lb 15½ oz macerated fetus. No major congenital abnormalities were noted. Following discharge she continued on her diet but did not report again until June 1971 when she was admitted and had a second pregnancy terminated at 16 weeks. Again, she disappeared until January 1974 when she was readmitted to the obstetric ward at about the 19th week of her third pregnancy. She had kept to her diet and had tested her urine for sugar from time to time without ever finding any. In view of her past obstetric experience she was started on chlorpropamide 100 mg daily in addition to her 2,000 calorie diet. She was then seen regularly as an outpatient and generally showed 0.75 per cent of sugar in the urine, but the blood sugar levels were always normal. The chlorpropamide was discontinued on 18th April, 1974, with no deterioration in diabetic control. At 37 weeks (16th May, 1974) she was delivered by Caesarean section of a 7 lb 7½ oz baby which, during its neonatal period, behaved like a 'diabetic baby', its blood sugar falling to low levels. After discharge she continued on her diet. During August 1974, sugar reappeared in the urine and on 15th August 1974 the blood sugar 2½ hours after breakfast was 227 mg/100 ml. For this reason she was started on 50 mg of chlorpropamide daily. Since then she has remained well and her urine has been sugar-free. A glucose tolerance test was repeated on 27th November 1974, when serum insulin levels were estimated (Table 2).

Table 2. Results of glucose tolerance test on patient D. B

| Blood sugar | Urine sugar (%) | Serum insulin |
|-------------|-----------------|--------------|
| Fasting 120 mg/100 ml | 4 μμ/ml | |
| ¼ hr 192 | 0.25 | 10 |
| 1 hr 208 | 1.00 | 13 |
| 2 hr 224 | 0.75 | 9 |
| 3 hr 204 | 0.75 | 10 |

She has been examined carefully for evidence of diabetic complications on several occasions but none has been found.

J. B. (aged 12 years) was started on a 1,200 calorie diet in September 1965. This cleared the glycosuria and after five days the diet was increased to 1,500 calories.
Glycosuria did not reappear until February 1966, when the blood sugar two hours after lunch was 215 mg/100 ml. She was therefore started on chlorpropamide 100 mg/day and the glycosuria disappeared. She has continued on this dose and on the 1,500 calorie diet ever since and has remained well controlled. She has no diabetic complications.

Mrs M. B. (70 years) had a partial thyroidectomy performed for hyperthyroidism in 1962. She has no diabetic symptoms and glycosuria has never been found; none of her relatives were known to be diabetic and her one child (patient H. B.) weighed 7 lb at birth. She now takes a light diet, shows no glycosuria and has no diabetic complications.

As part of the assessment of the family, a study has been made of the presence of a variety of organ antibodies in the blood of all but the original patient (C. B.) who does not live in the area. The positive findings are listed in Table 3.

Table 3. Positive results of the organ-antibody study on the diabetic members of the B family.

|                        | M. B. | H. B. | C. B. | D. B. | J. B. |
|------------------------|-------|-------|-------|-------|-------|
| Thyroid antibodies     | +     | -     | -     | +     | -     |
| Gastric parietal cell antibodies | -     | +     | -     | -     | -     |
| Anti-reticulum antibodies | -     | -     | -     | +     | -     |

(The presence of antibodies to gastric intrinsic factor, pancreatic islet cell and adrenal gland was assessed as well as the non-organic specific anti-nuclear, smooth muscle and mitochondrial antibodies.)

DISCUSSION
The four patients in the two younger generations of the family have shown very mild diabetes controllable by diet and oral treatment throughout the ten years of their known diabetes. Symptoms have been conspicuously absent except briefly in relation to infection in one girl. Such absence of symptoms in these three teenage diabetics is as unusual as is the ease with which their diabetes has been controlled. The eldest daughter, C. B., received insulin for two months, the second, D. B., for 36 hours, and the third, J. B., not at all, her diabetes being controlled by diet for the first three months. All three have taken chlorpropamide, two continuously and one (D. B.) intermittently, her diabetes being controlled for long spells by diet alone. Ketonuria was noted, briefly, only in one girl during her first spell in hospital and in another during pregnancy. Fluctuation in the severity of the diabetes has been demonstrated in one (D. B.) by repeated glucose tolerance tests (not all recorded here). The diabetic behaviour of these three teenage girls has thus been totally different from that of the usual juvenile onset diabetic patient...
and characteristic of maturity onset diabetes. However, two have shown some of the problems of the diabetic patient during pregnancy — toxaemia, stillbirth, heavy babies for the stage of their pregnancy and lowering of the renal threshold. The father (H. B.) has shown equally mild, easily controlled, diabetes, while the grandmother (M. B.) has mild biochemical diabetes only. None of the subjects observed over the ten year period has developed any diabetic complications. They thus conform to the pattern of mild familial diabetes with dominant inheritance described by Tattersall (1974) and the maturity onset diabetes of the young of Fajans and Conn (1960).

The antibody studies show the presence of anticytoplasmic thyroid antibodies in one subject of the first and third generations while gastric parietal cell antibodies were shown by the father and anti-reticulum antibodies by the youngest daughter. Pancreatic islet cell antibodies were not found in the grandmother, father and eldest daughter (blood was not available from two daughters). The grandmother has had overt hyperthyroidism treated by thyroidectomy and is now, 13 years later, under treatment for hypothyroidism. No conclusions can be drawn from these antibody findings in relation to the diabetes.

The serum insulin in one daughter, during her tenth year of diabetes, was at a low level, with a negligible response to the glucose load, but clearly the insulin response to her diet and 50 mg of chlorpropamide daily is sufficient to prevent marked hyperglycaemia and glycosuria. A delayed and subnormal insulin response to glucose was reported by Fajans and his colleagues (1973) in this type of diabetic patient, and low levels were also found by Tattersall (1974).

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