MEDICAL MEMORANDA

Growth-hormone Deficiency in Iatrogenic Hypothyroidism

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Utiger *et al.* (1962) found impairment of growth hormone response to insulin-induced hypoglycaemia in two out of five patients with hypothyroidism, and they and Iwatsubo *et al.*, Root *et al.*, and Brauman and Corvilain showed that the abnormality may be corrected by treating the hypothyroidism (Harrison *et al.*, 1968). Harrison and his colleagues showed that growth hormone output is normal in treated endemic cretins.

We report a case of iodide-induced hypothyroidism and dwarfism because on correction of the hypothyroidism at the age of 24 years not only was the growth hormone response to hypoglycaemia restored but the patient grew 23 cm in height and developed puberty.

Case Report

The patient, a 24-year-old watch repairer, was referred to hospital with signs of hypothyroidism that had developed gradually over

three years. He was of short stature and puberty had not developed. He had suffered from asthma from infancy and when aged 7 Felsol* Powders had proved so effective that he continued to take about three powders daily regularly up to the time of the present referral. When aged 11 he was found to have a goitre at routine school examination but was clinically euthyroid.

On examination he was of short stature (height 124 cm, weight 26.8 kg.), noticeably hypothyroid, and puberty had not developed (Fig. 1). There was an approximately threefold enlargement of the thyroid. A clinical diagnosis of iodide-induced hypothyroidism was made and Felsol was discontinued. Serum protein-bound iodine was 4.4 $\mu\text{g}/100\text{ ml}$, serum cholesterol 240 mg/100 ml, and urinary excretion of 17-oxosteroids 2.7 mg/24 hr. X-ray appearances of the pituitary fossa were normal. Thyroid antibodies were not detected in the serum. In a radioactive iodine uptake test five weeks later the uptake in the neck at 24 hours was 61% of the tracer dose.

Five months after Felsol had been stopped all features of hypothyroidism had remitted, the thyroid was almost normal in size, and the patient had grown 2 cm. Serum protein-bound iodine was 5.4 $\mu\text{g}/100\text{ ml}$; radioactive iodine uptake in the neck 50% of the tracer dose at 24 hr; urinary excretion of 17-oxosteroids and 17-hydroxycorticosteroids 4.1 and 2.5 mg/24 hr respectively, the latter rising to only 4.5 mg after the administration of metyrapone 500 mg four-hourly for 24 hours; and urinary pituitary gonadotrophin excretion 0.4 mg/24 hr (2nd International Reference Preparation), which was compatible with the prepubertal state but abnormally low for his age. Growth hormone production was not measured at that stage. Bone age was about 12 years (Greulich and Pyle, 1959).

One year after stopping Felsol the plasma 11-hydroxycorticosteroid response to lysine vasopressin and to insulin-induced

FIG. 1—The patient aged 22 years before withdrawal of Felsol.

FIG. 2—Growth rate after withdrawal of Felsol.

FIG. 3—The patient aged 28, 4 1/2 years after withdrawal of Felsol.

*Each Felsol Powder contains phenazone 768 mg, phenacetin 97 mg, caffeine 100 mg, combined phenazone 18 mg with iodine 12 mg, grindelia liquid extract 3 mg, and alcoholic (50%) extract of mistletoe (10:1) 2 mg.

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hypoglycaemia was normal, maximum plasma cortisol being 20.4 μg and 21.6 $\mu\text{g}/100\text{ ml}$ respectively. Serum growth hormone levels, however, measured by the radioimmunoassay method of Hartog *et al.* (1964), showed an abnormally poor response to insulin-induced hypoglycaemia. The levels fasting and at intervals after the administration of soluble insulin 0.1 unit/kg intravenously were 1.0 (fasting), 1.0 (30 min), 1.6 (60 min), and 1.0 (120 min) ng/ml, while corresponding blood sugars were 102 (fasting), 36 (30 min), 68 (60 min), and 85 (120 min) mg/100 ml.

Puberty developed at the age of 26, two years after the withdrawal of Felsol. He grew steadily (Figs. 2 and 3) and in July

1969 was 151 cm tall, weighed 35 kg, and the epiphyses at the knee were just beginning to close. Growth hormone response to insulin-induced hypoglycaemia became normal, growth hormone levels fasting and at 30-minute intervals after the administration of insulin 0.1 unit/kg being 1.4, 9.7, 50, 21, and 18.8 ng/ml. The corresponding blood sugars were 80, 30, 44, 53, and 58 mg/100 ml. The asthma was well controlled on disodium cromoglycate, though there was still evidence of airways obstruction ($FEV_1/FVC=0.75/1.4$).

Comment

This patient developed undoubted clinical hypothyroidism as a result of the long-continued administration of Felsol Powders. Possible explanations for the inappropriately normal level of serum protein-bound iodine and high radioactive iodine uptake were discussed by Begg and Hall (1963). The increase in iodine uptake strongly suggests that the patient's thyrotrophin response was normal.

Five months after discontinuing Felsol he was euthyroid but had a low gonadotrophin output and probable impairment of ACTH response. Lessof *et al.* (1969) reported a deficiency of ACTH output in some hypothyroid patients which usually improved with correction of the hypothyroidism. This patient's growth of 23 cm between the ages of 24 and 28, after the correction of hypothyroidism, accompanied by recovery of

the growth hormone response to hypoglycaemia, suggests that the dwarfism might have been mediated at least partly through growth hormone deficiency. Deficiency of thyroxine alone, however, lessens linear growth, growth hormone output being normal in some cases of juvenile hypothyroidism with dwarfism (Root *et al.*, 1967).

This case illustrates the difficulty of diagnosing primary hypopituitarism in the presence of hypothyroidism. The presence of circulating autoantibodies to thyroid is often useful in identifying patients with primary thyroid disease (Vallotton *et al.*, 1967), but they were not present in this case.

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Hepatotoxicity After Treatment of Schistosomiasis with Hycanthone

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A new drug, hycanthone methanesulphonate, has recently been introduced for the treatment of urinary and intestinal schistosomiasis. It is usually given as a single intramuscular injection at a dose of 3 mg/kg body weight (Clarke *et al.*, 1969). A transient rise in serum transaminase levels (SGOT and SGPT) has been observed after treatment with hycanthone and a case of jaundice has been reported (Cook and Jordan, 1971).

We report here a pronounced rise in bromsulphalein (BSP) retention and serum transaminase levels after hycanthone therapy in two young boys (in a series of eight patients) treated for *Schistosoma haematobium* infestation. In one of

the patients liver biopsies before and after treatment confirmed the development of acute hepatic cell necrosis.

Case 1

A 14-year-old boy was admitted to hospital complaining of dysuria and terminal haematuria of two years' duration. His general physical condition was excellent (weight 34 kg). The liver and spleen were not palpable.

Haemoglobin was 12.1 g/100 ml. Urine contained live eggs of *S. haematobium*, mean daily urinary egg excretion 46,000 (Bell, 1963). Repeated stool examinations were negative for *S. mansoni* eggs. Kidney function tests including phenosulphonphthalein excretion, creatinine clearance, blood urea nitrogen, and intravenous pyelography were normal. Pretreatment liver function tests showed no abnormality (see Table).

Two weeks after admission he was given a single intramuscular injection of hycanthone at a dose of 3 mg/kg (102 mg). One hour later he complained of severe headache and nausea and began vomiting. The vomiting was severe and repeated. Three days after the injection the serum transaminase levels had risen to the upper limits of normal. Because he continued to feel poorly and complain of anorexia and nausea the liver function tests were repeated seven days later. BSP dye retention had risen to 20%, SGOT to 325 units, and SGPT to 455 units. It took three weeks for the BSP and transaminase levels to return to normal. At that time he had recovered his appetite and felt much better.

Two months after treatment he again complained of dysuria and terminal haematuria. A mean urine egg count performed three months after the injection showed an egg reduction of only 60%. The hatching test was positive. He refused any additional treatment.

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Liver Function Tests

	Total Bilirubin (mg/100 ml)	BSP Retention (%) at 45 min (5 mg/kg)	SGOT (Sigma-Frankel Units)	SGPT (Sigma-Frankel Units)	Alkaline Phosphatase (Sigma Units)	Thymol Turbidity (Units)
Case 1:						
Before hycanthone	0.3	4	31	29	6.7	2.8
Three days after injection	0.3	20	40	35	6.8	3.5
Ten days after injection	0.3	20	325	455	6.8	3.5
Case 2:						
Before hycanthone	0.3	5	26	28	5	1.6
Second day after injection	1.6	58	2,150	1,840	5.8	2.8