Short reports

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Fanconi's aplastic anaemia with short stature

Absence of response to human growth hormone

The association of Fanconi's familial aplastic anaemia with a deficiency in circulating plasma growth hormone level has been described by Pochedly *et al.* (1971) and Zachmann, Illig, and Prader (1972). We report a further patient who was treated with human growth hormone and subsequently with oxymetholone.

Case report

The patient was a boy, birthweight 1.98 kg at 37 weeks' gestation. Though he was slow to gain weight, development was normal for the first few years. He sat up at 6 months and walked at one year. From the age of 3 to 5 years he had frequent purulent otitis which resolved after adenoidectomy. He was first seen by us in 1969, aged 8.6 years, because his parents thought him to be of small stature. He was pale and undersized, but alert, very co-operative and cheerful; a regular attender at school, he was in the upper section of the class appropriate to his age. His height was 107.3 cm and weight 15.4 kg. He was pigmented with small darker patches on the skin of the left side of his chest. He could not flex his left thumb to the normal extent.

Haematological investigations (age 8.6 years). Haemoglobin 6.1 g/dl, packed cell volume 21%, mean corpuscular Hb concentration 29 g/dl, platelet count 53 000/ μ l, white cell count of 2800/ μ l with polymorph neutrophils 1000/ μ l, lymphocytes 1400/ μ l, monocytes

300/ μ l, and eosinophils and basophils 50/ μ l. Fetal Hb level was raised at 8%. Bone marrow aspirate showed marked hypoplasia. Tests for deficiency of haematinic factors and for intestinal malabsorption were noncontributory.

Endocrine investigations. Plasma 11-OH corticosteroid was 16.4 μ g/100 ml at 8.00 a.m., 24-hour urine 17-oxosteroid was 0.8 mg, and 17-oxogenic steroid 3.4 mg. Protein-bound iodine 5.4 μ g/100 ml. Bone age from x-ray inspection of epiphyses at both wrists was estimated at 5 years; the pituitary fossa was not enlarged.

He showed evidence of partial deficiency of human growth hormone (HGH) with an inability to raise his plasma level of HGH above 8 ng/ml in response to insulin-induced hypoglycaemia on two separate occasions in 1969 and 1970 (Table). Under balance conditions a metabolic test of end-organ responsiveness to HGH was carried out. A 2000 calorie, normal protein diet was given for 12 days and 24-hour collections of urine made. The mean 24-hour urine nitrogen during the first 6 days was 10.1 g/24 hours (range 6.7-18.4). During 3 days of treatment with 10 mg HGH intramuscularly daily, mean urine nitrogen fell to 4.5 g/24 hours; during the subsequent 3 days it rose to 8.9 g/24 hours. This is equivalent to a 55% fall in 24-hour urine nitrogen excretion in response to HGH treatment and would be generally accepted as evidence of end-organ responsiveness to HGH.

Chromosome studies.

Bone marrow. Structural abnormalities were present in many cells. Dicentric chromosomes were present in 6 of the 10 cells counted and the chromosomes most frequently involved were those of group A and group B. Several cells contained chromosomes of the larger groups with chromatid gaps and breaks.

TABLE
Plasma growth hormone levels during insulin-induced hypoglycaemia

Time (min)	Age (years)					
	9.1		9.6		13.1	
	Glucose (mg/100ml)	HGH (ng/ml)	Glucose (mg/100ml)	HGH (ng/ml)	Glucose (mg/100ml)	HGH (ng/ml)
0	83	4	72	5	75	1
15	23	8	22	5	74	1
30	60	7	25	6	75	12
45	80	5	38	3	72	6
60	70	5	34	3	76	1
120	93	4	56	5	72	1

Peripheral blood. All 50 cells counted showed the normal chromosome complement 46,XY. Structural abnormalities of the chromosomes were common, involving chromosomes of groups A, B, C, and were present in 5 cells; 3 cells showed isochromatid gaps and breaks and at least one cell contained fragments. The chromosome findings were consistent with those previously described in Fanconi's anaemia (Swift and Hirschhorn, 1966; Perkins, Timson, and Emery, 1969).

Small stature, abnormality of the left thumb, pancytopenia associated with marrow hypoplasia, increased level of fetal Hb, and chromosome abnormalities confirmed the diagnosis of Fanconi's familial aplastic anaemia.

His clinical condition at age 8.6 years was good and as he showed only minimal symptoms referable to his anaemia, he was treated with folic acid, ascorbic acid, and iron. His symptoms gradually became more severe and by age 9.3 years he was unduly tired and unable to maintain his previous level of activity. He was given a blood transfusion, with much improvement. 3 months later his clinical condition had again deteriorated and he required further blood transfusion. He required 5 transfusions in 1970. Details of these and Hb levels are set out in the Fig.

When it became clear that he appeared to be at least partially growth hormone deficient and to respond to the test dose of exogenous HGH, it was felt reasonable

to treat him with a prolonged course of HGH. He received 10 mg twice weekly intramuscularly over a 12-month period. At age 11.3 years he had completed 12 months' HGH therapy (Fig.). Growth rate during the year before starting HGH was 6.0 cm/year and did not exceed 8.0 cm/year during treatment. His haematological status did not improve and he required 9 transfusions during his course of HGH. He was started on oral oxymetholone. There was little improvement in the anaemia over the next 3 months but subsequently a gradual rise in Hb; after 6 months it had risen to 12.4 g/dl. Since that time he has been seen at approximately monthly intervals and Hb has not fallen below 11 g/dl. During the year since the start of oxymetholone his height has increased to 134.6 cm (equivalent to a growth rate of 13 cm/year) and his weight to 28.1 kg. The dose of oxymetholone, initially 100 mg daily, was maintained at this level for 2 months and then reduced to 50 mg daily. After 6 months it was further reduced to 50 mg on alternate days and then to 25 mg on alternate days after one year. His white cell count has improved slightly and on occasions has been $>4000/\mu\text{l}$ but still has predominantly lymphocytes on stained smear. His platelet count, however, has not been altered and remains between 40 000 and 50 000/ μl .

Investigations were repeated aged 13 years. Bone age (Tanner/Whitehouse, Development Charts; Tanner, Whitehouse, and Healy, 1962) was now 13.6 years; plasma 11-OH corticosteroid 3 $\mu\text{g}/100\text{ ml}$ at 8.00 a.m. The bone marrow was much improved from the initial sample, being surprisingly cellular, with normal granulopoietic/erythropoietic ratio. Megakaryocytes were very scanty. An insulin hypoglycaemia test was attempted but adequate hypoglycaemia was not obtained; nevertheless a small rise in plasma HGH was found, presumably mediated by the stress of the procedure (Table).

Throughout the period of observation he has shown neither a tendency to excessive bleeding nor to serious infectious illness, and since going onto oxymetholone he has been very well, though he now has well marked signs of virilization with moderate growth of pubic hair and deepening of the voice (Tanner/Whitehouse grade III, Development Charts; Tanner *et al.*, 1962).

Discussion

Pochedly and his colleagues (1971) reported a case of Fanconi's anaemia in which plasma HGH did not rise above 3 ng/ml in response to either insulin-induced hypoglycaemia or arginine infusion, but they have not documented any details of treatment with HGH. Zachmann *et al.* (1972) reported 2 brothers with Fanconi's anaemia, both of whom were of short stature with inability to increase plasma HGH above 1.7 ng/ml in response to insulin-induced hypoglycaemia. The elder brother had a 10-day nitrogen retention test carried out with a fall in 24-hour urinary nitrogen excretion of 31.5% of the pretreatment level and showed a growth velocity over 2 years' HGH treatment of

FIG.—Height, Hb level, blood transfusion requirement, and bone age during treatment with HGH and oxymetholone in the patient. *Fracture in left arm.

7.4 cm/year, which is at least normal for the age group, but they did not record a pretreatment growth rate. It is probably significant that the younger sib is growing at a similar rate without HGH treatment.

The present case appears to be similar to both these reports with low and unresponsive levels of HGH, and the nitrogen retention after a short course of HGH was even more marked than that found by Zachmann *et al.* However, we have not found any evidence of growth acceleration in response to long-term HGH treatment and neither was there any effect on the anaemia. The response to oxymetholone therapy has been much more striking in growth rate, epiphyseal fusion, and improvement in haematological parameters. The transfusion requirement was not influenced by growth hormone and he needed to be transfused on 9 occasions during his year on growth hormone, although the Hb level has been satisfactory since some 6 weeks after starting oxymetholone.

The moderate anaemia of all prepubertal hypopituitary children of short stature has been shown by Jepson and McGarry (1972) to be related to a low excretion of the erythropoietin-stimulating factor and these authors suggest that both testosterone and growth hormone may play a part in the normal increase of erythrocyte values observed during growth and maturation. They showed that treatment with HGH induced bone marrow lymphocytosis with an increase in red cell mass, increased excretion of erythropoietin-stimulating factor in the urine, and expansion of the plasma volume. Testosterone was additive to HGH in some of these effects. However, none of their patients had a severe aplastic anaemia of the type recorded here. A patient with congenital hypoplastic anaemia, described by Steel, Butterworth, and Keay (1972), showed evidence of pituitary hypofunction after many transfusions and it was felt that the endocrinological defect was secondary to extensive deposition of haemosiderin within the pituitary gland. Our patient differs in that clear evidence of endocrine dysfunction existed before oral iron therapy and blood transfusion. From the endocrine point of view the classification of his short stature is uncertain. Though a brief effect was possible during the test dose, perhaps sustained nitrogen retention necessary for an increased growth rate was not possible in the face of the pre-existing basic defect of protein synthesis manifesting as pancytopenia.

Summary

A patient with idiopathic marrow hypoplasia associated with short stature and other anomalies

(Fanconi's anaemia) is described: treatment with human growth hormone for one year did not accelerate his growth rate or significantly affect his anaemia: androgen treatment considerably improved both features. Endocrine studies suggest that though he had poor and insufficient production of endogenous growth hormone to insulin-induced hypoglycaemia, the major defect in this syndrome is determined more at the end-organ than at the pituitary or gonadal level.

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Raised IgA in idiopathic pulmonary haemosiderosis

The aetiology of idiopathic pulmonary haemosiderosis (IPH) is still unknown. Various hypotheses such as congenital weakness or fragility of the capillaries, milk allergy, abnormal growth and function of the alveolar epithelial cells (Soergel and Sommers, 1962) have been suggested, but not confirmed. Steiner's (1954) theory of an autoimmune antigen-antibody reaction mechanism with the lung as the shock organ is supported by findings such