Effect of HGH replacement therapy on concentration of 15 serum proteins

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Minchin Clarke, H. G., Grant, D. B., and Putman, D. (1973). *Archives of Disease in Childhood*, 48, 608. **Effect of HGH replacement therapy on concentration of 15 serum proteins.** The effect of human growth hormone (HGH) therapy on the concentration of 15 individual serum proteins was studied in 13 HGH-deficient children. After 3 months' HGH therapy, 8 patients with isolated HGH deficiency showed a marked rise in serum transferrin with less striking changes in haptoglobin, haemopexin, IgG, and proteins numbered 41 and 45. No significant changes in these proteins were found in 5 patients with craniopharyngioma or generalized anterior pituitary failure.

The importance of growth hormone in protein metabolism has been recognized for many years, but little is known about the effects of human growth hormone (HGH) on serum protein concentration in man. Though Drash (1968) observed no change in the levels of albumin and globulin in hypopituitary patients treated with HGH, we considered it of interest to study the concentration of a number of serum proteins in patients receiving HGH therapy.

Patients and methods

Thirteen patients with evidence of HGH deficiency (Tanner *et al.*, 1971) were studied: 8 appeared to have

Received 4 January 1973.

isolated HGH deficiency, 2 had more generalized anterior pituitary failure, and in 3 HGH deficiency was due to craniopharyngioma. Details of therapy and growth acceleration during the first 6 months of treatment are given in Table I

Blood samples were collected by finger-prick before HGH therapy was begun and again after 3 months' treatment. The concentration of the following serum globulins was estimated by a modification of Laurell's quantitative immunoelectrophoresis (Clarke and Freeman, 1968) (Fig.). *Alpha₁-easily-precipitable glycoprotein* (α_1 PgP); *Gc-globulin* (Gc); *alpha₂-macroglobulin* (α_2 M); *caeruloplasmin* (Caer); *haptoglobin* (Hpt); *transferrin* (Trf); *haemopexin* (Hpx); *beta-lipoprotein* (β Lp), and proteins numbered 9, 41, 45, 53, and 99 (Freeman and Smith, 1970).

TABLE I
Clinical details in 13 patients receiving HGH treatment

Case no.	Diagnosis	Age at start of treatment (yr)	Increase in growth velocity during 1st 6 mth HGH therapy (cm/yr)	Weekly dose of HGH (IU)	Other treatment
1	Isolated HGH deficiency	7.1	8.4	20	Nil
2	Isolated HGH deficiency	8.5	4.2	20	Nil
3	Isolated HGH deficiency	9.2	8.4	20	Nil
4	Isolated HGH deficiency	9.3	6.2	10	Nil
5	Isolated HGH deficiency	12.5	5.0	20	Nil
6	Isolated HGH deficiency	15.5	3.2	10	Nil
7	Isolated HGH deficiency	17.9	3.6	10	Nil
8	Isolated HGH deficiency	17.9	1.8	20	Nil
9	General anterior pituitary failure	4.0	15.2	20	Cortisone acetate
10	General anterior pituitary failure	7.8	9.2	20	Cortisone acetate and thyroxine
11	Craniopharyngioma	13.0	8.8	20	Nil
12	Craniopharyngioma	17.2	4.0	10	Cortisone acetate and thyroxine
13	Craniopharyngioma	24.5	1.6	20	Nil

FIG.—Laurell electrophoresis of human serum.

Using this technique measurements cannot be given in absolute units, and results have been expressed in arbitrary units derived from the area under each protein peak.

The concentration of serum albumin (Alb) and γ G-immunoglobulin (IgG) was measured by the radial immunodiffusion method of Mancini, Carbonara, and Heremans (1965) using commercially available standards (Behringwerke AG).

The results were analysed using Student's paired 't' test.

Results

Patients with isolated HGH deficiency.

The results obtained in 8 patients with isolated HGH deficiency are summarized in Table II.

Each patient showed a rise in serum transferrin during therapy and the mean value after 3 months was higher than the pretreatment value ($P < 0.001$). A correlation was obtained between percentage change in transferrin concentration and increase in growth rate during the first 6 months of treatment ($r=0.79$, $P = 0.02$).

The mean values for haemopexin and protein number 41 also rose during treatment ($P < 0.05$).

The mean values for IgG, haptoglobin, and protein number 45 decreased during treatment ($P < 0.05$). One patient (Case 8) had subnormal

levels of IgG both before and after treatment (210–300 mg/100 ml).

Patients with craniopharyngioma or complete anterior pituitary failure. The mean values and SD for protein concentration before and after therapy are also given in Table II. No significant changes were shown in this group. In particular, there was no appreciable change in serum transferrin in the 2 patients with generalized anterior pituitary failure.

Discussion

It is widely accepted that growth hormone stimulates protein synthesis *in vivo*, but it is still uncertain whether this action is due to growth hormone itself or whether it is brought about by an intermediary such as sulphation factor (Daughaday, 1971). Using perfusion experiments, Clemens and Korner (1970) showed that growth hormone only increased liver protein synthesis in the presence of supplementary amino acids, while John and Miller (1969) found that growth hormone had no effect on the synthesis of plasma or liver proteins.

Although the present studies do not permit any conclusion on the effects of HGH on the rates of

TABLE II

Serum protein concentrations before and after HGH therapy in children with isolated growth hormone deficiency or generalized pituitary insufficiency

	Isolated HGH deficiency (8 cases)		General pituitary insufficiency (5 cases)	
	Pretreatment mean (SD)	Post-treatment mean (SD)	Pretreatment mean (SD)	Post-treatment mean (SD)
α_1 PGp	51.4 (8.7)	51.1 (7.6)	61.2 (10.8)	52.8 (6.7)
Gc	408 (59)	378 (29)	392 (68)	378 (45)
Caer	24.0 (3.4)	23.8 (3.7)	30.5 (4.0)	27.9 (3.4)
α_2 M	55.3 (9.8)	60.8 (5.8)	58.6 (13.6)	55.0 (11.7)
Hpt	205 (107)	103 (60)*	181 (51)	164 (35)
Hpx	448 (68)	508 (39)*	482 (33)	473 (85)
Trf	392 (55)	508 (38)†	431 (41)	485 (62)
β Lp	27.3 (8.3)	30.9 (5.1)	30.5 (5.4)	28.2 (4.1)
9	25.0 (7.9)	27.7 (5.2)	24.4 (7.9)	24.2 (8.0)
41	189 (40)	214 (20)*	221 (31)	175 (31)
45	139 (32)	100 (18)*	132 (24)	113 (11)
53	91 (35)	74 (14)	88.2 (4.1)	80.1 (12.7)
99	120 (31)	112 (18)	140 (39)	128 (23)
Albumin	5100 (1800)	4790 (1000)	4720 (500)	4925 (400)
IgG	1211 (543)	906 (443)*	1030 (301)	925 (445)

Note: Albumin and IgG expressed in mg/100 ml and remaining proteins in arbitrary units.

Significance of difference between pre- and post-treatment concentration: *P < 0.05, †P < 0.001.

synthesis and turnover of serum proteins in man, the results suggest that the metabolism of some serum proteins may be modified by HGH replacement therapy. Nevertheless, it must be appreciated that significant protein changes were seen only in patients with isolated HGH deficiency, and not in those where the hormone deficiency was secondary to pituitary pathology, such as craniopharyngioma. The most striking finding was an increase in serum transferrin during treatment, particularly in patients with isolated HGH deficiency. A similar rise in transferrin, associated with an increase in red cell mass, was described by Jepson and McGarry (1972) in a group of hypopituitary subjects treated with HGH. It seems likely that this rise in transferrin is related to increased iron turnover, secondary to increased haemoglobin synthesis. Similarly, the changes in haptoglobin and haemopexin found in patients with isolated HGH deficiency were probably related to changes in red cell metabolism after HGH therapy. Red cell mass is also dependent on thyroid function (Muldowney, Crooks, and Wayne, 1957), but it is unlikely that the inconsistent results obtained with general anterior pituitary failure were due to secondary hypothyroidism; 3 patients had normal plasma thyroxine levels and the other 2 were receiving replacement therapy with thyroxine.

The significance of the modest changes in proteins 41 and 45 in patients with isolated growth hormone deficiency is uncertain. It was not

possible to obtain suitable controls from normal children for this study, but comparison with adult control serum indicated that the changes in these proteins represented a return to normal levels during treatment. Protein 45 has been found to rise during acute phase response to trauma (Clarke, Freeman, and Pryse-Phillips, 1971) and has been tentatively identified as antichymotrypsin (Laurell, 1972).

Our failure to find any consistent changes in serum albumin during HGH replacement therapy is in agreement with results given by Drash (1968), and it appears that HGH has little effect on serum albumin concentration in man.

Pierpaoli and Sorkin (1969) have reported that adult mice treated with antiovine growth hormone serum show reduced levels of antibody synthesis. The above results indicate that HGH deficiency is not associated with depressed serum IgG levels which can be corrected by HGH therapy. Serum IgG levels were normal in all but one of our patients, and appeared to fall during treatment.

We thank Professor J. M. Tanner and Mr. R. H. Whitehouse for allowing us to use their clinical data.

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