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Primary somatomedin deficiency

Case report*

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Van den Brande, J. L., Du Caju, M. V. L., Visser, H. K. A., Schopman, W., Hackeng, W. H. L., and Degenhart, H. J. (1974). *Archives of Disease in Childhood*, **49**, 297. **Primary somatomedin deficiency: case report.** A child presenting with the clinical features of hyposomatotropism but with high immunoreactive plasma growth hormone is described. During short-term administration of human growth hormone (HGH) his response with regard to fasting blood-glucose and free fatty acids, plasma-somatomedin, urinary excretion of calcium, nitrogen, and hydroxyproline was minimal or absent. 6 months of treatment with HGH did not reduce the endogenous HGH secretion. Insulin secretion had not increased and plasma somatomedin levels remained extremely low. Over a period of 2 years of treatment, growth response and loss of subcutaneous fat were minimal. On serial dilution in radioimmunoassay, his growth hormone (GH) molecule yielded a parallel line with the HGH standard. In electrofocusing experiments the GH molecule was in the same *p*H range as growth hormone in acromegalic plasma and the major peak of clinical grade HGH (5·03 against 5·01 and 4·98).

It is concluded that an overall and specific diminished responsiveness to HGH is present in this patient. This includes a lack of generation of somatomedin, which is thought to be the cause of his short stature. There was no evidence of abnormality of the GH molecule.

Patients presenting with the clinical appearance of growth hormone deficiency, but in whom high levels of immunoreactive growth hormone were found, were first described by Laron, Pertzelan, and Mannheimer (1966). Since then additional patients were reported by Laron, Pertzelan, and Karp (1968), Merimee *et al.* (1968), Tanner *et al.* (1971), Najjar *et al.* (1971), Elders *et al.* (1971), and New *et al.* (1972). This paper describes a similar patient and adds evidence suggesting an overall and specific non-responsiveness to growth hormone.

Patients

Case 1. A White boy, was born at 37 weeks' gestation. Pregnancy had been complicated by hypertension during the last weeks. Birthweight 3250 g (+1·0 SD), length 44 cm (−2·6 SD) (Usher and McLean, 1969). During the first days of life he was noted to drink poorly and to vomit occasionally. Psychomotor development was normal. Growth was slow from early in life (Fig. 1). At the age of 2 years he had documented hypoglycaemic spells for which he was given cortisone (5 mg/day). An attempt to increase his growth rate with ethyloestrenol (Orgabolin, Organon) 0·5 mg/day during 6 months failed. Cortisone was discontinued at the age of 6 years when Perthes-like deformities were discovered in both hips. All treatment was withheld until he was aged 10 years 2 months when he was admitted for the present studies. Family history was negative for short stature. Father's height 170·7 cm (>10th centile), mother's height 155·7 cm (about 3rd centile) (Van Wieringen, 1972). There was no consanguinity.

Case 2. A White boy, aged 6 years 4 months at the time of diagnostic studies, with severe hyposomatotropic dwarfism and of similar body size as Case 1. He was selected to serve as a control. He was born by caesarean section, 3 weeks post-term after presentation in breech position. Pregnancy had been complicated by hyper-

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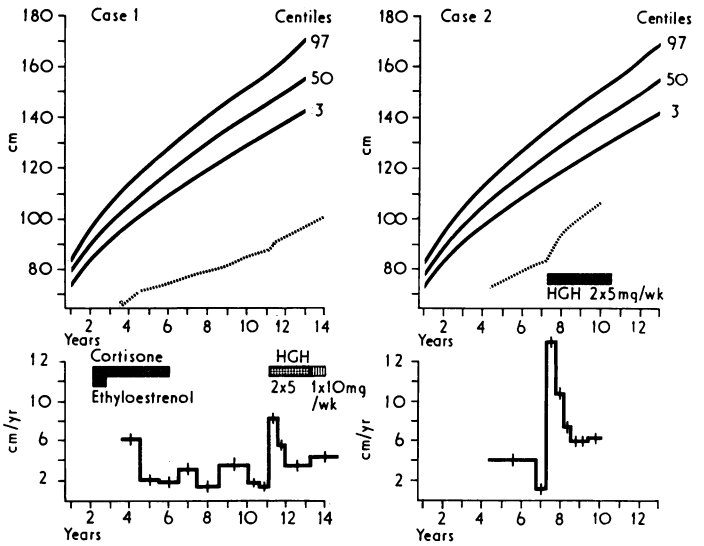


FIG. 1.—*Height is plotted against Dutch growth standards (Van Wieringen, 1972). Growth hormone administration caused only a slight increase in growth rate in Case 1. The control patient, Case 2, with isolated GH deficiency responded to GH treatment with a pronounced growth spurt.*

tension after the 36th week. Birthweight 3500 g (equal to the mean for gestational age), length 50 cm (−1·5 SD) (Usher and McLean, 1969). During the first days of life he drank poorly and vomited occasionally. He was noticed to grow slowly (Fig. 1). His psychomotor development was quite normal. He had had no history of hypoglycaemia and had received no medication before admission to hospital. Family history was negative for short stature. The parents were full cousins.

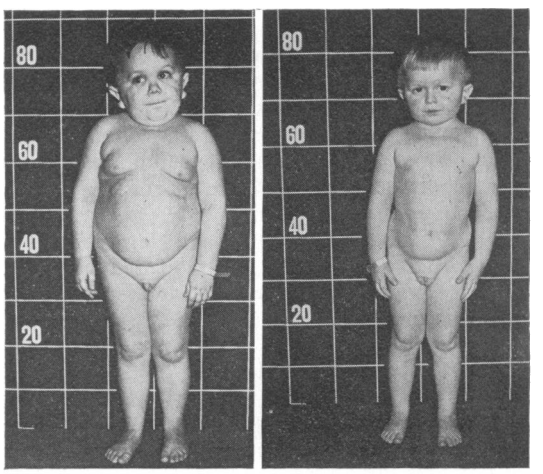
Materials and methods

Growth hormone and insulin were measured with a charcoal dextran radioimmunoassay (Schopman and Hackeng, 1971). Urinary total nitrogen, calcium, phosphorus, creatinine, and 17-hydroxysteroids, as well as blood glucose and free fatty acids were measured using routine methods (Fawcett and Scott, 1960; Dunsbach, 1963; Fiske and Subbarow, 1925; De Vries and Van Daatselaar as described by Gorter and De Graaf, 1955; Degenhart, 1974; Schmidt, 1963; Ko and Royer, 1967; Korovina, Vel'tishchev, and Lempert, 1966). Total urinary hydroxyproline was determined with the Hypronosticon test (Organon) (Goverde and Veenkamp, 1972). Plasma somatomedin was measured with a double isotope technique, using hypophysectomized rat or normal monkey rib cartilage (Van den Brande *et al.*, 1971b).

For the electrofocusing experiments, an LKB 8102 Ampholyne column (440 ml) was used with LKB ampholite ranging from *p*H 3 to 6. The procedure was as described earlier (Van Wyk *et al.*, 1971). Equilibration time was between 60 and 120 hours. Fractions were tested for their growth hormone content by radioimmunoassay.

Results

Physical examination. The physical appearance of both boys was very similar (Fig. 2). The abnormalities were more pronounced in Case 1 than in Case 2. Both were short, obese, and reasonably well proportioned. Some details are given in Table I. Their faces were small.



(*a*) (*b*)

FIG. 2.—(*a*) *Case 1 and* (*b*) *the control patient, Case 2, before treatment. Obesity was more pronounced in Case 1, their appearance being otherwise very similar.*

TABLE I

Anthropometric data before and during treatment

	Case 1				Case 2			
Age (yr)	11·1	11·6	12·2	13·3	7·3	7·8	8·4	9·5
Time after initiating growth hormone treatment (yr)	0	0·50	1·12	2·23	0	0·51	1·09	2·25
Length (cm)								
Supine	87·8	91·2	93·8	98·0	83·0	90·6	96·0	—
Standing	—	—	—	—	—	90·5	93·3	103·0
Span (cm)	88·0	90·2	97·0	97·0	81·5	88·5	96	102·0
Head circumference (cm)	51·0	51·5	51·5	51·6	48·2	48·3	48·8	49·4
Weight (kg)	15·7	17·9	19·0	20·0	10·2	11·3	12·8	15·5
Skinfold thickness (% of initial)	100·0	91·1	90·5	99·6	100·0	62·3	59·3	58·4

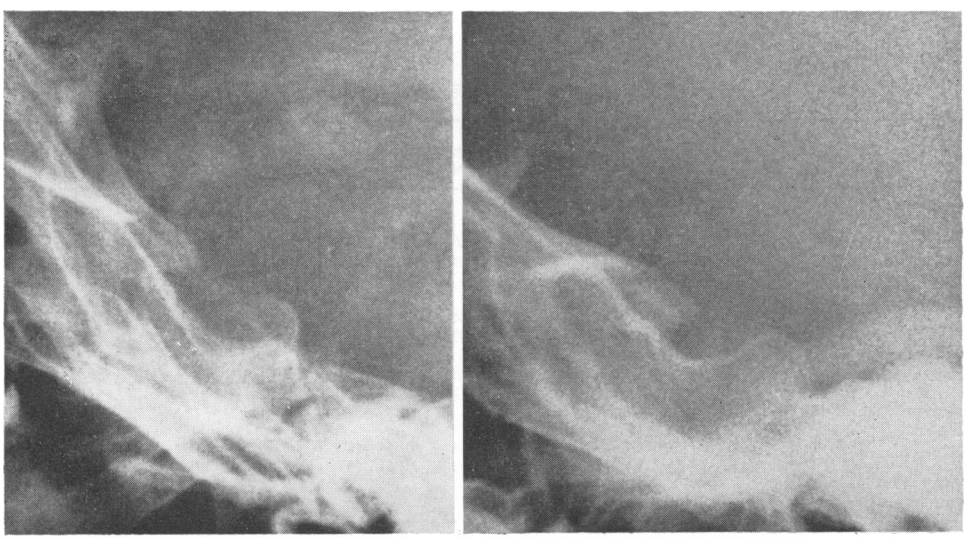
Particularly Case 1's ears were disproportionately large. The teeth were in poor condition. Both had small external genitalia with a short penis (2·5 cm Case 1, 1·5 cm Case 2), a hypoplastic scrotum, the contents of which could not with certainty be identified as testes. Eye grounds, visual fields, and detailed neurological examination were all within normal limits. Skeletal age was 6·6 years in Case 1 and 4·7 years in Case 2 (Tanner, Whitehouse, and Healy, 1962). On *x*-ray examination the skull bones were found to be very thin. Whereas Case 2's sella was small, in Case 1 an impression on the floor of the sella suggested a large pituitary gland (Fig. 3).

Baseline laboratory examination.

Thyroid and adrenal function. Cases 1 and 2, respectively. Protein-bound iodine 4·1 and 5·0 μg/100 ml. ^{131}I uptake 30 and 23, 4% of the dose after 24 hours. Metyrapone test (maximal 17-hydroxysteroid excretion on 250 mg at 4-hourly intervals for 2 days) 6·9 and 5·4 mg/m^2 per 24 hr. All these results were normal.

Plasma growth hormone was measured during intravenous infusion of arginine-monohydrochloride (0·5 g/kg infused in 30 minutes), and with insulin-induced hypoglycaemia (0·05 units/kg i.v.; blood glucose fell to 51% of the initial value in Case 1 and to 65% in Case 2). Case 2 showed almost no response, HGH reaching a maximum value of 2 μU/ml* during arginine infusion. Case 1 in

*1st IRP for Human Growth Hormone.



(*a*) (*b*)

FIG. 3.—(*a*) *The sella turcica of Case 1 showed an impression of the floor, whereas* (*b*) *that of Case 2 was small but otherwise normal.*

contrast had very high baseline values of HGH (average 69 μU/ml, range 60–76) which rose further to the extreme level of 508 μU/ml during insulin-induced hypoglycaemia.

Plasma insulin levels were also measured during the arginine infusion test and were low in both cases. Though their peak values were similar (Case 1 8, Case 2 9 μU/ml), Case 1 had a sustained baseline level between 4 and 6 μU/ml, whereas the baseline was less than 1 μU/ml in Case 2.

Plasma somatomedin measured in the hypophysectomized rat assay was equally low for both patients as compared to two acromegalics. This low value was found both when ^{35}S-sulphate and when the ^{3}H-thymidine incorporation was used as an index of somatomedin activity (Fig. 4).

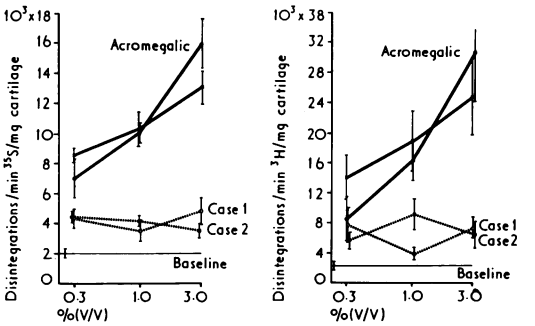


FIG. 4.—*Plasma somatomedin activity measured in the hypophysectomized rat assay using a dual labelling procedure. Within the limits of the concentrations used, no increased incorporation of ^{35}S-sulphate or ^{3}H-thymidine occurred with plasma from Case 1 or Case 2, while the plasma from two acromegalics was highly stimulatory.*

Short-term metabolic studies (Table II and Fig. 5). Human growth hormone, clinical grade,* was administered at a dose of 8 mg/m^2 per day at 8 p.m. for 7 days. Results obtained from the day after the second injection on have been selected for comparison with the baseline data, except for hydroxyproline excretion which is known to change slowly during GH treatment (Van Gemund, Vio, and Giesberts, 1967). For this reason, only the data obtained after the fourth administration of HGH were included. During these studies the patients were hospitalized and kept on a calorie- and nitrogen-constant diet.

Fasting blood glucose and free fatty acids were only slightly affected. Blood glucose increased somewhat in Case 2 and not in Case 1. Fatty acids did not change significantly.

Urinary excretion of Ca and P is expressed as their ratio since this reduced the daily fluctuation considerably. A slight but significant increase was noted in Case 1, while Case 2 showed a very large rise.

*Prepared by N. V. Organon Oss by a modified Raben-extraction procedure and kindly supplied by the Dutch foundation for the study of growth. The content in immunoreactive HGH of this preparation is 1·45 1° IRP/mg.

TABLE II

*Effect of short-term growth hormone administration**

	Baseline Mean ± SEM (no.)	On treatment Mean ± SEM (no.)	% change	P (baseline versus treatment)†
Fasting blood glucose (mg/100 ml)				
Case 1	76·75 ±3·7 (4)	72·30 ± 2·0 (5)	− 5·8	NS
Case 2	64·25 ±5·2 (4)	81·04 ± 2·24 (5)	+ 26·1	<0·05
Fasting plasma free fatty acids (mEq/l.)				
Case 1	1·080±0·060 (4)	1·248± 0·124 (5)	+ 15·6	NS
Case 2	1·231±0·270 (4)	1·375± 0·116 (5)	+ 11·7	NS
Urinary Ca/P ratio				
Case 1	0·060±0·003 (3)	0·085± 0·012 (5)	+ 41·7	<0·05
Case 2	0·085±0·004 (3)	0·315± 0·038 (4)	+270·6	<0·01
Urinary nitrogen/creatinine ratio				
Case 1	22·57 ±0·34 (3)	19·44 ± 0·54 (5)	− 13·9	<0·005
Case 2	25·73 ±2·51 (3)	10·50 ± 0·41 (6)	− 59·2	<0·001
Urinary hydroxyproline/ creatinine ratio				
Case 1	67·60 ±3·71 (3)	57·4 ± 2·37 (4)	− 15·1	<0·05
Case 2	104·23 ±5·60 (3)	197·6 ±23·25 (4)	+ 89·6	<0·01

*HGH dose 8 mg/m² per day (see text).
†By Student's 't' test. NS, not significant.

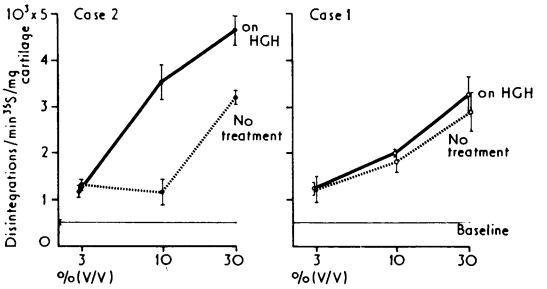


FIG. 5.—*Plasma somatomedin activity measured in the normal monkey assay using a dual labelling procedure. Plasma from Cases 1 and 2 before starting treatment (no treatment), and on the 4th–5th day of HGH administration at 8 mg/m² per day are compared. Note that the dose response curve obtained with plasma from Case 1 does not change, in contrast to the potency of Case 2's plasma. ^{35}S-sulphate and ^{3}H-thymidine incorporation were identical (the latter is not shown).*

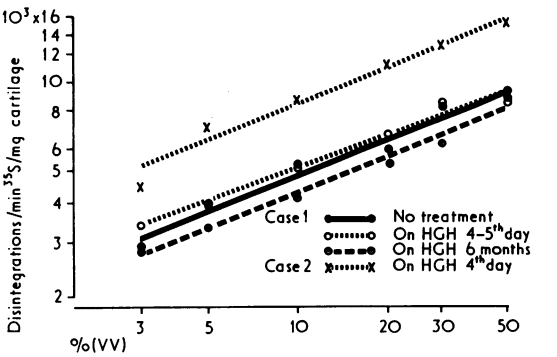


FIG. 6.—*Plasma was incubated over a wide range of concentrations in the normal monkey assay using ^{35}S-sulphate incorporation as index. Dose response curves obtained with plasma before treatment, after 4 days of administration of HGH (8 mg/m² per day), and after 6 months of treatment with HGH 5 mg bi-weekly, are identical. To confirm that this assay would pick up an active sample, Case 2's plasma on the 4th day of HGH treatment was also measured.*

Urinary nitrogen/creatinine ratio fell slightly in Case 1 and drastically in Case 2. The fall was significant for both patients, but the differences between them were large.

Urinary hydroxyproline/creatinine ratio decreased somewhat in Case 1 and doubled in Case 2.

Plasma somatomedin was measured in pretreatment plasma and on the fourth day of GH treatment. In baseline conditions both patients were indistinguishable. On treatment the somatomedin activity of Case 2 rose to approximately three times the baseline levels, whereas Case 1 remained unchanged, both when the results were expressed as ^{35}S-sulphate and as ^{3}H-thymidine incorporation.

Effect of long-term GH treatment.

Linear growth and skinfold thickness. Over periods of 2 years before and on treatment, Case 1's growth rate increased from 3·1 cm/year to 4·6 cm/year as compared to an increase from 3·3 to 9·2 cm/year in the control patient, Case 2. Over the same period of treatment, average skinfold thickness, measured with a Harpenden caliper at 8 sites, after an initial decrease to 90·5% of the initial value, increased again to 99·6% in Case 1, while it decreased to 58·4% in Case 2 (Table I).

Skeletal maturation advanced 2·3 years in Case 1 and 2·5 years in Case 2 over the same 2-year period (Tanner *et al.*, 1962).

Plasma somatomedin activity. As shown in Fig. 6, dose response curves with Case 1's plasma before treatment and after 4 days and 6 months of growth hormone administration did not differ.

Plasma growth hormone and insulin levels. An arginine tolerance test was repeated in Case 1 after 6 months of treatment. The test was done 36 hours after an HGH injection. The results are shown in Table III. Treatment had not resulted in a decreased endogenous HGH response, nor had it stimulated insulin secretion in response to arginine infusion.

Some immunological and physicochemical characteristics of endogenous growth hormone in Case 1. In order to study possible differences in immunological characteristics, plasma was serially diluted, growth hormone was estimated by radioimmunoassay, and the slopes obtained were compared. No significant deviation from parallelism could be shown (Fig. 7).

In order to find possible differences in charge, plasma from Case 1 was electrofocused and compared both with plasma from an acromegalic and with HGH (same preparation as used for treatment). GH was localized by radioimmunoassay.

Initially, GH in Case 1's plasma focused at a wide peak with a suggestion of two maxima (Van den Brande *et al.*, 1971a). After improving the technique by selecting the more appropriate *p*H range of 3 to 6 instead of 5 to 8, and using the same

TABLE III

Arginine infusion before and after 6 months of growth hormone administration*

Time (min)†	−15	−1	+15	+30	+45	+60	+75	+90	+120	+150
Plasma growth hormone (μU 1st IRP/ml)										
Before treatment	63	75	105	118	170	470	508	295	133	—
After 6 months' treatment	217	216	141	192	315	228	180	198	222	198
Plasma insulin (μU/ml)										
Before treatment	6	4	4	6	8	6	4	4	5	—
After 6 months' treatment	4	2	2	3	4	2	2	2	2	2

*Arginine hydrochloride 0·5 g/kg body weight i.v. over a 30 min period after overnight fast.
†Before (−) and after (+) initiation of infusion.

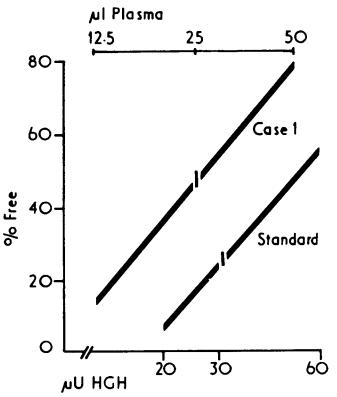


FIG. 7.—*Plasma from Case 1 was serially diluted and measured in the HGH radioimmunoassay. Each of the points on the standard curve is an average of 4 determinations. The plasma was measured in duplicate at each dose level. HGH is expressed in μU 1st IRP of HGH. No deviation from parallelism is demonstrable (F: 4·8–P: 0·05).*

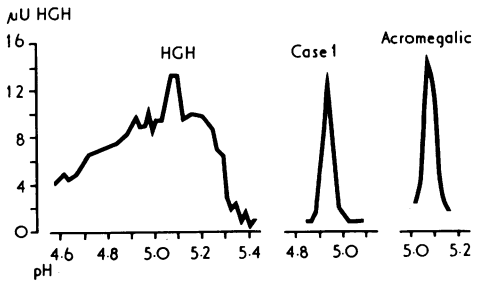


FIG. 8.—*Examples of electrofocusing of human growth hormone. From left to right: HGH (clinical grade, same preparation as in the metabolic studies, 0·72 mU), 2 ml plasma respectively from Case 1 and an acromegalic. In repetitive experiments the GH of all three preparations was found between the extremes of* pH *4·93 and 5·14. Average peak positions were HGH 4·98, Case 1 5·03, acromegalic 5·01.*

plasma sample, a sharp single peak was repeatedly found at an average *p*H of 5·03. In acromegalic plasma, GH focused in a single zone at an average *p*H of 5·01. Finally, HGH (clinical grade) yielded a broad zone of immunoreactive material with a maximum at *p*H 4·98. Examples are shown in Fig. 8. Within the limits of the technique we found the GH from these 3 sources to behave indistinguishably.

Discussion

At first most of the patients studied by Laron *et al.* (1968) seemed to respond to exogenous HGH with nitrogen retention, lipolysis, and increased growth rate. More recently, however, after a longer period of observation, the authors concluded that the metabolic and growth responses of their patients were variable but mostly lacking (Laron *et al.*, 1971). This is in agreement with the findings by others (Merimee *et al.*, 1968; Tanner *et al.*, 1971; Najjar *et al.*, 1971; Elders *et al.*, 1971; New *et al.*, 1972). Laron *et al.* (1971) favour the hypothesis that the GH molecule in such patients might have an abnormal structure, lacking biological activity but with the preservation of its immunological characteristics. The subnormal response to exogenous HGH could be the consequence of an unsuccessful competition with the endogenous molecule for binding sites. Daughaday *et al.* (1969) found low plasma somatomedin levels both before and while on treatment with HGH in Laron's patients. They suggested that defective somatomedin generation may be responsible for the growth failure, while the other abnormalities such as lack of lipolysis, nitrogen retention, and calciuria may be the expression of a more generalized defect in growth hormone response. New *et al.* (1972) came to similar conclusions. Our patient, Case 1, also presents with a complete picture of hyposomatotropism, including not only short stature and the typical appearance, but also hypoglycaemia,

insulinopenia, and low plasma somatomedin levels. Noteworthy is the short length at birth with slightly increased weight. Laron *et al.* (1968) also found short birth length in half of their patients. Some GH dependency of intrauterine growth at the end of pregnancy is thus suggested.

The endogenous growth hormone, present at very high levels in plasma, cannot be distinguished from normal growth hormone, either from its immunological behaviour, or from its isoelectric point.

Our results with short-term, high dosage treatment with HGH confirm previous reports: metabolic indices of growth hormone effect such as blood glucose, nitrogen retention, calciuria, and hydroxyproline excretion are little if at all altered. Somatomedin is low both before and while on treatment. The finding of others (Laron *et al.*, 1971; Tanner *et al.*, 1971; Najjar *et al.*, 1971; New *et al.*, 1972) that chronic treatment failed to induce the expected increase in growth rate was also confirmed in our patient. In addition, similarly to the observation of Tanner *et al.* (1971), we found a slight temporary decrease of the skinfold thickness as measured by caliper, followed by an increase. By radiography, however, Tanner *et al.* noticed little change in fat or muscle. While Elders *et al.* (1971) reported that in acute conditions the endogenous GH secretion could not be suppressed by exogenous administration of the hormone, we found that prolonged treatment also was not effective in this regard. Insulinopenia and low plasma somatomedin levels, which had been shown by others to be resistant to acute GH treatment (Laron *et al.*, 1971; Elders *et al.*, 1971; New *et al.*, 1972) were still unchanged after 6 months of administration of the hormone.

All these findings suggest a specific and overall impaired responsiveness to growth hormone. The alternative hypothesis of an abnormal endogenous GH molecule lacks support at present.

While in patients such as ours all effects of GH are diminished, its failure to induce somatomedin seems to be the most crucial. Since somatomedin is supposed to mediate the growth-promoting effect of GH (Daughaday *et al.*, 1971), the extreme short stature of our patient is most likely attributable to his somatomedin deficiency.

Studies of the characteristics of the GH receptors in these patients, and evaluation of their responsiveness to exogenous somatomedin should contribute to the elucidation of the pathogenesis of this syndrome.

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