Pluriglandular Syndrome with Hyperinsulinism. Cardiomegaly as a Possible Complication of Diazoxide Therapy

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T K, girl, aged 8

History: Well until age of 8, when, in December 1965, she had a 'vacant attack' lasting thirty minutes, in which she was unable to recognize her parents. During the next year she had further episodes characterized by pallor, drowsiness and staggering gait, and later complicated by generalized convulsions. The attacks lasted up to forty-five minutes and increased in severity and frequency. The symptoms were relieved by giving food and she gained 12 kg in weight over eleven months.

In December 1966, at the age of 9 years, she had a severe generalized convulsion during an intercurrent infection associated with diarrhœa and vomiting, and was admitted to the Hospital for Sick Children, Great Ormond Street, under the care of Dr John Wilson. She was drowsy, and dehydrated with bilateral ptosis, hypotonia areflexia and bilateral extensor plantar responses. Blood sugar 20, serum calcium 11·1 mg/100 ml. Intravenous glucose was required for forty-eight hours and she made a slow but complete neurological recovery within a week.

Her father was found to have hypercalcæmia but was asymptomatic. There is no other family history suggestive of endocrine adenomata.

Relevant investigations: Fasting blood glucose was 20–40 mg/100 ml; fasting serum insulin (Dr David Grant) 60–120 microunits/ml; fasting serum calcium 11·1–12·8, phosphorus 2·0–4·3 mg/100 ml. Alkaline phosphatase 17–24 K-A units/100 ml. Blood urea 28 mg/100 ml.

X-rays showed left renal calcification but there were no bone changes.

Urine calcium 4–5 (normal <6) mg/kg/24 h. Creatinine clearance 93 ml/min; urinary VMA 3·4 and 2·9 mg/24 h. Tests of thyroid, adrenal cortical, pituitary and gastric function were normal.

Course and treatment: The association of hyperinsulinism with hypercalcæmia made the diagnosis of multiple endocrine adenomata likely. The immediate problem was control of the hypoglycæmia. Frequent carbohydrate meals supplemented with oral glucose had already produced obesity and in addition tended to precipitate reactive hypoglycæmic episodes.

Substitution of fructose for glucose was later used at the suggestion of Dr Vincent Marks, in an attempt to minimize the reactive hypoglycæmia, and proved helpful. Diazoxide 7·5 mg/kg/day together with chlorothiazide 500 mg/day (Samols & Marks 1965) failed to control symptoms or blood sugar and insulin levels. Subtotal pancreatectomy was performed by Mr David Waterston on 11.4.67 and histology showed diffuse pancreatic microadenomata. Severe hypoglycæmic attacks recurred two days post-operatively and the fasting serum insulin levels were 80–160 microunits/ml. Diazoxide was therefore restarted and

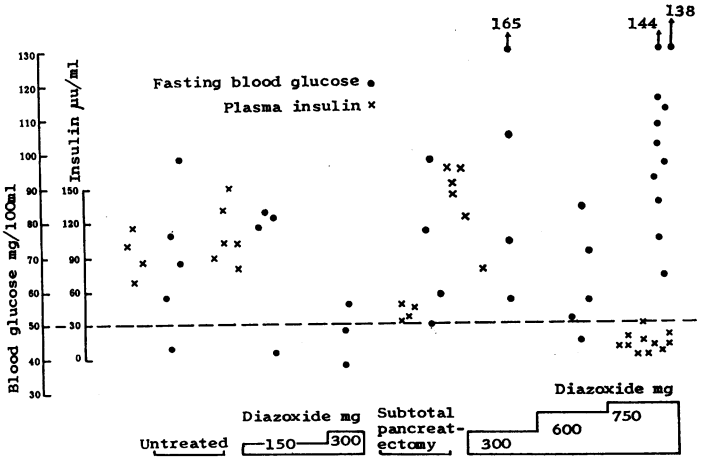

Fig 1 *Effect of diazoxide and subtotal pancreatectomy on blood glucose and serum insulin levels over a period of approximately one year. Note: Chlorothiazide was given throughout the period of diazoxide therapy. The horizontal line indicates the approximate upper limit of normal of the serum insulin and the lower limit of normal of the blood glucose*

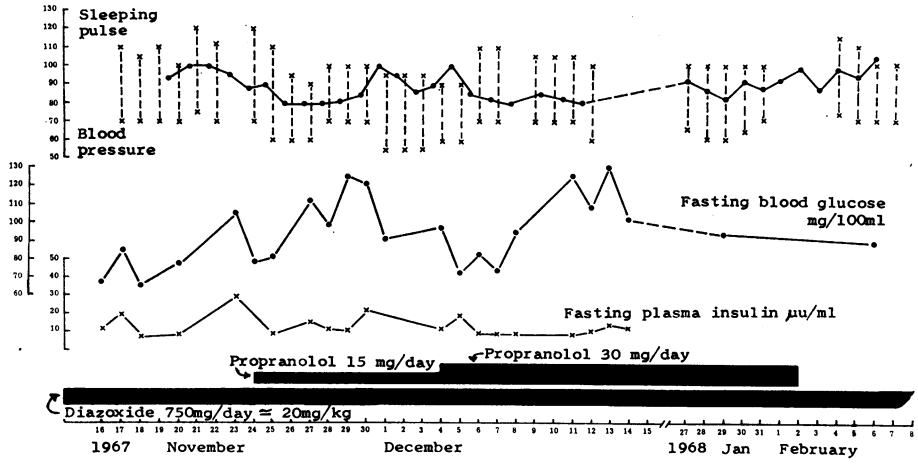

Fig 2 *Effect of propranolol on blood pressure, sleeping pulse rate, blood glucose and serum insulin levels*

the dose increased to 20 mg/kg/day before satisfactory control was achieved (Fig 1). Chlorothiazide 250–500 mg daily was given throughout.

Six months after starting treatment with diazoxide, a marked tachycardia was noted and a chest X-ray showed cardiomegaly, which had not been present on previous films. There was no evidence of congenital or rheumatic heart disease and thyroid function was normal. It was thought that the adrenergic action of diazoxide (Staquet *et al.* 1965) might be responsible for a hyperdynamic circulation and propranolol 15–30 mg/day was given to block this effect (Fig 2). The symptoms improved, there was a small but significant reduction in sleeping pulse rate, and the heart size was reduced, although considerable cardiomegaly persisted with electrocardiographic evidence of left ventricular strain after three months of treatment. During this period there were no hypoglycæmic episodes and no change in fasting serum insulin levels. The hypercalcæmia persisted, with some increase in renal calcification, and an elective parathyroidectomy has been performed. Subsequently the serum calcium levels have returned to normal.

Comment

The pluriglandular syndrome is very rare in childhood (Ballard *et al.* 1964, Underwood & Jacobs 1963) and cardiomegaly has not been included in any description. Of the complications of diazoxide therapy so far described (Baker *et al.* 1967) only hirsutism was present in our patient. The cause of the cardiomegaly remains unexplained and we suggest that it may be a further complication of high-dose diazoxide therapy.

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Congenital Clubfoot with ? Central Core Disease of Muscle

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M W, boy, born 10.1.60

History: Bilateral talipes equinovarus was present at birth, after a normal pregnancy with apparently normal fœtal movements. Denis Browne splints were applied within twenty-four hours but had to be removed after a week due to reaction to the strapping. Plaster boots were fitted for three months, followed by a further three months in splints. His motor power appeared normal and he stood with support by 1 year and walked unaided at 16 months.

The deformities recurred. At 2¼ years the feet were manipulated under general anæsthesia and plaster casts applied for six weeks. There was no correction, and bilateral elongation of the tendo