Effect of Human Growth Hormone Treatment for 1 to 7 Years on Growth of 100 Children, with Growth Hormone Deficiency, Low Birthweight, Inherited Smallness, Turner's Syndrome, and Other Complaints

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Tanner, J. M., Whitehouse, R. H., Hughes, P. C. R., and Vince, F. P. (1971). *Archives of Disease in Childhood*, **46**, 745. **Effect of human growth hormone treatment for 1 to 7 years on growth of 100 children, with growth hormone deficiency, low birthweight, inherited smallness, Turner's syndrome, and other complaints.** (1) Human growth hormone (HGH) has been given for one whole year or longer to 100 patients, aged 1·5 to 19 years, participating in the Medical Research Council Clinical Trial of HGH. Each patient was measured 3-monthly for a control year before treatment, and the majority for a control year after the first treatment year. All measurements were made by one anthropometrist. Radiographic measurements of widths of bone, muscle, and fat in calf and upper arm were made. Methods and standards for assessing the significance of a given height acceleration are presented.

(2) The characteristics at diagnosis are given of 35 patients with isolated GH deficiency or hyposomatotrophism (HS), 18 with craniopharyngiomas and other CNS lesions, 3 with multiple trophic hormone deficiency, 18 with low birthweight short stature, 4 with hereditary smallness and/or delay in growth, 4 with psychosocial short stature, 1 with high resting HGH and low somatomedin, 6 with Turner's syndrome, and 11 with other diagnoses.

(3) 29 of the 35 HS patients were boys and 13 had an abnormally small penis and ill-developed scrotum. Only 2 were sibs. Parents averaged 40th centile for height. 4 children developed growth-suppressing antibodies, and had to cease treatment. The mean standard deviation score (SDS) for height at diagnosis was −4·7, range −2·6 to −7·3. Bone age SDS averaged −3·2, range −0·8 to −5·7. Skinfold SDS averaged +0·91. Limb muscle width SDS averaged about −3·0. GH peak in insulin hypoglycaemia averaged 4·7 ± 0·7 μU/ml, range 1 to 13.

(4) A category of partial growth hormone deficiency is defined as patients with GH peaks of 7–20 μU/ml inclusive and height velocity SDS in the year before treatment between −1 and −2. Total HS patients have GH peaks of 1 to 6 μU/ml inclusive and height velocity SDS of <−2. Partial HS patients are accelerated by HGH and should be treated; but their average acceleration is below that of total HS patients.

(5) There was a highly significant relation (r = −0·64) between blood GH peak level and pretreatment height velocity in the HS patients.

(6) The LBW patients were 10 boys and 7 girls; all the boys had normal genitalia. The average height SDS at diagnosis was −3·7; parents' height centile averaged 50th, bone age SDS −1·8, skinfold SDS −0·9. GH peaks were all above 30

μU/ml. Pretreatment heigh: velocity SDS averaged −1·0 in contrast to −2·8 for the HS patients.

(7) The characteristics at diagnosis of patients with hereditary short stature and/or growth delay, psychosocial short stature, and some diagnostic problems are discussed.

(8) HGH was given, usually 20 IU/wk in 2 doses/wk, for between 1 and 7 years to all these patients. The average first year acceleration (treatment year less pretreatment year velocity) in the HS patients was 6·0 cm/yr (9·1 less 3·1). There was a strong negative correlation of acceleration with pretreatment velocity, r = −0·58. The relation with age was only --0·25. In years subsequent to the first, the velocity fell, following the familiar catch-up curve. If HGH was stopped after several years of continuous administration, however, zero or near-zero height velocity ensued. Once started, HGH should be given till the end of childhood.

(9) Skinfolds decreased on treatment and muscle widths increased in the HS and craniopharyngioma patients. The largest changes were in the first 3 months; after 4 or 5 years of treatment skinfolds on average had returned to the high pretreatment level. When HGH was stopped muscle widths actually decreased. Craniopharyngioma patients responded like HS though to a lesser degree.

(10) No useful height acceleration occurred in LBW patients, with two possible exceptions. An increase of about 1·0 cm/yr on treatment was balanced by a regulatory deceleration of nearly the same amount in the post-treatment year. The same was true of the small/delay and the Turner's syndrome patients. The psychosocial patients were treated at home, and failed to respond. Two patients with glycogen storage disease did not respond.

(11) Craniopharyngioma and HS patients over the bone age of about 14·0 in girls and about 15·5 in boys seem usually to be unresponsive to HGH. Advanced chronological age is immaterial, so long as bone age is low.

(12) The aetiology of hyposomatotrophism is discussed, and the question of isolated versus multiple pituitary deficiencies. The view is put forward that thyroxine should not be given unless a clear and specific thyroid deficiency has been demonstrated. Sex hormones should never be given before the possibilities of HGH are exhausted.

(13) Evidence is offered in favour of the view that the normal adolescent growth spurt is produced by androgens and testosterone acting additively. In the absence of GH, the adolescent spurt may occur, but is probably reduced in extent. In HS and craniopharyngioma patients, HGH should be administered throughout puberty. In patients who fail to develop spontaneous puberty, sex hormones may be started after bone ages of about 13 in girls and 15 in boys have been reached.

(14) Limited evidence is given that doses of over 40 IU/wk produce a little greater effect than 20 IU/wk. Doses of 10 IU/wk probably produce less effect than 20 IU/wk, but may be more efficient per IU given: current research is testing this.

(15) HGH treatment is strikingly successful in suitable cases. Its availability depends entirely on pathologists throughout the United Kingdom sending all possible glands for processing. At present the supply is very good compared with that of most other countries; the efforts of all pathologists are sought to make it still better.

Human growth hormone (HGH) was introduced for the treatment of children with short stature due to growth hormone deficiency 13 years ago (Raben, 1958). In correctly selected patients it is very successful, as studies in Switzerland (Prader, et al., 1964, 1967; Ferrandez et al., 1970), Norway (Seip and Trygstad, 1966; Trygstad, 1969), Sweden (Westphal, 1968), the United States (Wright et al., 1965; Parker and Daughaday, 1968; Goodman, Grumbach, and Kaplan, 1968; Soyka et al., 1970), Japan (Shizume et al., 1970), and the United Kingdom (Tanner and Whitehouse, 1967a) have shown. Much remains to be worked out however on the selection of patients, the criteria of partial growth hormone deficiency, the test of whether a patient is responding or not, the ultimate prognosis for adult height, the optimal dosage schedule, and other matters.

This paper describes a series of 100 patients treated with HGH. Its particular features compared with previous series are (i) it is larger in numbers; (ii) every patient has had a full control year of measurement before treatment followed by at least a full year of treatment, to obviate the seasonal effect on growth; (iii) all measurements were done by the same anthropometrist; (iv) measures of muscular width and subcutaneous fat have been made by radiography.

The patients were those participating in the Medical Research Council Clinical Trial; preliminary reports on their growth and skinfold responses to HGH (Tanner and Whitehouse, 1967a, b), and full descriptions of the development of antibodies (Chalkley and Tanner, 1971) and of the metabolic responses to short-term administration of HGH (Clayton, Tanner, and Vince, 1971) have already appeared.

As a matter of terminology, we agree with Trygstad (1969) that the word 'dwarf' should be dropped. It has a curiously sinister and magical sound in the ears of parents and patients, who all too often imagine some unalterable *lusus naturae*. 'Short stature' creates a different and more accurate impression; or 'restricted growth' may be used, as in the newly-founded Association for Research into Restricted Growth.

Material and Methods

One hundred patients (the roundness of the figure is quite fortuitous) have so far been measured at set intervals in the Department of Growth and Development and treated with HGH for a year or longer. All were participants in the national clinical trial of HGH being carried out by the Medical Research Council Sub-Committee on Human Pituitary Hormones. Patients were referred by their physicians to a panel of the Sub-Committee and admitted to the trial after completion of a series of clinical, auxological, and biochemical tests, designed to establish diagnosis and give a pretreatment baseline. Where possible, patients attended the Department's Growth Disorder Clinic for measurements and bone age assessments so that these were done in a uniform manner and by a single anthropometrist. The patients remain under the clinical care of the referring physician, but he is requested only to change any ancillary treatment as part of a planned trial procedure, or where absolutely necessary for the patient's welfare. The first patients in the national trial began treatment in 1959, and in January 1971 87 patients in all were on treatment and 43 coasting (see below): 45 have been treated and taken off permanently.

Diagnosis. The numbers of patients treated in each diagnostic category are shown in Table I. The differential diagnosis of children with short stature

TABLE I

Numbers of Patients Treated in Each Diagnostic Category

Diagnosis	Number Treated
(1) Hyposomatotrophic (HS) or 'isolated' GH deficiency	35
(2) Craniopharyngioma	15
(3) Other CNS tumours	3
(4) Panhypopituitarism	3
(5) Low birthweight (small-for-dates)	18
(6) Small/delay	4
(7) High resting HGH, low somatomedin	1
(8) Psychosocial short stature	4
(9) Uncertain diagnosis	4
(10) Turner's syndrome	6
(11) Steroid-induced short stature	2
(12) Coeliac disease	2
(13) Other metabolic disorders	3
	100

presents some problems and in this series was based on the observations which follow. We have placed growth-hormone-deficient patients in the 'hyposomatotrophic' category unless there was clear evidence of additional thyroid or adrenal insufficiency (see discussion), in which case they were classified as 'panhypopituitary'.

In taking the *history*, particular attention was paid to emotionally disturbing factors in the home environment, and on interview to the relation of the child and parents. *Birthweight* standard deviation score (see below) with allowance for mother's midpregnancy height and weight was assessed using the standards of Tanner and Thomson (1970). Systemic disease, especially malabsorption and kidney disorder, was investigated thoroughly by the referring physicians. *Skull x-rays* were done in all patients, and full *skeletal surveys* in those who presented a diagnostic problem. *Karyotypes* were done in girls whose diagnoses were at all in doubt. (Since nearly 50% of ovarian dysgenesis patients, with short stature but no webbing, have positive nuclear sexing associated with isochromosomes or mosaicism (Polani, 1970), buccal smears are insufficient.)

Tests of *thyroid function* were required before admission to the trial. In most instances the PBI was measured (Foss, Hankes, and Van Slyke, 1960, modified) and in some the ^{131}I uptake before and after TSH administration. The lower limit of normal for PBI in our laboratory is $2 \cdot 5$ $\mu g/100$ ml. Tests of *adrenal function* were also required before entry. Most of the present patients had their peak 24-hour excretion of 17-hydroxycorticoids measured after three days of intramuscular ACTH (synacthen, 20 IU/day). The lower limit for normal children is placed at 20 mg/24 hours (Clayton, Edwards, and Renwick, 1963).

In all recently admitted patients, blood *growth hormone levels* were estimated by radioimmunoassay during an insulin hypoglycaemia in which true blood glucose fell to 50% or less of the fasting value, and below 50 mg/100 ml. Additionally or alternatively the GH

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response to an oral dose of Bovril was measured (Jackson, Grant, and Clayton, 1968). The relation between the two tests has been shown to be close (Grant *et al.*, 1970). The lower normal limit of the peak value attained in either test is about 20 μU/ml. We are greatly indebted to Professor Clayton and her staff for these and other biochemical estimations.

Antibodies to HGH were estimated at the beginning of treatment and every three months during treatment. The results have already been reported (Chalkley and Tanner, 1971). No patients had significant levels of antibodies before treatment; on treatment 4 out of the 100 developed antibodies to a degree sufficient to stop the growth response permanently. These 4 patients are placed separately in the Appendix Table, and

omitted in calculating the means and SDs given in Table II.

Until recently patients were required to have a *metabolic balance test* of the effect of HGH before beginning treatment. We have already reported the results of this (Clayton, Tanner, and Vince, 1971), giving in that paper the same case number to each patient as is given here. We showed, in 55 patients, that the metabolic test was not generally much additional help in diagnosis, and, within a given diagnostic category, did not at all predict the amount of growth response of individual patients. It has, therefore, been dropped as a routine requirement.

Ratings of sexual development were made on the scale of 1 to 5 for genitalia or breast development, and pubic

TABI

Means and SDs of Measurements at Initial Di

	HS (isolated GH Deficiency)			Craniopharyngioma and Other Tumours		
	No.	Mean	SD	No.	Mean	SD
Bone age SDS	30	−3·21	1·30	17	−2·99	1·71
Chron. age less bone age (yr)	32	3·29	1·50	17	3·21	1·48
Height SDS for chron. age	32	−4·66	1·07	18	−3·75	1·55
Height SDS, parents allowed for	20	−5·42	1·23	—	—	—
Height SDS for bone age	31	−1·58	1·65	18	−1·61	1·33
Sitting height SDS	29	−4·56	1·06	14	−3·53	1·40
Skinfold trans. SDS (av. triceps + subscap.)	30	0·91	0·83	14	1·27	0·79
Birthweight (kg)	30	3·38	0·51	5	3·20	—
Birthweight SDS; gest. and M. ht. allowed for	30	−0·21	0·97	5	−0·46	—
Mid-parent height SDS	32	−0·17	1·16	13	0·64	0·84
GH peak after insulin (μU/ml)	25	4·7	3·4	7	3·1	1·9
GH peak after bovril (μU/ml)	21	5·7	3·1	5	4·0	—
17 OH after ACTH (mg/24 hr)	24	21·04	11·03	—	—	—
PBI (μg/100 ml)	27	4·61	1·10	—	—	—
Limb bone width SDS	18	−3·02	0·92	11	−2·26	1·03
Limb muscle width SDS	18	−2·92	1·20	11	−2·52	0·88
Limb fat width SDS	18	2·15	2·90	11	3·12	2·53
Height velocity pretreatment year (cm/yr)	30	3·15	1·18	12	2·67	0·38
Height velocity 1st treatment year	28	9·10	2·43	12	6·13	1·35
Height velocity posttreatment year	14	2·20	0·74	7	1·39	0·93
Height acceleration 1st treatment year	28	6·00	2·82	12	3·48	1·37
Ht. vel. SDS (chron. age) pretreatment year	20	−2·76	1·08	2	−2·70	—
Ht. vel. SDS (bone age) pretreatment year	27	−3·28	1·36	7	−3·17	1·94
Ht. vel. SDS (chron. age) 1st treatment year	19	4·26	2·22	2	3·80	—
Bone age velocity pretreatment year	31	0·86	0·58	12	0·59	0·48
Bone age velocity 1st treatment year	28	1·18	0·49	12	0·65	0·55
Bone age velocity post treatment year	13	0·79	0·38	6	0·76	0·34
Ht. vel. % expec./bone age vel. % expec. pretreatment year	19	0·85	0·34	2	0·45	—
Ht. vel. % expec./bone age vel. % expec. 1st treatment year	20	1·61	0·74	2	0·45	—
Ht. vel. % expec./bone age vel. % expec. posttreatment year	10	0·70	0·45	—	—	—
Average skinfold trans. SDS; begin treatment year	28	0·96	0·80	8	1·28	0·73
Average skinfold trans. SDS; end 1st treatment year	25	0·32	0·70	6	0·77	0·61
Bone age velocity pretreatment year	16	0·86	4·08	9	1·07	3·42
Bone age velocity 1st treatment year	24	2·19	0·94	11	2·01	0·99
Bone age velocity posttreatment year	18	1·46	1·31	7	0·78	0·70
Limb muscle velocity pretreatment year	15	0·43	12·03	9	3·51	19·88
Limb muscle velocity 1st treatment year	24	7·75	5·53	11	4·85	5·78
Limb muscle velocity posttreatment year	18	−1·91	4·40	7	0·24	8·76
Limb fat velocity pretreatment year	15	1·81	5·57	9	5·86	8·81
Limb fat velocity 1st treatment year	24	−3·81	4·51	11	−7·11	6·15
Limb fat velocity posttreatment year	18	8·83	8·41	7	7·92	11·41

hair development (separately) using the Tanner (1969) scales. Size of testes was measured using the Prader orchidometer. In patients who showed some degree of sexual development the absolute velocities or SDS (see below) over the period in question have been placed in brackets in the Appendix Table, and omitted in calculating the means and SDs given in Table II. The ratings at the end of the year concerned have been indicated outside the brackets.

Anthropometric measurements. Height, weight, four skinfolds, sitting height, upper arm, thigh and calf circumferences, biacromial and bi-iliac diameters, and bicondylar diameters of humerus and femur were measured, always by the same anthropometrist.

Height was measured using the apparatus and technique illustrated in Fig. 1. The patient, dressed only in underclothes, stood on the footplate of the stadiometer, with heels together and head in the Frankfurt plane (that is, with the lower border of the orbit in the same horizontal plane as the external auditory meatus). The top of the stadiometer, being counterbalanced, rested lightly on the patient's head. The patient then stretched upwards fully, aided by relaxing the shoulders and by the anthropometrist applying gentle upward pressure on the mastoid processes, and encouraging him verbally. The recorder saw that the heels did not come off the ground, holding them down if necessary. The height was read from a digital counter attached to the stadiometer. This technique mini-

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sis (first 7 rows) and in Relation to Treatment

	Low Birthweight			Small/Delay		Psychosocial		Turners	
No.	Mean	SD	No.	Mean	No.	Mean	No.	Mean	
17	−1·78	1·35	4	−3·55	4	−2·90	6	−2·28	
17	1·46	1·14	4	2·95	4	2·70	6	2·23	
17	−3·65	0·83	4	−4·03	4	−5·00	6	−4·15	
12	−4·56	1·01	2	−5·20	—	—	2	−3·80	
15	−1·78	1·69	3	−0·67	4	−2·53	6	−2·50	
16	−3·61	0·81	4	−3·85	4	−4·88	6	−3·33	
17	−0·88	1·03	4	−0·58	4	−0·60	5	0·50	
17	1·86	0·38	4	2·85	4	3·08	6	2·69	
17	−3·08	0·67	4	−0·88	3	−0·63	6	−1·05	
16	0·26	0·83	4	−1·23	3	−0·40	6	−0·25	
9	34·44	—	—	—	2	28·0	—	—	
13	33·1	—	2	29·0	4	31·0	—	—	
15	22·35	7·76	2	8·4	3	15·6	3	28·6	
16	5·24	0·95	2	5·0	4	5·5	4	5·0	
12	−2·82	0·44	3	−2·12	4	−3·42	2	−2·05	
12	−2·53	1·03	3	−2·29	4	−3·20	2	−1·12	
12	−0·77	0·88	3	0·28	4	−0·08	2	1·82	
16	5·26	1·47	4	5·30	4	4·42	5	2·86	
12	6·70	1·58	4	6·30	4	4·78	5	3·90	
7	5·13	0·45	—	—	3	3·17	5	1·80	
12	0·89	1·24	4	0·88	4	0·35	5	1·00	
14	−0·97	1·21	2	1·50	3	−1·53	—	—	
14	−1·38	1·23	4	−0·20	4	−2·05	2	−2·35	
11	0·47	1·12	2	1·20	2	0·0	—	—	
15	0·97	0·44	4	0·73	4	0·83	4	0·90	
12	1·11	0·28	3	1·37	4	1·13	4	0·63	
7	1·17	0·58	—	—	3	1·03	5	0·36	
13	0·88	0·30	4	1·33	4	0·95	3	0·60	
12	1·05	0·38	3	0·90	4	0·60	3	1·13	
7	1·00	0·59	—	—	3	0·50	3	2·33	
16	−0·71	0·80	4	−0·65	4	−0·68	4	0·0	
12	−0·63	0·97	3	−0·87	3	−0·68	3	0·10	
8	1·65	1·71	—	—	3	3·75	—	—	
15	1·78	1·25	—	—	4	0·19	4	1·00	
8	1·34	1·10	—	—	4	1·36	5	1·43	
8	−0·04	7·31	—	—	3	1·00	—	—	
15	4·79	4·14	—	—	4	3·82	4	−0·54	
8	1·60	4·88	—	—	4	8·14	5	0·41	
8	−0·08	5·11	—	—	3	−1·66	—	—	
15	−0·30	2·31	—	—	3	−3·83	4	1·18	
8	3·29	4·17	—	—	4	4·43	5	2·46	

mizes variation in posture due to tiredness or boredom, which may otherwise amount to 1 or even 2 cm. A good anthropometrist can repeat his reading to 0·3 cm or less on 95% of occasions, and two well-trained observers should seldom differ by more than 0·4 cm.

The accuracy of measurement is particularly important where calculation of increments or velocities of growth are concerned since there are two errors involved, which may summate. Casual observers without special training may differ in their measurements by 1·5 cm, and two summating errors of this magnitude introduce large errors into a yearly velocity and make a three-monthly velocity meaningless.

Skinfolds were measured as illustrated in Fig. 2. A double fold of skin and subcutaneous tissue was picked up between the thumb and forefinger, pulled away from the underlying muscle, and measured by application of the Harpenden skinfold caliper, which has a constant jaw pressure of 10 gm/mm². Four folds, on the left side of the body, were measured; but only those taken over the triceps and under the scapula are considered here, as these are the only ones for which standards for British children are available (Tanner and White-house, 1962). The triceps measurement was taken half-way between the tip of the acromion and the posterior border of the olecranon process, in a line passing directly up the centre of the arm from the olecranon; the subscapular measurement was taken just below the angle of the scapula, with the fold vertical or slanting slightly downwards and outwards. The frequency distributions of these measurements are

skewed, and throughout logarithmic transformations were used (Edwards *et al.*, 1955).

Sitting height was taken using the Harpenden anthropometer. The patient sat on a table top with thighs supported and legs hanging unsupported over the edge, and the backs of the knees nearly touching the edge. His back was stretched up straight by the measurer running a finger up his spine from bottom to top, and his head was held in the Frankfurt plane. We find this measurement more reliable than the measurement of vertex-pubes ('upper segment'), and standards for British children exist for it (Tanner, 1972).

The remaining measurements and the photogrammetric photographs were done as described by Tanner (1964).

Skeletal maturity (bone age). This was estimated from the bones of the left hand and wrist, using the method of Tanner, Whitehouse, and Healy (1962) which rates each of 20 bones separately on a defined scale (1–8) of maturity. We think this has both theoretical and practical advantages over the Greulich-Pyle atlas method; greater accuracy and more information is obtainable, and standards for British children exist. (The Greulich-Pyle standards lead to the average normal British child being 6–8 months retarded.) The radiographs for this method do however need very careful attention to positioning and technique: the tube must be centred precisely over the head of the third metacarpal and 76 cm above it, and the wrist placed absolutely straight, with a line passing through its
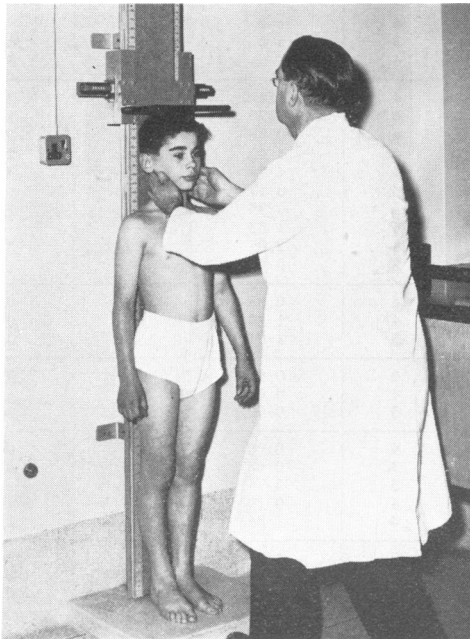
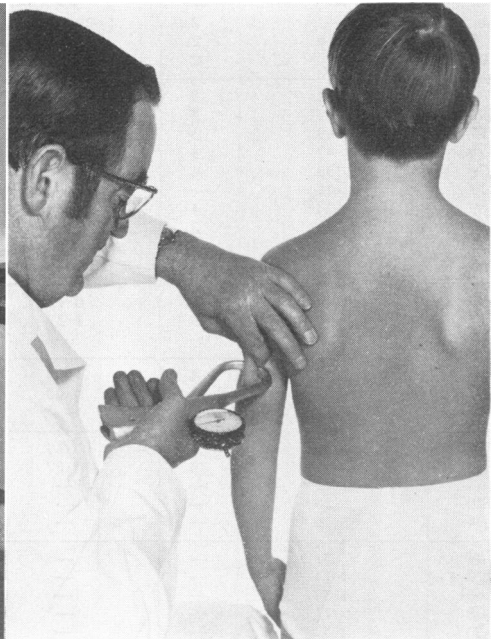

FIG. 1.—*Measurement of height.*

FIG. 2.—*Measurement of triceps skinfold.*

centre continuing directly down the length of the middle finger. The standard deviation of bone age by this method is 0·5 'years' at age 2·0, rising to 0·8 at age 4·0, 0·9 at age 5·0, and 1·0 at age 6. From then it remains constant till about 14 in girls and 16 in boys, after which it is unreliable. Thus standard deviation scores (SDS, see below) can readily be calculated.

Radiographic measurements. At certain times in some patients radiographic measurements were made, of the bone, muscle, and fat diameters midway down the left upper arm and at the maximum muscle diameter of the left calf. The technique was that described by Tanner (1964; see also 1962; Appendix). The upper arm was taken in the lateral view so that the two epicondyles appeared superimposed on the film: the central vertical plane of the arm was exactly 5 cm in front of the film, and the anode of the x-ray machine was exactly 2·5 m from the film. The calf film was taken with the foot pointing directly towards the anode, the weight equally on both feet, the central plane of the calf 10 cm in front of the film and the anode-film distance also 2·5 m.

A lead marker was placed on the upper arm at the level at which the triceps skinfold was measured; a line was drawn on the radiograph passing down the long axis of the upper arm as nearly as possible parallel to the skin borders, and a line perpendicular to this was drawn across the arm at the marked level. The widths of the whole arm and the anterior and posterior fat areas were measured along this second line. The humerus was measured at right angles to its own long axis, as near as possible along this line. Fat width was the sum of the two measurements; muscle width was obtained by subtraction.

In the calf radiograph a line was drawn perpendicular to the long axis of the tibia, at the maximum width of the calf muscle. The widths of total calf, lateral and medial fat, tibia, and fibula were measured along this line. 'Bone' represents tibia only and 'muscle' was obtained by subtracting fat and tibia breadths from total width. The fibula width is included in muscle, therefore.

Normal standards for age for these limb tissue widths were available from unpublished data on the Harpenden Growth Study (see Tanner, 1962). SDS (see below) were calculated for the sum of the arm and calf widths of bone muscle and fat.

Treatment procedure. In general the treatment design was as follows. There was a *pretreatment year* during which measurements, bone age assessment and photogrammetric photographs were made at 3-monthly intervals. An uninterrupted year of treatment followed (*first treatment year*), with the same schedule of measurements. The patient then entered a second control year of no HGH treatment (*coasting year*), during which measurements were made at 6-monthly intervals, and biochemical tests repeated if necessary. The stature velocity during the first treatment year was compared with the velocity during the pretreatment year, and if a

significant and clinically useful increase, or acceleration, had occurred during treatment, the patient proceeded to a second year of HGH treatment, if hormone was available. Treatment thereafter is planned to be continuous, provided a velocity significantly above that in the pretreatment year is maintained (see assessment of growth response below), until such a time as an adult height within normal limits is achieved, or can be brought about by inducing an adolescent growth spurt.

A small number of patients, started on HGH before the above procedure was established, have been treated continuously, without the 'coasting' year. Some of these have had a year off treatment after 3 or 4 years on, and have subsequently been restarted on treatment. These long-term patients are discussed separately in the 'Results' section.

Hormone and dose. Pathologists throughout the United Kingdom have been requested to send pituitary glands from all necropsies to Dr. A. S. Hartree, Department of Biochemistry, Cambridge, and the response has been very good. Currently about 60,000 pituitaries a year are being collected and forwarded, preserved in acetone. The GH preparation was made by Dr. Hartree, using her modification of Raben's original method (Hartree, 1966). The potency of the batches varied from 0·6 to 1·2 IU/mg; the great majority of doses used were between 0·8 and 1·2 IU/mg. The potency was assayed by the 10-day increase in body weight in hypophysectomized rats compared with that produced by the international reference preparation (D. R. Bangham and M. Cotes, 1970, personal communication). The preparation was free of measurable thyroid-stimulating or gonadotrophic activity. Since October 1970 the hormone has been prepared by a modified Wilhelmi procedure, which produces a greater yield, amounting to about 10 mg powder per gland (Hartree, 1972).

The HGH was administered by intramuscular injection in saline, or, latterly, sodium lactate buffer. Two injections per week have been used throughout the trial. The standard dose has been a nominal 20 IU/wk, but, due to batch potency differences, this has varied from 18 to 24 IU/wk. Doses of half this (a nominal 10 IU/wk) have recently been used in alternate patients, but only 2 of these are in the 100 reported here. Periods of double dose (40 IU/wk) have been given to a few of the long-term children, and are reported below. The small differences in dose due to batch variation had no detectable influence on growth response.

Assessment of growth status and response. All measurements (including bone age) are presented in terms of Standard Deviation Scores (SDS). If X is the measurement, $\bar{x}$ the mean at the relevant age, or bone age, and s_x the SD at that age, then

$$SDS = \frac{X - \bar{x}}{s_x}.$$

All SDS have a standard deviation approximating 1·0 if the population they come from is normally distributed.

The standards used for height, weight, height velocity, and weight velocity were those of Tanner, Whitehouse, and Takaishi (1966). We have taken the individual-type (longitudinal) standards (Table V, VI, IX, and X of that article) for ages over 8 in girls and 10 in boys. This enables meaningful SDS to be calculated up to the age of 10 in girls and 12 in boys; but above this the adolescent growth spurt of the standard makes their application to prepubescent children erroneous. Over the ages of 18 in boys and 16 in girls SDS are again valid. Since the bone ages of many of our patients are retarded, we have calculated the SDS for height and other measurements in relation to bone age (BA) as well as chronological age (CA).

Sitting height standards are cross-sectional (Tanner, 1972). For skinfolds we have used the log transformations of triceps and subscapular folds and then taken the average of the two SDS. The skinfold standards are also cross-sectional. For bone age, standard deviations diminish rapidly as full maturity is attained, and no SDS for ages over 16·0 in boys and 14·0 in girls have been calculated.

Height SDS, with allowance for parents' heights was assessed in children age 2·0 to 9·0 using the standards of Tanner, Goldstein, and Whitehouse (1970).

Height velocity during the pretreatment year was estimated by fitting a straight line to the five quarterly measurements and taking its slope. Velocity during the treatment year was estimated in the same way, giving the average velocity over the year, even though the growth response on treatment is not really linear, being greater at the beginning of the year and subsequently less (see Results). In the coasting year only 3 measurements are available for fitting the line; in later treatment years 5 measurements are again available. The velocity standards apply to velocity over the whole-year periods only and would give erroneous SDS if applied over periods of less than a year (see Tanner *et al*, 1966, p. 614). Seasonal differences in growth rates (Tanner, 1962) may be very great in normal children; indeed on average children grow about 3 times as rapidly in their fastest quarter-year as in their slowest (Marshall, 1971). Thus a change of velocity of 5 cm/yr from one 3-monthly period to another (especially if from winter to spring) is to be expected, and a change of over 10 cm/yr is not exceptional. Reports of growth responses to treatment based on periods of less than a full year should be viewed very critically.

The *height response to treatment* was measured by the amount the velocity in the treatment year exceeded that expected in the absence of treatment, that is, by the treatment acceleration. Since a normal child is decelerating from birth to adolescence, the expected velocity diminishes from year to year by an amount which can be obtained from the British standard velocity curves (Tanner *et al.*, 1966). This is approximately 1 cm/yr each year from 2 to 4, 0·5 cm/yr from 4 to 6, and 0·2 cm/yr each year from 6 till puberty. These figures apply only to children growing at about normal

rates before treatment; a child growing at a slower than normal rate would probably decelerate more gradually too. One method of compensating for the diminution would be to use the average of the pretreatment and posttreatment control years as the baseline for comparison with the treatment velocity, but we would have to be sure that the posttreatment velocity had been unaffected by the treatment year. There is evidence (see Discussion) that in the post-treatment year a 'regulatory deceleration' occurred, at least if treatment was successful. Thus the average of pre- and posttreatment years would overestimate the treatment acceleration, just as comparison with the pretreatment year alone would underestimate it. On balance we prefer the latter alternative and have used the treatment velocity less pretreatment velocity figure as the treatment acceleration, uncorrected, in the Tables.

No formal standards for acceleration are available against which to judge the significance of the change of velocity on treatment. However, the longitudinal data of the Harpenden Growth Study (Tanner *et al.*, 1966) show that over the age of 3 to 10 years (within which most of our patients fall, especially if bone age rather than chronological age is considered) the standard deviation around the mean acceleration is approximately 1 cm/yr per year. Thus normal children very seldom have as large a change of velocity as ± 2·0 cm/yr from one whole year to another whole year. (If smaller time intervals are taken, this no longer holds and the limits of normal velocity and acceleration get much wider, partly because of seasonal variation and partly because of the increased relative contribution of measuring error.) We have therefore taken 2·0 cm/yr per yr as the lowest 'significant' acceleration. This is a very conservative limit, for an increase of velocity of even 1·5 cm/yr occurs very seldom in normal growth before puberty. We are concerned primarily, however, with treating patients who respond to a clinically useful degree.

Since velocity standards are not available for skinfolds or sitting height the treatment response has been estimated simply by the change of SDS from beginning to end of treatment.

One important problem is to see whether on treatment the height has advanced relatively more or less rapidly than the bone age, since the final predicted adult height depends on this. Methods for testing this to date are rather unsatisfactory. We have used the ratio:

$$\frac{\text{height velocity/expected height velocity for CA}}{\text{bone age velocity/expected bone age velocity}} .$$

Results

The results will be given in two sections: (1) *Characteristics at diagnosis* and (2) *Response to HGH treatment*.

Characteristics at Diagnosis

Table II gives means and SDs for a number of

the variables measured. The main diagnostic groups of patients (see Table I) are considered separately. In the Appendix Table (not published here, but available from the authors on application) this information is given for each patient together with sex, height, weight, age, and bone age at diagnosis; and clinical details of gestation, postnatal course, and other treatment. The 4 HS cases who developed growth-suppressing antibodies (1A.32 to 1A.35) and 1 LBW patient (5.18) who clinically appeared different from the others have been omitted in calculating the means and SDs in Table II.

In Fig. 3 are illustrated 3 typical patients with HS short stature, contrasted with 3 typical LBW
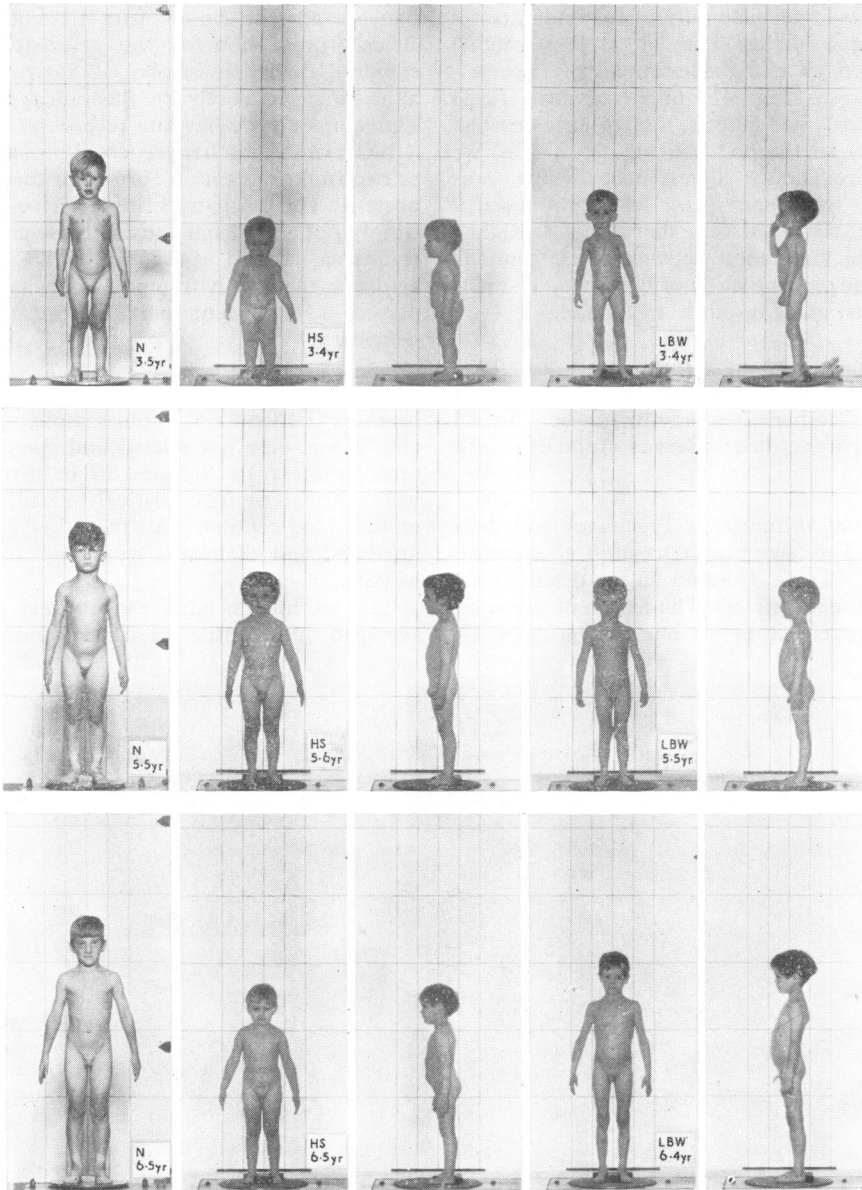
FIG. 3.—*Three typical patients with isolated GH deficiency (HS) contrasted with 3 typical low birthweight patients with short stature, and 3 normal children of the same age.*

patients and 3 normal boys close to the 50th centile of the same age.

Hyposomatotrophic, or 'isolated' GH deficiency patients (Group 1).

Sex incidence and genital development. Out of 35 patients, 29 were boys, and of these 13 had an abnormally small penis and ill-developed scrotum. Only 3 of these had bilaterally undescended testes however, and a further 3 unilateral undescended testes. The more extreme examples of this maldevelopment (see Fig. 4) quite resembled fused labia and an enlarged clitoris, though only one had hypospadias. In the one patient (No. 1A.34) we observed throughout adolescence, which was spontaneous, the penis grew to about normal thickness, but remained very short (Fig. 4, Right). There was no association between small genitalia and the degree of retardation of bone age, of smallness in height, or of response to ACTH.

Age. Age at diagnosis varied from 1·5 to 19·1 years, which reflects the present case-finding circumstances rather than anything else. In all patients the parents had observed stunted growth from infancy.

Gestation and birthweight. Pregnancy and delivery were said to have been normal in all except 6 (see Appendix Table, Column 25 for details; only 3 were breech deliveries). The length of gestation was 39–41 weeks except for one case each of 37, 38, and 42 weeks. The mean birthweight was 3·4 ± 0·1 kg. When adjusted for gestation and mother's size, the SDS for birthweight ranged from −2·1 to +1·5 and averaged −0·2 ± 0·2. Since the standardizing group were very well supervised Aberdeen women, with the heaviest babies recorded in any survey in Britain, it is probable that the average and range of the HS patients accords closely with that of the general British population of the relevant time. The standard deviation of the SDS score was 0·97, approximating closely the theoretical figure of 1·0. Unfortunately we have no records of birth length.

None of the mothers reported prolonged labours or neonatal problems. Subject to the fact that the obstetric and neonatal histories have mostly been simply obtained from the mothers, and are by no means as detailed as we would like, we have no evidence that birth trauma or neonatal conditions played a significant part in causing the GH deficiency.

Familial incidence. There was one pair of brothers (1.1. and 1.5) in our sample. The mother and father were not related and there were three other brothers, 1st, 3rd, and 5th in birth order, who were normal though relatively small, as was the mother (3rd centile). All the other patients were unrelated and their sibs within normal limits for height.

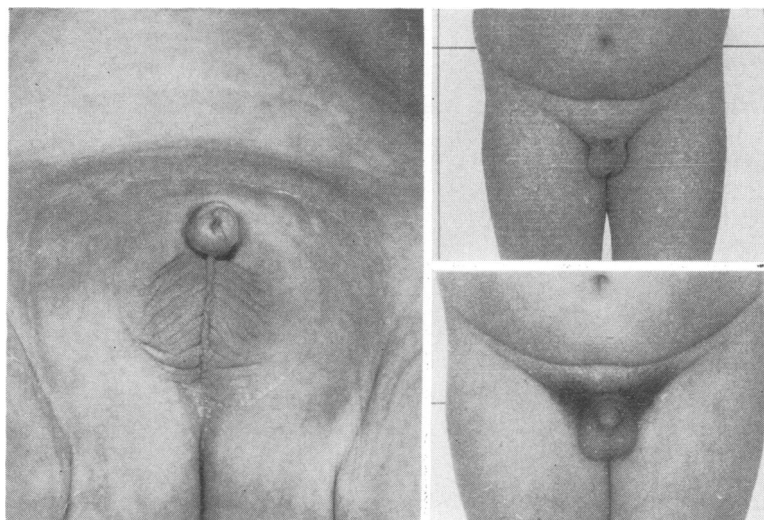The parents' heights ranged very widely, but averaged 40th centile for fathers and 36th centile

FIG. 4.—Left, *example of small penis and ill-developed scrotum in HS patient (No. 1.3 aged 2·4).* Right, *to show degree of development of hypoplastic penis at adolescence (No. 1A.34, above aged 14·4, below aged 19·6).*
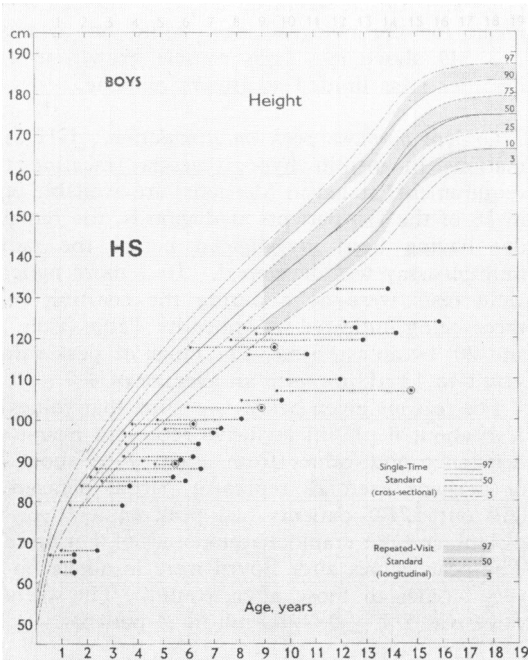
FIG. 5.—*Height at diagnosis, HS boys, plotted against chronological age* ●, *and bone age* *. *The length of the dotted horizontal line indicates the absolute bone age retardation in each patient. Partial deficiency cases* ⊙.

FIG. 6.—*Weight for CA at diagnosis, HS* △, *LBW* □ *psychosocial (P), and uncertain (Q) patients.*

for mothers. The mean midparent SDS was $-0 \cdot 2 \pm 0 \cdot 2$. The parents of No. 1.29 were both Spanish and probably well within the normal range for their own population. Apart from these, three fathers and one mother were below the 1st centile, which, considering the social background of our sample, is probably not an abnormal proportion. We have been able to do an insulin hypoglycaemia test on one of these fathers (of $1 \cdot 21$), whose height was $160 \cdot 0$ cm; the GH peak value was 40 µU/ml.

Height and weight. The absolute heights are given in the Appendix Table and plotted, both against chronological age and bone age, in Fig. 5 (boys only). All patients were much below the 3rd height centile for chronological age (CA), though about half were above it when plotted at bone age (BA). The height SDS for CA ranged from $-2 \cdot 6$ to $-7 \cdot 3$, with a mean of $-4 \cdot 7$. When parents' height was allowed for the mean SDS, $-5 \cdot 4$, was still lower and the range was $-3 \cdot 2$ to $-7 \cdot 9$.

Since bone age was retarded, height for bone age was within normal limits in many cases. The mean SDS was $-1 \cdot 6$, range $-5 \cdot 1$ to $+1 \cdot 7$.

There was no relation of height SDS, either for CA or BA, to age of the child. Children diagnosed at ages 1 to 7 years inclusive averaged $-4 \cdot 7$ SDS (for CA) and the remainder $-4 \cdot 6$. This may be because the worst cases are diagnosed at younger ages, and the less affected only later when their smallness reaches the same relative degree.

Weight. This is plotted for CA in Fig. 6, together with values for the low birthweight and some other patients.

Bone Age. Bone age was always retarded, as can be seen in Fig. 5 by the length of the lines joining the circles and stars. The average degree of retardation was $3 \cdot 3$ years, but this absolute difference naturally depends somewhat on age, negative BAs not being obtainable. Thus the bone age SDS is a generally better index: it averaged $-3 \cdot 2$, with a range of $-0 \cdot 8$ to $-5 \cdot 7$. It was significantly related to age, those under age 8 averaging $-2 \cdot 7$ SDS and those over 8 $-3 \cdot 8$ SDS. None of these patients had had prior treatment with anabolic steroids; two ($1 \cdot 1$, $1 \cdot 25$) had had small doses of cortisone.

Sitting height. The SDS for sitting height,

for comparison with SDS for height, is given in Appendix Table, Col. 12. The mean value was −4·6, compared with −4·7 for height. Thus there is no evidence that the trunk-limb proportions of the HS children were different from those of normal children of the same size. (The value for patient 1·22, in brackets, has been omitted from the calculations, since she is Negro, and thus had longer limbs and a shorter trunk than our standards, being for Whites, predicate.)

Skinfolds. The skinfolds are plotted in Fig. 7 and 8, together with those of the LBW and psycho-social patients. When the transform values of triceps and subscapular folds were averaged nearly all HS patients were above the mean for the normal population. (We have more recently seen two who were below average; both belonged to families living in straitened economic circumstances.) The range of SDS was −1·0 to +2·5 with a mean of 0·91 ± 0·15. The younger patients were somewhat fatter than the older ones, those under 8 years averaging +1·3, the remainder +0·5.

Limb bone muscle and fat. Individual values of bone muscle and fat widths in calf and arm are not given, but in Table II the means and standard deviations are displayed. In the HS patients both

bone and muscle averaged about 3 SD below the mean for chronological age, while fat averaged 2·2 SD above it. Thus muscle growth in this disorder is as limited as growth of bone.

Growth hormone peak on stimulation. GH estimations in insulin hypoglycaemia (meeting the requirements stated in Methods) are available only in 18 of the HS patients at diagnosis, the remainder having been investigated before the radioimmunoassay was developed. In 7 more patients valid tests were done during the coasting year, these being indicated in Appendix Table (Cols. 19 and 20) by an asterisk. The range of peak values was 1 to 13 μU/ml with an average of 4·7 ± 0·7.

For reasons given below, we think that values of 1 to about 6 μU/ml inclusive represent near-total deficiency and values from about 7 to about 15 or perhaps even 20 represent partial deficiency. (All our LBW patients had peak values over 30 μU/ml, and our craniopharyngiomas of 6 or under.) The peak values after Bovril were in all instances very similar to those after insulin. The average value was 5·7 ± 0·7 μU/ml, in 21 patients.

17-hydroxycorticoids and PBI. Excretion values for 17-hydroxycorticoids after ACTH are available for 24 patients. The figure given is the maximum excreted during any of the 24-hour periods during
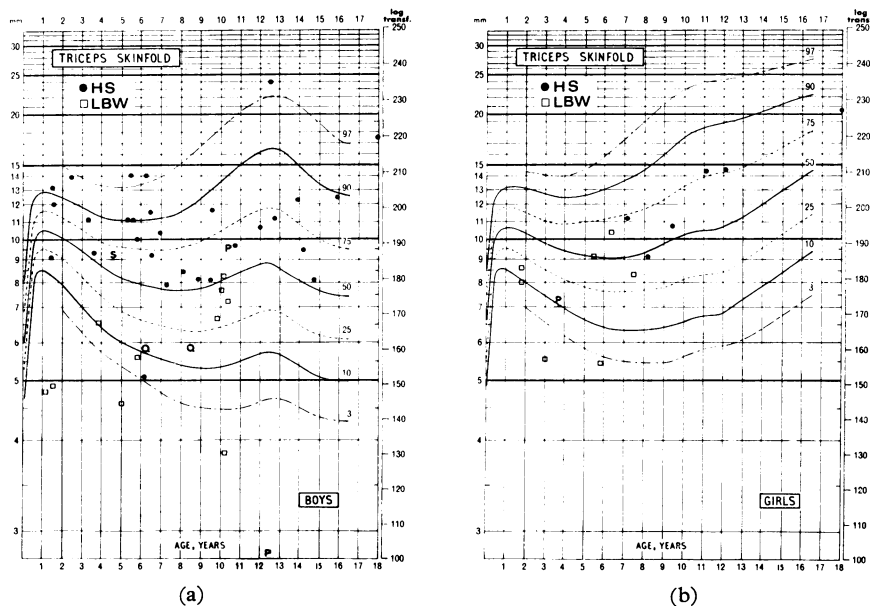

(a)   (b)

FIG. 7.—*Triceps skinfolds, HS, LBW, and other patients, boys and girls.* (*S, somatomedin lack; P, psychosocial; Q, uncertain.*)

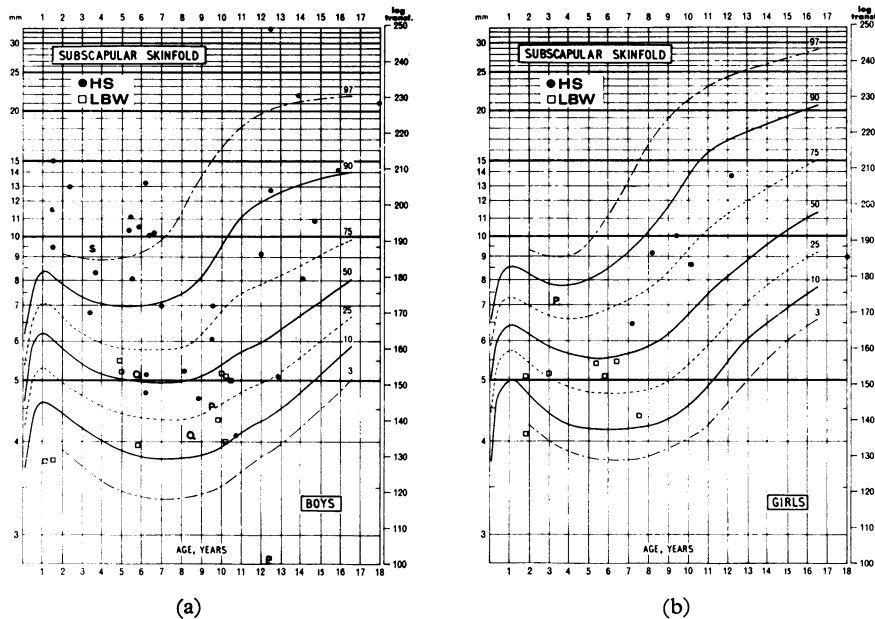(a)   (b)

FIG. 8.—*Subscapular skinfolds, HS, LBW, and other patients (see Fig. 7), boys and girls.*

or following the 3 days of ACTH administration. A number of the patients have low values but we cannot detect anything in common between them.

All the PBI values were within normal limits for our laboratory except for one unaccountably high one. The mean was $4 \cdot 6 \pm 0 \cdot 2$ μg/100 ml, which is slightly (but insignificantly, $t = 1 \cdot 4$) below the mean for the LBW patients though above the mean for normals which is $3 \cdot 8$ in this laboratory. There was no relation between PBI and pretreatment velocity or between PBI and acceleration.

Pretreatment height velocity. After the patient has been studied for a year, we have an estimate of pretreatment height velocity. The SDS scores for CA ranged from $-0 \cdot 9$ to $-4 \cdot 5$ with a mean of $-2 \cdot 8 \pm 0 \cdot 2$ in the 20 patients in whom they can be calculated. (The older patients would give a false figure because of being compared with adolescent spurt velocities in the standards, see Methods.) There are more patients (28) available for computing height velocity for bone age; the average SDS $(-3 \cdot 3 \pm 0 \cdot 3)$ is lower than for chronological age since the bone ages are retarded.

The absolute velocities are plotted in Fig. 9 together with velocities of the LBW and some other patients. All patients plotted are prepubescent, so those over age 11 should be judged in relation to an imagined extension of the pre-

pubertal velocity lines. There are 8 HS patients above the 3rd centile (hence within accepted 'normal limits'); we have reason to think that the 5 of them marked with a circle have partial deficiency only (*see below*).

Pretreatment height velocity and GH peak. There was a highly significant relation ($r = 0 \cdot 64$, 18 cases) between these two variates, as illustrated in Fig. 10 (GH levels at diagnosis and on coasting are both included, and estimates of SDS have been made for the two patients just over the standard age limits). The regression was $0 \cdot 24 \pm 0 \cdot 02$ (cm/yr on μU/ml). The presumed partial deficiency cases are ringed; they lie in the section of the graph bounded by $-2 \cdot 0$ SDS and 6 μU/ml GH peak. The values for the percentage decrease in nitrogen retention in the metabolic test, where known, are put beside the points. The agreement is good.

Pretreatment height velocity and skinfolds. There was no significant correlation between pretreatment height velocity and skinfold SDS at diagnosis or at beginning of treatment.

Pretreatment bone age velocity. The bone age velocity in the pretreatment year was usually less than the norm of $1 \cdot 0$; the average was $0 \cdot 86 \pm 0 \cdot 1$ 'years' per year. Height velocity was more depres-
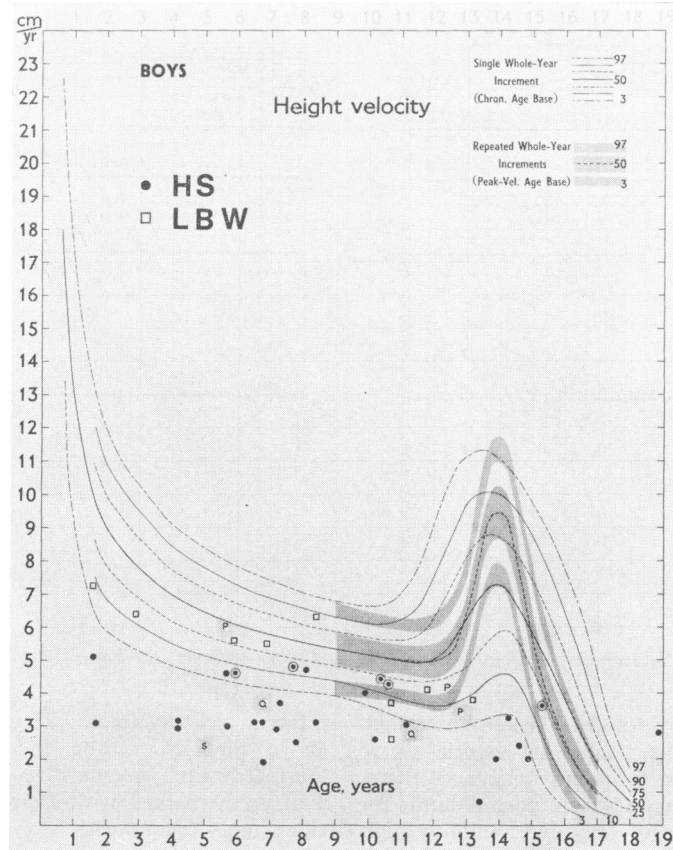
FIG. 9.—*Height velocity in pretreatment year, HS* ●, *LBW* □, *psychosocial (P) and somatomedin-lacking (S) boys. Partial deficiency cases* ⊙.

sed than bone age velocity. The fraction *Height velocity in % expected/BA velocity in % expected* averaged 0.85 ± 0.08. During the pretreatment year, therefore, the patients were becoming increasingly short for their bone age. Thus their predicted adult height was becoming steadily lower.

Partial deficiency. A number of patients seemed probably to be only partially GH deficient. No. 1.18 is an example: he was the least absolutely small, being only -2.6 SD for height. His parents were both tall people, and when this was allowed for his height SDS became -4.0; however this is still fourth largest of the HS groups. His skinfolds were only at 0.2 SDS and his peak GH in insulin hypoglycaemia was 13 μU/ml, and 11 after Bovril. On a subsequent test in his coasting year the peak GH was 11 in hypoglycaemia. His genitalia were normal. In the metabolic balance test his decrease of nitrogen excretion was 24%, again at the lower border of the HS patient range (Clayton *et al.*, 1971). His pretreatment height velocity was

4.5 cm/yr, which was only -0.9 SDS for chronological age, the highest of all the HS patients. On treatment his velocity became 7.7 cm/yr (see Fig. 17 below) and in the posttreatment year it sank to 4.3 cm/yr. His skinfolds fell on treatment from 0.6 SD at the beginning to 0.0 at the end of the year. Thus he seems to have had a perfectly good, if not spectacular, response to HGH.

We think on balance that patients 1.6, 1.12, 1.19, 1.22, and 1.28 are also only partially deficient. Their details can be inspected in the Appendix Table, where they are marked with a P. These are the cases in Fig. 10 with peak GH levels of 7 μU/ml or over, together with pretreatment height velocity SDS between -1.0 and -2.0. They all responded to HGH treatment, as illustrated in Fig. 17 below.

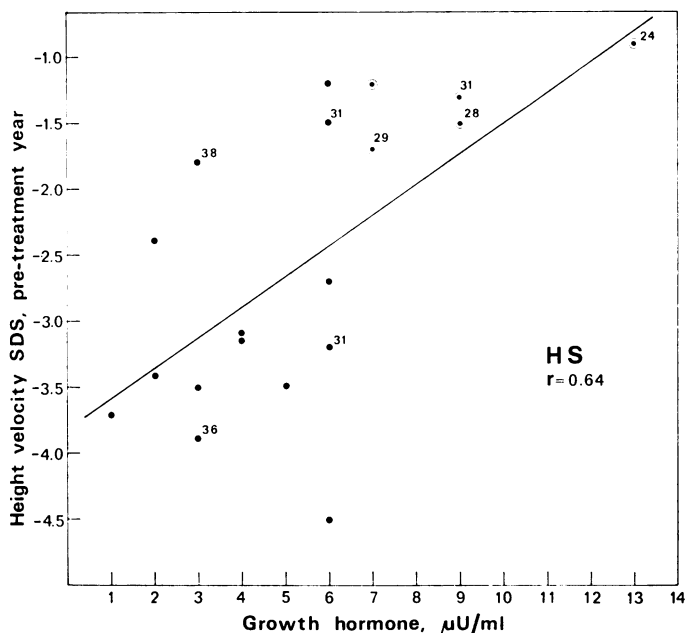**Antibody-developing patients.** Four HS patients developed antibodies during treatment to

FIG. 10.—*Relation in HS patients between height velocity SDS for CA in pretreatment year and peak GH value on insulin hypoglycaemia. The values by some of the points are percentage decrease in nitrogen excretion in 3-day metabolic test. Partial deficiency cases are those ringed.*

a degree that stopped their growth response and precluded further HGH treatment (Chalkley and Tanner, 1971). There seemed to be nothing in their pretreatment investigation which distinguished them from the other HS patients. All were boys: 2 had normal and 2 had small genitalia. Height and height velocity were similar to the others. One had a rather low birthweight; unfortunately we lack measurements of birth length to compare with the patients of Illig *et al.* (1970).

Craniopharyngioma and other CNS lesion patients (Groups 2 and 3). There were 15 patients with craniopharyngiomas (Group 2), and 3 with other CNS tumours (Group 3). The means below are for both groups combined.

Seven of the craniopharyngioma patients were male and 8 female. At diagnosis they were older than the HS or LBW patients, most having developed the main symptoms between age 5 and 10. All except 4 had had the tumour removed or aspirated. Nos. 2.8 and 2.11 had had radiotherapy, and in 2.10 and 2.15 the tumour had not been treated.

Substitution therapy varied, as shown in the Appendix Table, Col 26.

Height, weight, and bone age. The height SDS

varied from $-1 \cdot 2$ to $-6 \cdot 5$, with a mean of $-3 \cdot 8$ $\pm 0 \cdot 4$. Sitting height averaged the same. Bone age SDS ranged from $0 \cdot 0$ to $-5 \cdot 9$, with an average of $-3 \cdot 0 \pm 0 \cdot 4$, which is as retarded as the HS patients. Patients on cortisone did not differ from those without it either in height SDS or bone age SDS.

Skinfolds were all above the mean, with an average SDS of $1 \cdot 3 \pm 0 \cdot 2$, which is slightly above even the HS patients. Patients on cortisone did not differ from those who were not.

Growth hormone, 17-hydroxycorticosteroids, PBI. GH levels were 6 µU/ml or less in those in whom they were determined (though there seems no reason why some of this group should not be partially deficient). The 17-hydroxycorticosteroid values were normal and the PBIs mostly reflect the treatment status.

Pretreatment height velocity. Puberty was far advanced in one patient (2.15), partly due to the administration of oestrogens; her bone age was nearly adult and her pretreatment height velocity nearly zero. In 4 other patients, signs of spontaneous puberty were present by the end of the pretreatment year. These 5 have been excluded from

the pretreatment velocity average which was 2·7 ± 0·4 cm/yr, range 0·3 to 4·3 cm/yr.

Panhypopituitary patients (Group 4). These 3 patients who had evidence of panhypopituitarism but no tumour are not very different in their pretreatment status from the HS patients. All were on thyroid treatment, though it was not clear whether 4.3 really needed it. He underwent spontaneous puberty and might be a simple HS. One out of the two male patients with panhypopituitarism had small genitalia.

Low birthweight (LBW) patients (Group 5). *Appearance* (see Fig. 3). All these patients had, to a greater or less degree, the typical facial appearance of LBW children. 10 were male and 7 female. All the males had normal genitalia. 10 of the 17 had noticeable asymmetry and were thus classifiable as Silver's syndrome (see Tanner and Ham, 1969). Patient 5.18 seemed different, with muscular hypertrophy and a face resembling the birdheaded dwarfs of Seckel (1960); she is not included in the averages. *Age at diagnosis* was lower than for the HS, perhaps because the low birthweight alerted the parents and doctors.

Gestation and birthweight. Pregnancy was said to have been normal except in 3 (see Appendix Table, Col. 25). 4 were born at 36 weeks, the remainder between 38 and 42. The mean birthweight was 1·86 ± 0·1 kg, and the SDS, when length of gestation, parity, and mother's height were allowed for, was −3·1 ± 0·3. Apart from 5.11, who should perhaps really be classified with the small/delay group, all were −2·0 SDS or less. There was little in the mothers' accounts to indicate any definite intrauterine pathology or neonatal difficulties; we have no data beyond this.

Familial incidence. Few of the sibs were reported as having had low birthweight or short stature. The average birthweight SDS of the sibs was −0·29 ± 0·2, and the mean of the within-family average differences of sibs less propositi was −2·89 ± 0·2 SDS. The parents' heights ranged from the 10th to the 97th centile. None were below the 10th and the average centiles were fathers' 51 and mothers' 44, with average midparent SDS + 0·26 ± 0·2. This is not significantly different from the average of the HS parents.

Height, weight, and bone age. The height SDS varied from −2·6 to −5·9 with an average of −3·7 ± 0·2. When parents' height was allowed

for, the mean dropped to −4·6 ± 0·3. Height SDS for bone age averaged −1·8 ± 0·4.

There was no obvious relation between height SDS and age of the child; it seems that these children maintain about the same centile throughout their growth, at least till adolescence.

The average SDS for sitting height was −3·6, the same as for height.

Bone age SDS varied from +0·5 to −4·3, with a mean of −1·8 ± 0·3. In contrast to the HS patients, 3 of these 17 LBWs had BA equal to or greater than CA.

Skinfolds The skinfold values are plotted in Fig. 7 and 8. The range for SDS of the average of triceps and subscapular folds was +0·9 to −3·0 and the average −0·90 ± 0·3. All except 2 LBW patients were below the mean. There was nearly complete separation of HS and LBW patients, only 2 of each overlapping into the range of the other.

Limb bone muscle and fat. The mean SDS of limb bone muscle and fat widths are given in Table II. The muscle was as relatively reduced as the bone, as in the HS cases. The fat, in contrast to the HS situation, was also reduced, with a mean SDS of −0·76 ± 0·2. This was similar to the mean skinfold SDS.

Growth hormone, 17-hydroxycorticosteroids, PBI. GH peak values following insulin hypoglycaemia were available on 4 patients at diagnosis and a further 5 in the coasting year. All were over 30 μU/ml. Bovril stimulation values were in agreement. The 17-hydroxycorticosteroid excretions after ACTH were low in a number of patients, but the meaning of this is unclear. The PBIs were normal and averaged 5·1 ± 0·24 μg/100 ml.

Pretreatment height velocity. The pretreatment height velocity SDS averaged −0·97 ± 0·3 (for CA, 14 cases) compared with the figure of −2·76 for the HS patients. The boys' velocities are plotted in Fig. 9; only one is above the mean for CA, but only one below the 3rd centile. The bone age pretreatment velocity averaged 0·95 ± 0·1 'years' per year and the height velocity/bone age velocity ratio averaged 0·87 ± 0·06.

Small/delay patients (Group 6). There are four patients who are small because either: (1) they have simply inherited small stature from their parents (*hereditary short stature*); (2) they are delayed in maturation and will eventually reach the expected height for their parents' size, which is itself normal (*growth delay*); (3) they have a combination of (1) and (2) (*small/delay*).
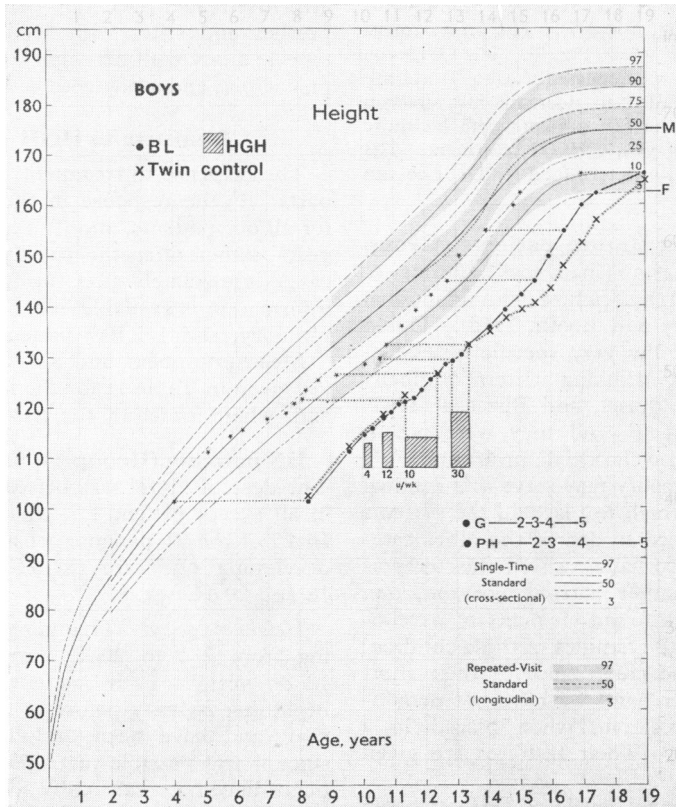
FIG. 11.—*Height growth of identical twin brothers, both with growth delay, one treated with HGH.*

Patient No. 6.2 represented a pure delay in growth (Fig. 11). He was an identical twin; his brother was 0·6 kg heavier at birth. His mother was diagnosed as tuberculous at 7 months' pregnancy and admitted to a sanatorium, and the twins were separated from her and in various foster homes until they were 18 months old. The relationship with the parents after they were reunited was good. The patient's bone age at diagnosis, when CA was 8·3, was only 3·9 'years', giving a SDS of −4·3. When treatment began at CA 10·0 years, BA was still only 5·8 'years'. GH estimations were not available. His pre-treatment height velocity was high, being +2·9 SDS, a value inconsistent even with partial GH deficiency. Both he and his twin eventually reached the expected adult height, about the 15th centile. The diagnosis therefore was pure delayed growth. HGH treatment had clearly no effect, as can be seen in Fig. 11. Patient No. 6.4 was similar. Patient No. 6.3 was also probably a case of growth delay, but complicated by psychosocial problems.

Patient 6.1 illustrates best among all our patients the difficulty in differential diagnosis, and for this reason is presented in detail in Appendix 1.

High resting HGH, low somatomedin (Group 7). A few patients with short stature have the ability to secrete immunoreactive GH, and indeed have high values even without stimulation; but their GH fails to stimulate the production of somatomedin, a substance found in the blood, and previously named 'sulphation factor' for its ability to cause increased uptake of radioactive sulphate by the costal cartilages of hypophysectomized rats.

Our series contains one such patient; a boy born by elective caesarean section, weight 3·74 kg, at the end of a normal pregnancy. He had a small penis, ill-developed scrotum and descended testes. His mother was at the first centile for height, and her grandfather was small, though not her father. The patient had a very prominent forehead and depressed snub nose. When first seen at age 4·5 years he had a

height SDS of $-5 \cdot 8$, bone age SDS $-2 \cdot 3$, and skin-folds SDS $+1 \cdot 4$ (see Fig. 6 and 7). His pretreatment height velocity SDS was $-4 \cdot 0$ (Fig. 9). His GH level, even before stimulation, was repeatedly 20 to 30 μU/ml. On metabolic test he failed to decrease his nitrogen excretion as much as the HS patients and he quite failed to grow during a year's HGH treatment. His somatomedin level, kindly determined by Dr. Leo van der Brande, was low.

Psychosocial short stature patients (Group 8).
It is now well established that stunting of growth may occur in association with emotional difficulties (MacCarthy and Booth, 1970). Our 4 patients did not have the very specific obsessive-compulsive eating and drinking pattern originally described by Powell, Brasel, and Blizzard (1967) as 'deprivation dwarfism', and they were not at first recognized as psychosocial problems. We are aware that this category may serve as a residual dumping-ground in which to place all the patients who cannot be allocated to one of the other categories. We believe we have resisted this temptation (by keeping another category of *uncertain diagnosis*) and we have found elements of psychosocial dysharmony in the families of these children, which seem to be the chief cause of their short stature. On the other hand we have not demonstrated that they accelerate when placed in a different environment. Their histories are given in the Appendix.

All 4 produced normal levels of GH on being tested in hospital, though this does not exclude the possibility that they suppressed their GH secretion in their home environment.

Cases of uncertain diagnosis (Group 9).
There were 3 patients in whom the diagnosis remained very uncertain. Their histories are given in the Appendix. The first 2 of these may well be further cases of partial or even intermittent GH deficiency. Their peak GH levels varied from 14 μU/ml to 23 μU/ml on different occasions and both responded to HGH to a significant but low degree. The third patient probably had some form of chondrodystrophy.

Turner's syndrome (Group 10).
We have treated 6 patients with Turner's syndrome. Karyotypes are given in the Appendix Table. The average SDS for height was $-4 \cdot 2$ and for bone age $-2 \cdot 3$. The skinfolds were about average; birthweight tended to be small. GH response was only known in one case; it was normal.

Miscellaneous patients (Group 11).
Finally, there are two patients with juvenile rheumatoid arthritis treated over long periods with steroids; a brother and sister with glycogen storage disease type 1; a boy with hereditary sex-linked hypophosphataemia; and a boy with coeliac disease.

Response to HGH Treatment
The response to treatment will be given in two parts: (1) the response in the first year, available for all our patients, and (2) response in subsequent years, either after the coasting year or, in some cases, immediately after the first year. The latter information is available only for 7 HS, 2 panhypopituitary, and 1 LBW patients.

Means, numbers, and SDs of the various groups are given in Table II for the first year of treatment and, where available, the posttreatment year.

HS patients (Group 1): first treatment year.
The dose of HGH was between 15 and 24 IU/wk in all except patient 1.5, where it was 45 IU/wk. In 25 of the 31 patients considered (the antibody-developing ones are excluded), it was between 18 and 20 IU/wk.

Height velocity. Treatment began at ages ranging from $2 \cdot 2$ to $20 \cdot 1$ years, bone ages $0 \cdot 0$ to $13 \cdot 8$ 'years'. Four patients showed signs of beginning puberty before or during the treatment year, and have been excluded from the means since it was possible that their increase in velocity might have been caused by adolescence rather than HGH. It is very rare for the adolescent spurt to begin in boys before the testes enlarge and the pubic hair appears, so we are fairly safe in excluding puberty by these criteria; the same would not necessarily be true in girls, in whom the height spurt is placed relatively earlier in relation to breasts and pubic hair (see Marshall and Tanner, 1969). Most of these patients were boys.

The mean pretreatment height velocity was $3 \cdot 1 \pm 0 \cdot 2$ cm/yr and the mean velocity during the first year of treatment was $9 \cdot 1 \pm 0 \cdot 5$ cm/yr, an increase of $6 \cdot 0$ cm/yr. The range of increase was $1 \cdot 8$ to $12 \cdot 8$ cm/yr: all except 3 patients (2 of them partial HS) accelerated by over $3 \cdot 0$ cm/yr.

In Fig. 12 are plotted the mean absolute rates of growth during each of the 3-month periods before and during treatment, and the 6-month periods after treatment. Though in individual patients the 3-monthly velocity is affected by seasonal variation, the averages of a number of patients are not so much affected, since about half started in April, and half in October. The solid line shows the total number of cases, varying from 22 to 29; the broken line shows the 11 cases followed in pure longitudinal fashion, avoiding bias. There is little
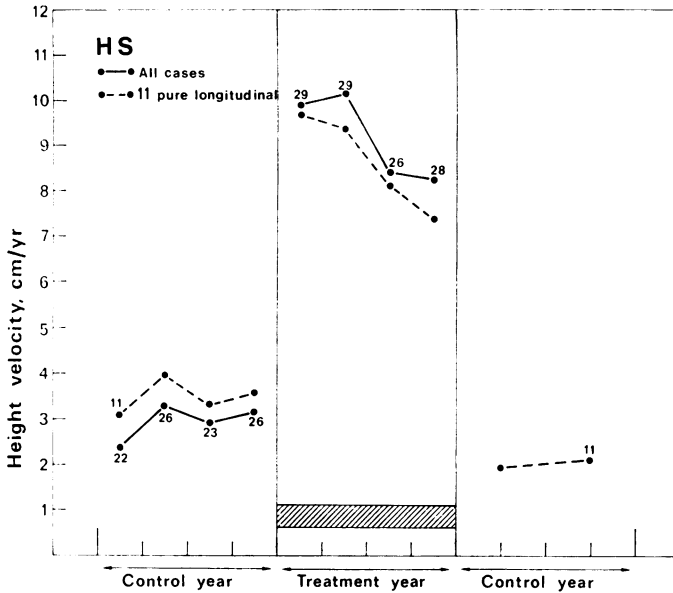
FIG. 12.—*Mean height velocity during 3-monthly periods before and during, and 6-monthly periods after, treatment; HS patients. Total series (numbers in graph); and 11 patients present on each measuring occasion.*

difference between the lines. The treatment year curve shows the typical catch-up (Prader, Tanner, and Von Harnack, 1963; Tanner, 1963). The lower velocity during the posttreatment year compared with the pretreatment year in the 11 cases ('regulatory deceleration') is considered below, under *Discussion*.

The absolute velocities and accelerations are to some extent affected by the age of the patient (see on), and hence height velocity SDS, where they can be calculated, are really preferable. The mean pretreatment SDS was $-2 \cdot 8 \pm 0 \cdot 2$ and the treatment SDS $+4 \cdot 3 \pm 0 \cdot 6$ (in successive quarters $5 \cdot 1$, $5 \cdot 4$, $3 \cdot 9$, $3 \cdot 2$). The treatment year SDS ranged from $1 \cdot 3$ to $10 \cdot 0$. The treatment mean for the five prepubescent partial HS patients was $+3 \cdot 2$, a little less than for the remainder. For bone age the average height velocity SDS was $-3 \cdot 3 \pm 0 \cdot 3$ cm/yr pretreatment, and during treatment $+2 \cdot 9 \pm 0 \cdot 4$ cm/yr. Due to concomitant changes in bone age, therefore, the treatment acceleration of height for bone age was less than for chronological age.

Bone age velocity averaged $0 \cdot 86 \pm 0 \cdot 1$ 'years'/yr in the pretreatment year and rose to $1 \cdot 18 \pm 0 \cdot 1$ in the treatment year. The quarterly mean velocities in the treatment year were not greater at first than later, as in height: though subject to much variation, it seemed as though bone age velocity increased

rather than decreased from the first to the fourth quarter. There was an immediate decrease on cessation of treatment, but not to below pretreatment levels: thus there was no indication of a regulatory deceleration.

Bone age is not so greatly accelerated as height, as the change in the ratio '*Height velocity in %* expected/*Bone Age velocity in % expected*' shows. In the pretreatment year this averaged $0 \cdot 85 \pm 0 \cdot 08$; in the treatment year $1 \cdot 6 \pm 0 \cdot 1$ and in the posttreatment year $0 \cdot 70 \pm 0 \cdot 1$.

Relation of height acceleration to pretreatment velocity, GH peak, and age at treatment. Fig. 13 shows the relation between the acceleration in the first year of treatment and the velocity in the pretreatment year. The correlation coefficient for the 27 HS patients (of both sexes but nonpubertal and excluding the patient with the high dose of HGH) was $r = -0 \cdot 58$. The regression had the slope $b = -1 \cdot 19 \pm 0 \cdot 3$. Thus the lower the pretreatment velocity the greater the response, as might be expected. The craniopharyngioma patients are also indicated in the Fig.; for them, interestingly, the correlation is the same, and the regression almost exactly parallel, but with treatment velocity 2 cm less for given age.

The absolute treatment velocity in the HS patients had a lower correlation, $-0 \cdot 11$, with pre-
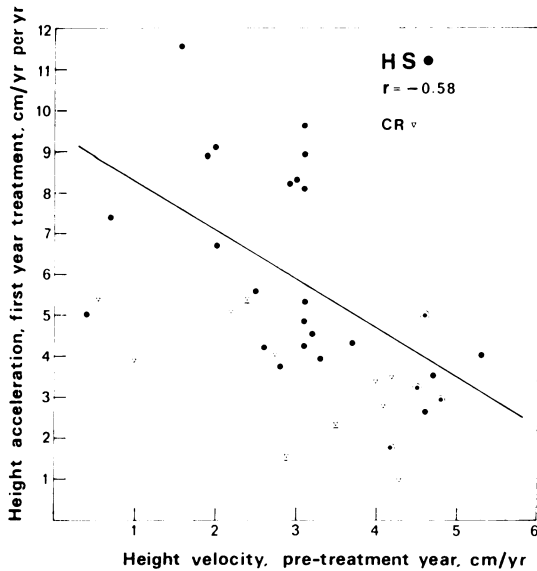
3

FIG. 13.—*Relation between height acceleration in first year of treatment (treatment velocity less pretreatment velocity) and velocity during pretreatment year. Regression line is for HS patients only, on 18–20 IU/wk HGH. Craniopharyngioma patients also indicated, as* ▽

treatment velocity. Since both treatment and pretreatment velocities were somewhat correlated with age (see below), the partial correlation between acceleration and pretreatment velocity with age constant was calculated but did not differ from the initial correlation of −0·58. A plot using height velocity SDS before and during treatment looked very similar to Fig. 13, with r = −0·45.

The correlation between height acceleration and the peak GH level on insulin hypoglycaemia, either at diagnosis or during the coasting year, was −0·19, which fails to reach the 5% level of significance. Height acceleration was not closely related to chronological age at treatment (r = 0·25, $P < 0·05$). Absolute velocity during treatment did relate significantly to age, however, with r = −0·54, and the regression: velocity (cm/yr) = 11·6 − 0·26 (± 0·08) age (yr). In the pretreatment year there was still some positive correlation between velocity and age (r = 0·33) even in these GH-lacking patients.

Sitting height was accelerated by treatment to about the same degree as leg length. Before treatment the sitting height SDS averaged − 0·66 ± 0·1, and after it −0·60 ± 0·1. At the end
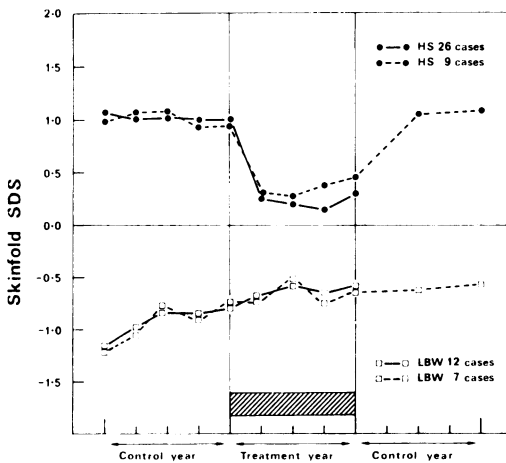
FIG. 14

FIG. 15

FIG. 14.—*Mean skinfold SDS (average of triceps and subscapular) at 3-monthly intervals before and during first year of HGH treatment and at 6-monthly intervals after treatment. HS and LBW patients.*
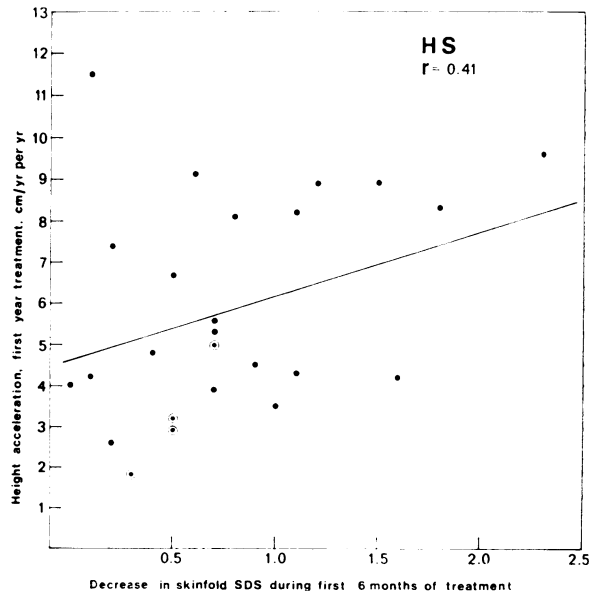
FIG. 15.—*Relation between decrease in skinfold SDS during first 6 months of treatment and height acceleration during first treatment year; HS patients. Partial HS* ⊙.
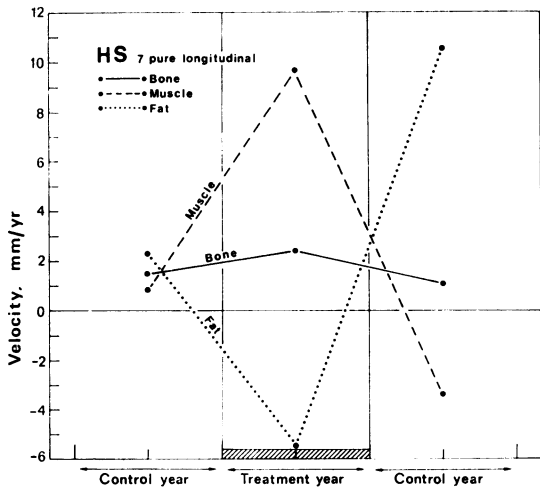
FIG. 16.—*Mean velocities of widths of bone, muscle, and fat measured in radiographs of upper arm and calf, before, during, and after HGH treatment. HS patients, pure longitudinal series.*

of the posttreatment year the average was again -0.66 ± 0.2 (14 cases only).

Skinfolds were decreased on treatment, as shown in Fig. 14, where the means for the HS and for the LBW patients are given. Most of the decrease occurred in the first 3 months of treatment, and most of the posttreatment rise probably occurred equally quickly. The amount by which the skinfold decreased in the first 6 months was related to the height acceleration, as shown in Fig. 15. The correlation was 0.41 (24 cases).

Radiographic bone muscle and fat velocities. The radiographs of calf and upper arm enabled us to calculate the velocities of bone width, muscle width, and fat width at the level described. The values for the two limbs have been summed. The means have had to be calculated on a somewhat varying number of patients, since not all were x-rayed each 3 months. We have included only patients whose velocity was estimated over at least a 6-month period of the relevant year; the majority

(a)

(b)
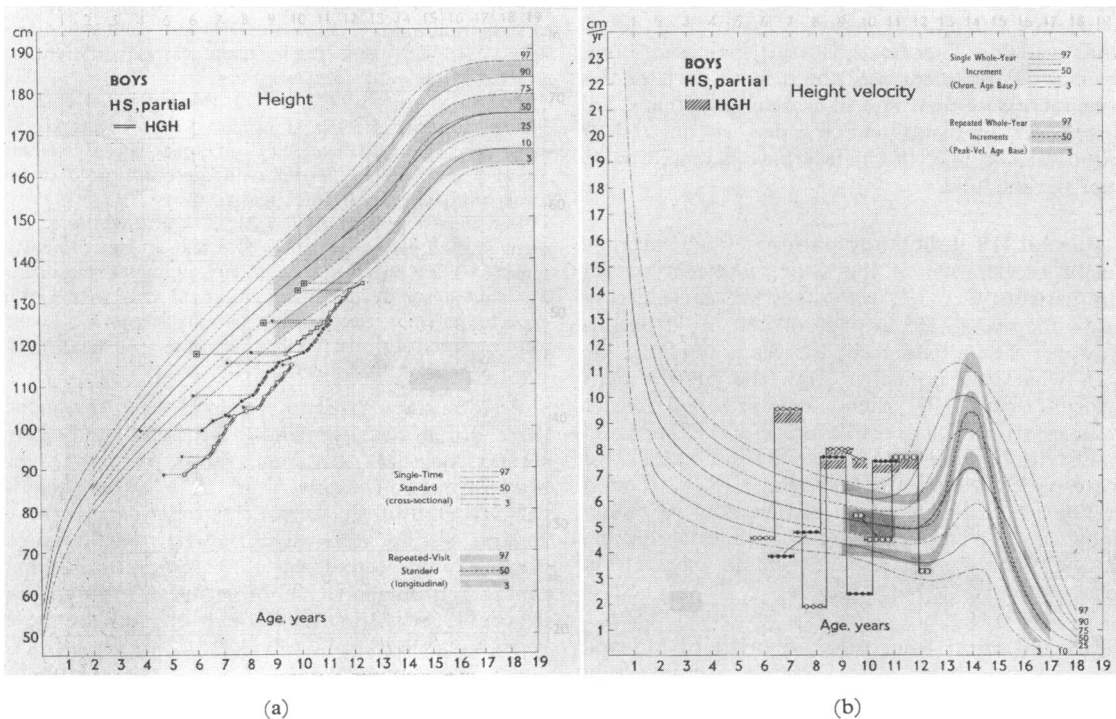
FIG. 17.—Left, *height growth and response to HGH in 3 HS patients, presumed only partially GH deficient.* O–O No. 1.6; No. 1.12; ⊡–⊡ No. 1.18. *Double line signifies treatment with HGH.* Right, *height velocity on and off treatment.*

have 2 or 3 x-rays extending over 9 or 12 months for each of the years.

The means for the HS patients are given in Table II. The increased velocity of bone and muscle on treatment, and the decreased velocity of fat can be readily seen. Probably a better estimate of the changes, however, is given by the 7 patients who were followed in the pure longitudinal way through the 3 years, and it is the means for these which are plotted in Fig. 16.

The changes in muscle width were particularly striking. Examination of the 3-monthly values showed that the increased velocity was greatest in the first 3 months, just as the fat loss was greatest then. Not only did muscle increase proportionately more than bone on treatment, but when treatment ceased muscle width actually diminished, just as fat width did during treatment. Bone, on the other hand, continued to grow in the posttreatment year at about the same rate as before treatment. In the posttreatment year there was a large increase in fat, carrying the absolute fat width to a higher SDS than it was at the beginning of treatment. We have been able to measure the width of bone cortex and medulla separately in the humerus of some, but not all, the x-rays. From the limited data available it seems that the increased bone velocity on treatment was due to both parts of the bone increasing their rate of widening, perhaps the cortex predominantly. Ferrandez et al. (1970) found the cortex of the metacarpals increased more than the medulla.

Partial HS deficiency patients. The average height acceleration of the 4 prepubescent partial HS patients was 3·2 cm/yr per yr, considerably below the overall HS average of 6·0 cm/yr per yr. However the partials' response was not out of line with what was predicted from the pretreatment velocity, which in them averaged 4·5 cm/yr compared with the overall average of 3·2 cm/yr.

The height and height velocity curves of 3 of these patients, Nos. 1.6, 1.12, and 1.18 are plotted in Fig. 17. The treatment responses were highly significant and large enough to be clinically important. Certainly such patients should have HGH treatment.

HS patients: long-term treatment. Seven HS patients have been treated continuously, without a coasting year. All have been taken off HGH, either for a year, or for 6 months only, at some point in their treatment.

The height and height velocity curves of 4 of these patients are shown in Fig. 18. In the lower left hand graph the 3-monthly velocities are shown, dotted, for illustration. The yearly velocities, in solid lines, are the important ones, however. The dose of HGH is shown in the charts.

The response of our longest-term patient, No. 1.5, is quite typical, though perhaps his very high velocity in the first year was partly due to his dose of HGH being twice as much as that of any other patient. His velocity diminished as he approached the 3rd centile (which is his mother's) despite constancy of the exogenous HGH. When the dose was doubled for 6 months, he did appear to respond somewhat, though this may have been only a seasonal effect. When HGH was stopped, his velocity fell to zero. When restarted, he showed no evidence of a catch-up, his velocity being in line with those of his previous, decelerating, curves. There were no signs of puberty when he was last seen.

His brother, No. 1.1, was started on HGH younger than any of our other patients. In the height 'distance' curve (left) he caught up right to the 10th centile and then for a year continued along it, despite the dose of exogenous hormone having been constant. He stopped growing when taken off HGH and resumed again when the hormone was restarted. The velocity curve shows more detail. The very low 3-monthly velocity at age 2·7 years may be related to his having had pyelonephritis, and subsequently a ureteric implant operation to stop reflux from the bladder: there seems to have been a catch-up (exceeding the usual seasonal differences) as soon as the operation was over.

The third patient, No. 1.3, is the boy illustrated in Fig. 3, top panel. He showed a very typical HGH response; again his velocity dropped sharply when HGH was stopped. In his case there appeared to be some catch-up when HGH was restarted.

The fourth patient, No. 1.21, is a girl whose treatment started relatively late. She had an exceptionally retarded bone age but no evidence of hypothyroidism. She had a steady catch-up, and will end within the expected normal range for her parents' heights. There were no signs of puberty when last seen. In the period off HGH she slowed down greatly.

Besides these patients on long-term treatment there are a number who have completed their second year of treatment following their first posttreatment, coasting year. The mean height velocity SDS in the second treatment year of these patients did not differ significantly from the mean velocity in the second year of the long-term patients treated continuously. The year off did not appear to confer any significant catch-up for the next year on; it seems to be time lost.

The *height velocity SDS* in each year of treatment is shown in Fig. 19, the coasted and the continuously-treated patients being combined. The square points represent the whole HS group; from these it can be seen that the long-term patients are, from this point of view, a good sample

of the total. In the first year the SDS averages around 4·5, but by the fifth year has fallen to around 1·5. One can expect velocity within normal limits usually to be reached in about 4 years. We have no indication however that the velocity eventually goes below average, unless antibodies develop or treatment is stopped.

Fig. 20 shows the *mean skinfold SDS* at the end of each year of treatment. The skinfold reached its minimum level in most cases after six months of treatment (see above); by the end of the first year already some drift back toward the pretreatment skinfold level was apparent, and this continued in years subsequent to the first; by the end of 5 years of treatment the skinfolds, on average, were back where they started, at about +1·0 SDS.

The *bone age velocity*, stimulated in the first year of treatment, likewise drifted back, but by the end of 4 years on average had reached not the pretreatment figure of 0·9, but the normal average of 1·0. The averages for the first 4 years of treatment were 1·3, 1·3, 1·1, and 1·0 'years' per year.

Craniopharyngioma and other CNS lesion patients (Groups 2 and 3). The 18 patients of this group were also given 18 to 20 IU/wk HGH, with the exception of Nos. 2.1, 2.11, and 2.12 who were on a nominal half dose, actually 8 IU/wk. Other treatment is detailed in the Appendix Table. No changes of treatment occurred between the pretreatment and the treatment years. 6 of the 18 showed signs of puberty in the pretreatment year; 5 of these were girls. No further patients developed puberty in the treatment year. The pubescent patients have been omitted from the averages in Table II.

In general the responses to HGH in height, skinfolds, and muscle measurements were similar to those of the HS patients, though less in extent. There were, however, some exceptions.

Height velocity. The pretreatment velocity of the non-pubescent patients averaged 2·7 ± 0·4 cm/yr, giving a mean acceleration of 3·4 ± 0·4 cm/yr compared with 6·0 cm/yr for the HS patients (who are, of course, younger). Individual patients had accelerations ranging from 1·0 to 5·4 cm/yr. 3 were under 2·5 cm/yr.

The treatment acceleration was negatively related to the pretreatment velocity, just as in the HS patients. In Fig. 14, above, the regression line is for the HS patients only. The open triangles show the craniopharyngioma patients. All lie below the HS regression line, indicating that their response to HGH is considerably less than that of

the HS patients of comparable pretreatment velocity. The regression line for the craniopharyngioma patients is nearly parallel to the HS line, and approximately 2 cm/yr below it; the correlations for the two series of cases are similar.

Two of the lowest accelerations (1·0 cm/yr and 2·3 cm/yr) occurred in boys (2.5 and 2.11) whose growth status was not really abnormal. Both were prepubescent; their pretreatment velocities of 4·3 cm/yr and 3·5 cm/yr were brought up on treatment to 5·3 cm/yr and 5·8 cm/yr, a quite normal preadolescent rate. Both patients should reach normal adult height when the adolescent spurt, induced if necessary, is finished.

Of the 6 *pubescent patients* (5 girls and 1 boy), 2 girls (2.10 and 2.15), failed to respond at all, for the obvious reason that their period of possible growth was over. Their bone ages were 14·4 and 14·6 'years' (girls approach their final bone age at about 15·5 'years'), their puberty ratings were 3,4 in one case and 5,5 postmenarcheal, in the other. Another girl (2.8), treated at a bone age of 13·7 'years', ratings 3,1, was approaching her pre-spurt height like the boys described above, and responded only slightly.

However two girls (2.13 and 3.3) who had bone ages of 11·8 'years' and 12·7 'years' with puberty ratings of 3,1 and 3,1 when treatment began, responded well, with accelerations of 3·2 and 3·6 cm/yr.

Bone age velocity increased only insignificantly on treatment in the prepubescent cases, from a mean of 0·6 ± 0·1 to 0·7 ± 0·2 'years'/yr. This marks a contrast with the HS patients.

Skinfolds fell in all patients who responded. Though most were too old for an SDS to be calculated, the absolute fall in transforms was rather less than that shown by HS patients. The curve of response was similar, with a sharp fall by 3 months and a tendency to regain pretreatment status by the end of the treatment year. The correlation between fall in skinfold SDS at 6 months and height acceleration, seen in the HS patients (Fig. 15 above), was not present in the craniopharyngioma patients.

Limb bone muscle and fat width changed comparably with those of the HS patients. Muscle velocity increased just as in Fig. 16 though to a lesser degree; it fell to below zero in the post-treatment year. Fat widths fell during treatment, following exactly the shape of the HS curve.
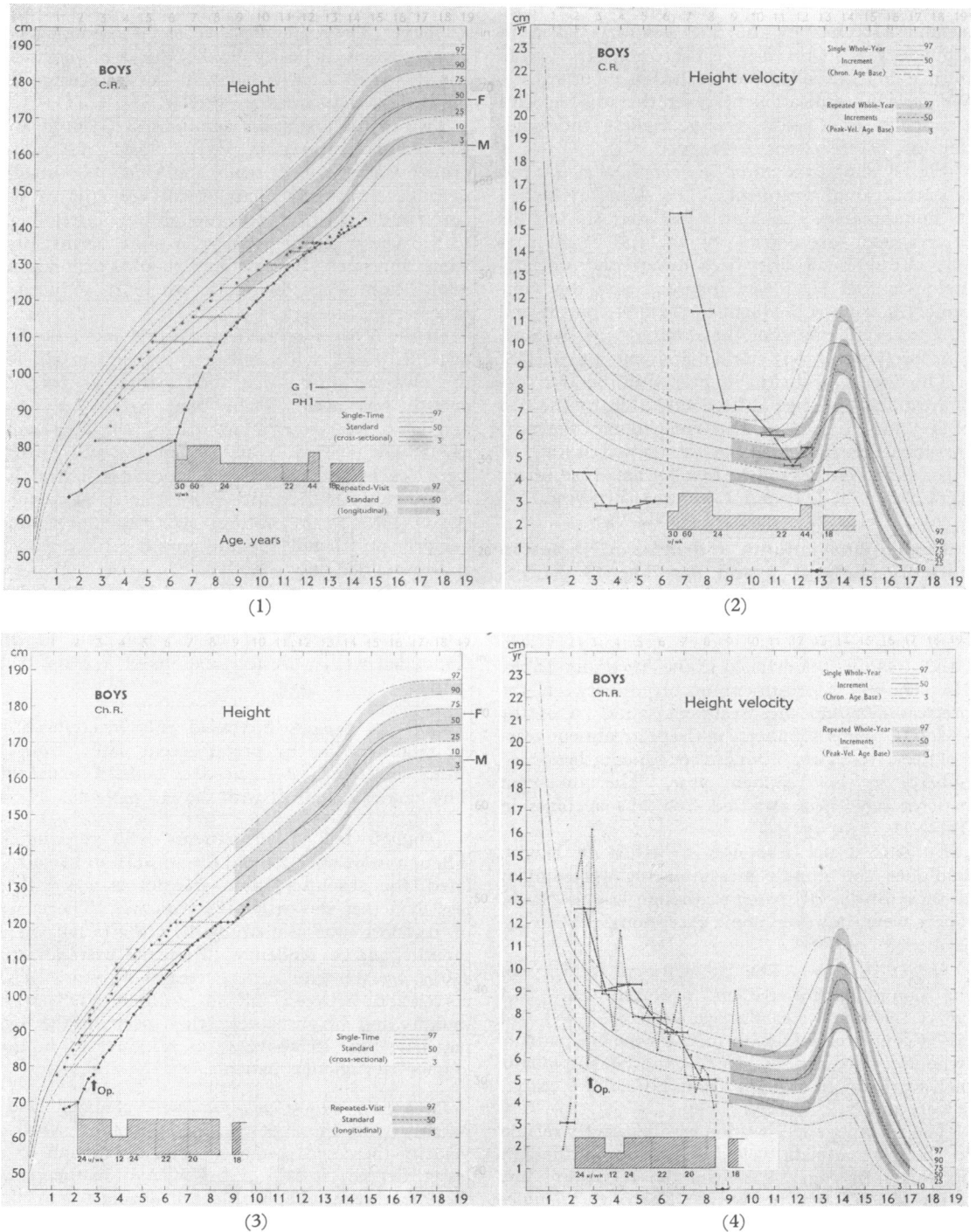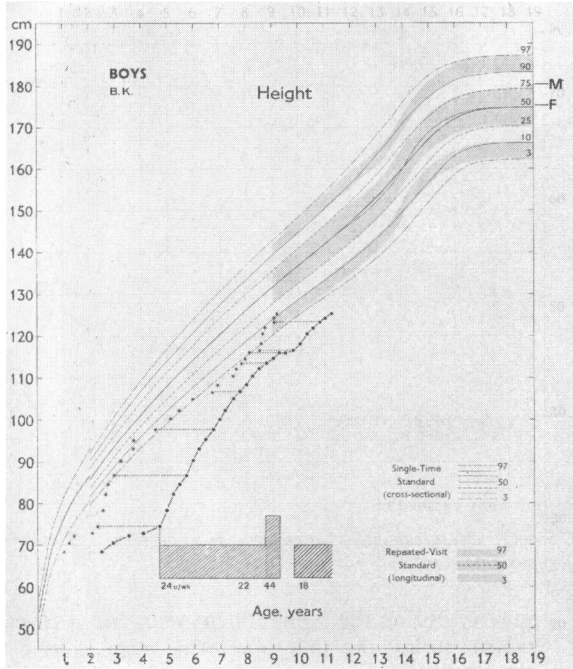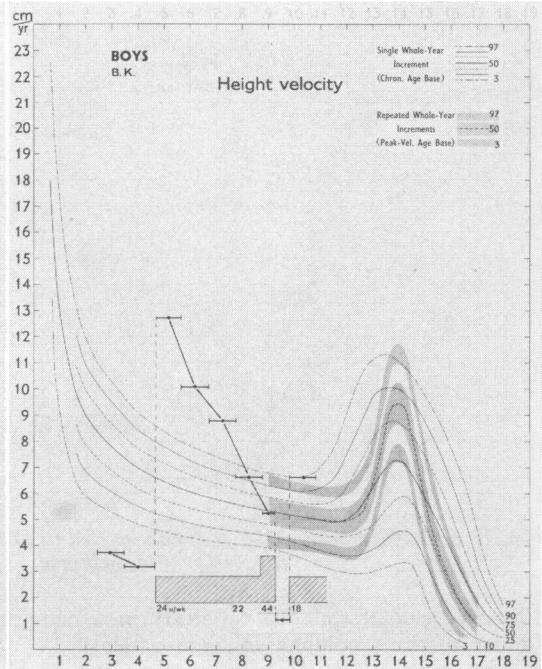
Panhypopituitary patients (Group 4).

FIG. 18.—*Height and height velocity curves of 4 HS patients on long-term treatment. Height plotted at CA* ●, *at BA* *, *HGH dose and puberty ratings as indicated. In velocity chart yearly values solid lines, 3-monthly*
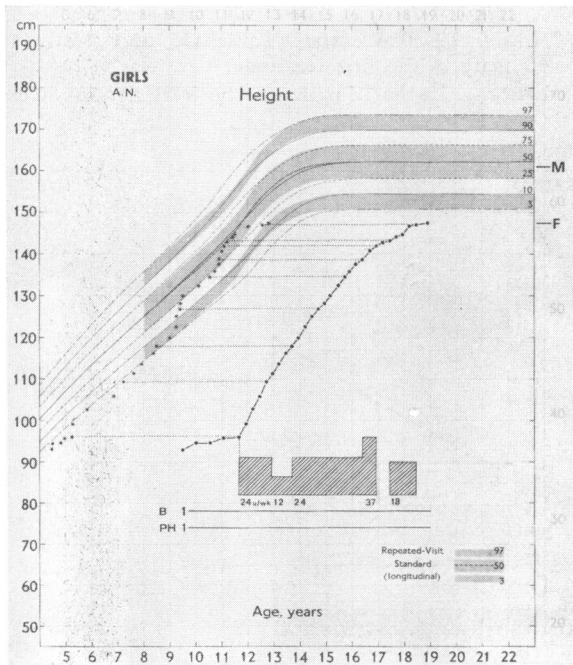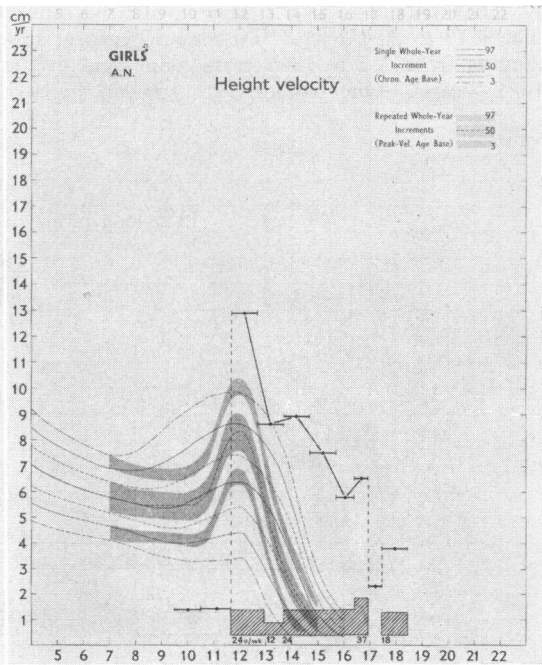
(5)

(6)

(7)

(8)

values dotted lines, (1) and (2) C.R. No. 1.5; (3) and (4) his brother Ch.R. 1.1.; (5) and (6) B.K. No. 1.3;
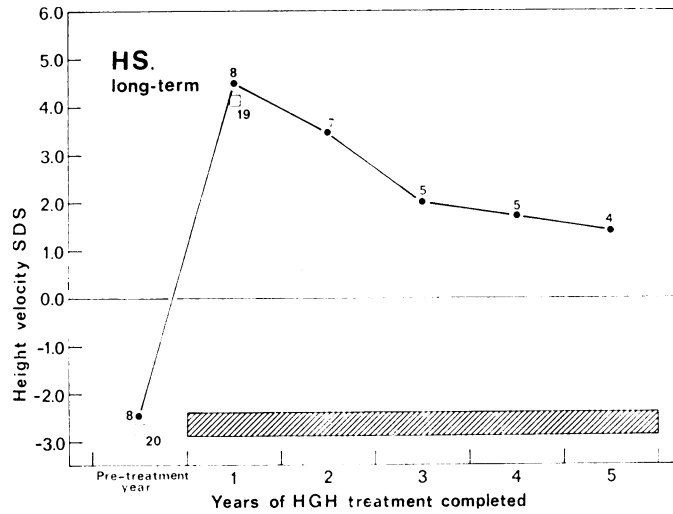*(7) and (8) A.N. No. 1·21.*

FIG. 19.—*Height velocity SDS pretreatment and in first 5 years of treatment. Long-term HS patients. Numbers for each point as indicated.* □ *represents total HS patient group.*

These patients responded to HGH in a manner similar to the craniopharyngioma patients.

LBW patients (Group 5). The dose for the 17 LBW patients was the same as for the others, that is 18 to 20 IU/wk. Treatment began at ages ranging from 2·2 to 13·7 years, bone ages 0·0 to 14·1 'years'. One patient 5·16 showed signs of

puberty during the pretreatment year, and 4 others did so during the first treatment year. These 5 patients have been excluded from the means.

Height velocity. The mean pretreatment velocity was 5·3 ± 0·4 cm/yr (Table II), and the mean velocity in the first treatment year was 6·7 ± 0·5 cm/yr. In the 12 patients who were nonpubescent
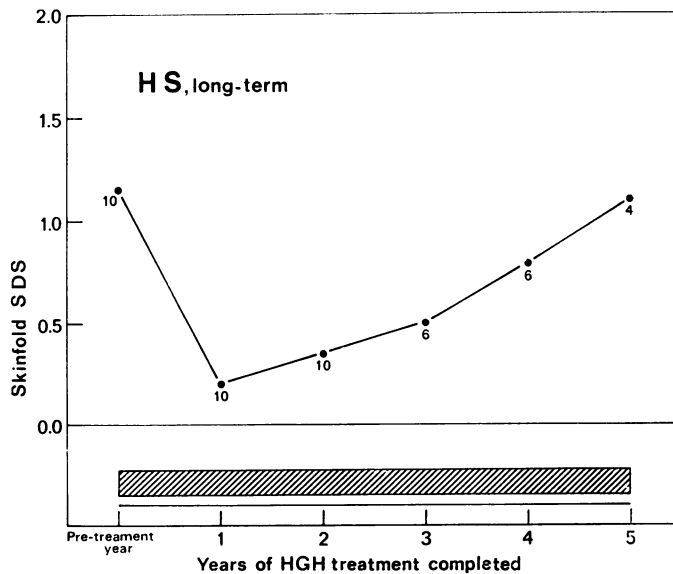

FIG 20.—*Skinfold SDS at end of pretreatment year and of first 5 years of treatment. HS patients. Numbers as indicated.*

during the treatment year, mean acceleration was 0.9 ± 0.4 cm/yr per yr, the pretreatment velocity being a little higher than in the others.

This barely significant and clinically unimportant mean gain from treatment masks a considerable variation between the responses of different children. The 2 youngest children had accelerations greater than 2 cm/yr per yr and when adjusted for the quite large decrease in velocity expected at these ages the true accelerations must be reckoned at about 3 cm/yr per yr, a clinically useful amount unless cancelled by a regulatory deceleration (see below). Similarly No. 5.1 showed a response which can hardly be considered insignificant statistically or clinically, since treatment caused a net gain of about 2.8 cm to the child's height. On the other hand some of these patients failed to show any response whatever to HGH (Nos. 5.7, 5.11).

Fig. 21 shows the 3-monthly height velocities for the total group and for the 7 patients who constitute a pure longitudinal series. Evidently there was an increase in height velocity during the first 3 months, but the response diminished and by the end of the year the velocity, on average, had returned to about the pretreatment value. In the posttreatment year the velocity fell below that in the pretreatment year, to a degree which is a little more than that expected from the normal fall of velocity with age, so that by the end of this year the average net gain from treatment was a negligible 0.5 cm.

The 4 children who showed an apparently significant response in their first year were continued

on treatment, one without a coasting year, and 3 with coasting years. No. 5.2 (Tanner and Ham, 1969, patient L.M.) had a definite increase of velocity from 6.4 to 9.0 cm/yr in his first year of treatment and in the second and third years he remained at the 80th centile of velocity. In the fourth year of treatment, despite a doubled dose of HGH, the velocity fell to its pretreatment centile level, about the 25th. The height SDS remained at -2.0, to which during the previous years it had risen from -3.6. At this stage a year off treatment was given, and during this the height velocity continued exactly as in the previous year. Whether the HGH has been useful in this patient is very hard to say, since no adequate early control exists.

In the case of No. 5.1, however, illustrated in Fig. 22, HGH has certainly had a significant though not spectacular effect. This patient had a GH peak level of 32 μU/ml on insulin hypoglycaemia, so presumably was not a partial HS as well as LBW. Though treatment brought his height SDS for CA down from -4.8 to -3.1, his height for BA has always been normal, and has remained unaltered. Possibly his diagnosis is 'LBW plus delay'. It seems likely, however, though not certain, that in his case HGH has added, so far, some 5 cm to his stature.

Bone age velocity increased insignificantly from a pretreatment mean of 0.97 ± 0.1 'years'/yr to 1.11 ± 0.1 'years'/yr. In 5 out of the 7 patients it fell again in the posttreatment year but the mean posttreatment figure does not differ significantly from
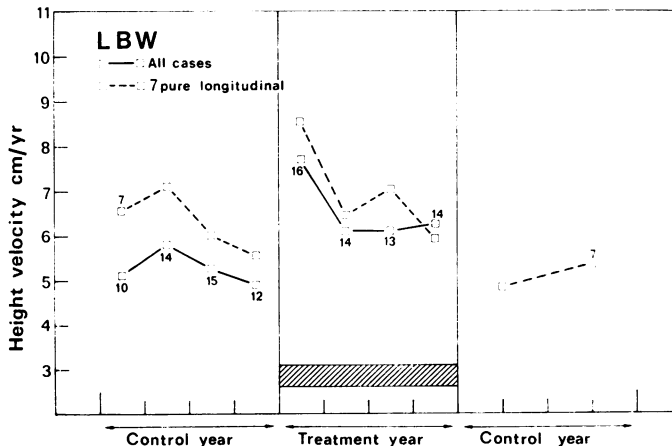

FIG. 21.—*Mean height velocity during 3-monthly periods before and during treatment, and 6-monthly intervals after treatment. LBW patients. Total series (numbers in graph) and 7 patients present on each measuring occasion (cf Fig. 13).*
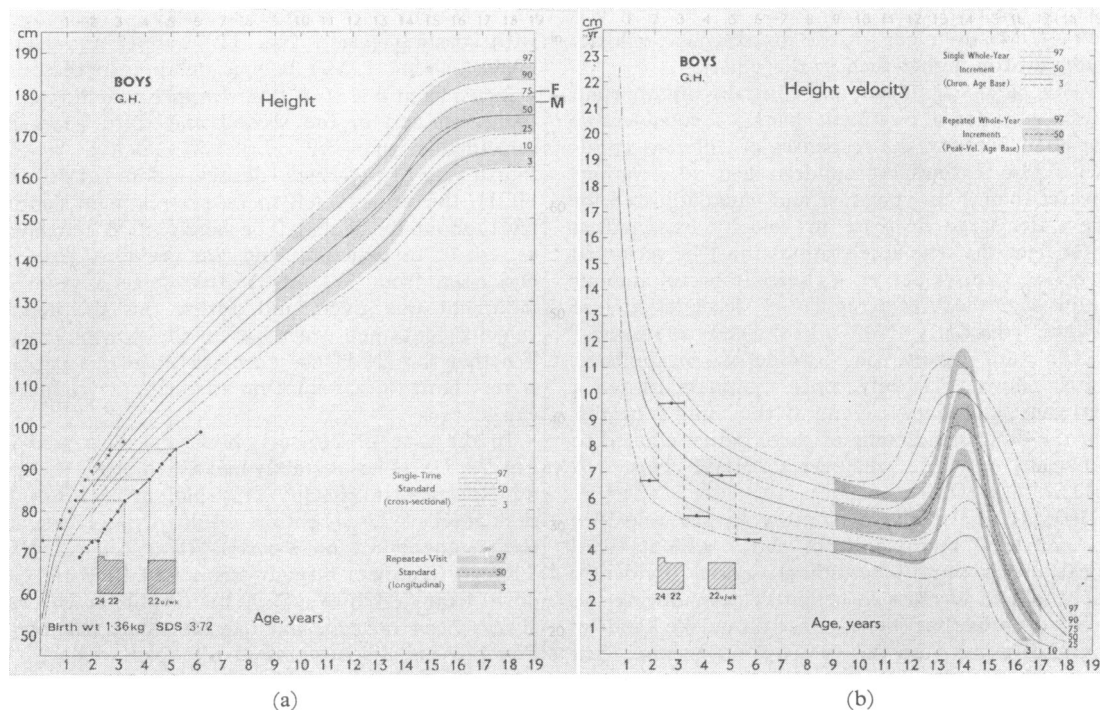
FIG. 22.—*Height and height velocity of LBW patien twho apparently responded significantly to HGH (No. 21).*

the treatment one. The ratio 'Height velocity in % expected/Bone Age velocity in % expected' did not differ significantly between the three periods.

Skinfolds were unaltered on average during treatment, in contrast to those of the HS patients (see Fig. 14, above). Many individual patients actually increased their skinfolds during treatment. The *limb fat width* on radiography, however, showed a quite definite mean decrease during the first 6 months of treatment and the expected rise after treatment stopped. There seemed also to be a rise in *muscle width velocity* during the early part of treatment, and a fall when treatment stopped. It seems that the tissue responses in the LBW patients are similar to those of the HS, as perhaps one might expect, but on a very much reduced scale.

Small/delay patients (Group 6). No. 6.1 responded to HGH like LBW or Turner's syndrome patients. No. 6.2, the twin with pure delay, did not respond at all. No. 6.3 with delayed growth, perhaps complicated by psychosocial factors, increased height velocity by 2·0 cm/yr

but had a posttreatment velocity greater than the pretreatment, which may well indicate that the treatment year increase was not really due to HGH, but to removal of emotional difficulties. In No. 6.4 the situation was confused by puberty beginning.

High resting HGH, low somatomedin. This patient showed an absolute lack of response to HGH in height though his skinfolds decreased, and increased again during the posttreatment year. The radiographs however showed little change in fat or muscle.

Psychosocial short stature (Group 8). All these 4 patients had their treatment in their usual home environment. None showed a significant acceleration in height. One only (8.2) showed a drop in skinfolds, followed by a posttreatment rise. This also showed in the x-rays, though there were no muscle changes. No. 8.4, despite his extremely low level of fat, showed a clear loss of fat in the limb radiographs on treatment, followed by a rise in the posttreatment year. He showed a slight increase in muscle velocity also.

Cases of uncertain diagnosis (Group 9).
No. 9.1 was accelerated by exogenous HGH from
3·7 cm/yr to 7·4 cm/yr and had a clear fall of skin-
folds despite having produced peak GH values on
hypoglycaemia and Bovril of 23 and 23 μU/ml
before treatment, and 14 and 18 μU/ml during the
coasting year. Presumably the diagnosis is partial
HS. No. 9.2 also showed a small but significant
height acceleration, and the limb width responses
were clear cut and of the HS type. Despite her
scapulohumeral muscular dystrophy, muscle width
velocity was increased, and fat width decreased
on treatment, and the reverse occurred in the post-
treatment year, the muscle velocity being actually
negative. No. 9.3 showed no height nor skinfold
response. There are no limb x-rays available.

Turner's syndrome patients (Group 10).
The 5 patients with Turner's syndrome who showed
no development of either breast or pubic hair
before or during HGH treatment had a mean pre-
treatment height velocity of 2·9 cm/yr, rising to
3·9 cm/yr during treatment (Table II). The post-
treatment mean velocity was 1·8 cm/yr. Thus an
acceleration averaging 1·0 cm/yr during treatment
was almost entirely cancelled by a posttreatment
regulatory deceleration amounting to about 0·6
cm/yr, leaving an overall trivial rise of 0·4 cm/yr.

Among the Turner's syndrome cases there were
no good examples of exceptional children who seem-
ed to respond, as there were among the LBWs.
The greatest acceleration was shown by 10.1, but
she had the greatest regulatory deceleration also.

Bone age velocity fell from 0·9 'years'/yr pre-
treatment to 0·6 'years'/yr during treatment,
followed by 0·4 'years'/yr after treatment. It
seems likely that these changes were independent
of treatment and represent the gradual falling
behind of bone age shown by these patients after
the age of 7 or 8.

Skinfolds showed no significant change.

Miscellaneous patients (Group 11). One
patient (11.2) with rheumatoid arthritis failed to
respond to HGH, even in doses of 60 IU/wk, while
on high doses of steroids, equivalent to 50 mg of
cortisone per day. In the other (11.1), 3 mg/day
prednisone did not prevent the height velocity
returning to normal levels when HGH was given,
though whether actually because of the HGH is not
certain.

The brother and sister with glycogen storage
disease did not increase their height velocity on
HGH. Their skinfolds fell slightly.

The patient with hereditary hypophosphataemia
did not significantly increase his velocity or de-
crease his skinfolds on HGH nor did the patients
with coeliac disease, whose GH responses to hypo-
glycaemia were normal.

Discussion

**Differential diagnosis of children with short
stature.** The chief difficulty in differential diag-
nosis is distinguishing between the HS, small/delay,
and psychosocial categories. Occasionally malab-
sorption is present with very little clinical history,
and full investigation, including jejunal biopsy,
may be imperative. Similarly Turner's syndrome,
especially if a mosaic, may be impossible to diag-
nose without a karyotype, and this should be done
in any girl who cannot be placed for certain in one
of the other categories. Hypothyroidism also may
be present without obvious clinical signs and should
be routinely excluded. The specific syndromes
(see Smith, 1970) for example De Lange's, and the
Prader-Willi syndrome sometimes are impossible
to rule out with certainty. To exclude low-
birthweight short stature requires the use of up-to-
date charts such as those of Tanner and Thomson
(1970). Even then doubt arises when one has a
child born early at a weight which is normal for
gestation; there seem to be some children whose
early birth is itself a symptom of intrauterine
damage, and these may constitute a group of
'Russell or Silver syndrome not small for (early)
dates'. Patient No. 6.1. (see p. 779) may be one
of these.

Many of the patients referred for differential
diagnosis of small stature fall in the category
small/delay. We prefer this terminology to any of
the existing ones. In particular we recommend the
total discontinuance of the word 'primordial'.
The current diagnosis 'delayed puberty' or 'con-
stitutional delayed puberty' obscures the fact that
in the great majority of cases the delay is present
not just at puberty, but throughout the whole of
childhood.

These children simply have a tempo of growth
which is *lentissimo*, for reasons not yet understood
(see Tanner, 1969). An example of such a patient
is No. 6.2 (Fig. 11). There is at present some
debate as to whether the level of GH reached on
stimulation is lower in these than in non-delayed
children (Frohman, Aceto, and MacGillivray,
1967; Kaplan *et al.*, 1968; Frasier, Hilburn, and
Smith, 1970); we cannot offer any firm evidence on
this point.

Patients with growth delay are nearly always
small for parental height, though they are within

normal limits for parental height if looked up at
their bone age, rather than their chronological age.
There are some patients in the small/delay category
however who are simply '*hereditary small stature*'
and have no delay at all. When looked up on
charts which allow for parental height these child-
ren are no longer small.

The distinction of growth delay from partial
HS depends on GH response; it may even be that
the two categories shade into one another, though
there is as yet no positive evidence for this. The
point is important, for if some or all small/delay
patients are suffering from partial GH deficiency,
as some experienced investigators in this field
believe, then they should respond to, and be given,
HGH. This is one of the still unsettled problems.

Differentiation of children with growth delay
from those with short stature due to psychosocial
problems can only be done by careful history and
observation, possibly by lack of GH response to a
test done in the home and ultimately by removal to
another environment.

The HS and LBW patients are usually distin-
guishable at sight (see Fig. 3), despite their similar
stature. Not only do the LBW usually have the
characteristic facial appearance and incurved short
fifth fingers, they are usually also very lean, and the
boys' genitalia are well developed. The HS boys
are usually fat and about half have maldeveloped
genitalia. GH levels rise to 20 μU/ml or over
after Bovril or in adequate insulin hypoglycaemia
in the LBWs, and stay below it in the HS patients.
Bone ages are usually much less retarded in the
LBWs, averaging $-1 \cdot 8$ SDS as opposed to
$-3 \cdot 2$ (Table II). Some LBWs actually have
advanced bone ages; no HS in our experience has
this, but a small proportion of HS patients have
bone ages just within normal limits. The cranio-
pharyngioma patients tend to resemble the HS.

**HS: diagnosis and aetiology: isolated versus
multiple deficiences.** In the early days of HGH
work it was supposed that most cases of GH
deficiency had a generalized 'hypopituitarism' with
all or most functions of the anterior pituitary
affected. We now realize that discrete deficiencies
of each hormone and of each releaser may occur
for metabolic, developmental, or other reasons.
In our clinic, in a paediatric hospital, isolated GH
deficiencies outnumber multiple ones. In Good-
man *et al*.'s (1968) series of non-tumour cases, 16
patients were classified as isolated, 7 GH- and
TSH-deficient, 4 GH- and ACTH-deficient, and
8 GH-, TSH-, and ACTH-deficient. ACTH lack
was diagnosed on a metyrapone test, TSH lack by

PBI level. In Prader *et al*.'s (1967) series, 8 out of 18
patients were given HGH alone, while 10 'needed
therapy . . . with thyroid preparations in substitu-
tion doses' during all or part of the treatment
period. But these authors add that this 'simul-
taneous treatment with thyroid preparations did
not enhance growth'. Trygstad (1969) gave
thyroid seldom and considered its use should be
avoided unless there was a clear indication for it.
Evidently different diagnostic criteria are being
used for TSH and ACTH deficiency in different
centres, and different thresholds are adopted for
treatment with thyroid. Goodman *et al*. consider
some of their patients developed thyroid deficiency
insidiously before and during treatment. We have
not treated any of our HS patients with thyroxine
and their growth responses are as good as or better
than others in the literature. Between the isolated
and multiple cases neither Goodman nor Prader
found any difference in pretreatment appearance.

We can offer no useful opinion on the question of
ACTH deficiency. Possibly as many as a third of
the HS patients had it, judged by the test used;
but this may not be entirely satisfactory, and these
patients responded just as well as the others and
have never shown any clinical signs of adrenal
deficiency. Soyka *et al*. (1970) found the same.

A deficiency of gonadotrophins cannot be diag-
nosed till puberty, and in our classification of HS
we make no distinction between those who will
and those who will not show this deficiency when
the time comes. Neither we nor anyone else has
reported enough cases of pubertal age to allow a
good estimate of the proportion of cases who fail to
show spontaneous puberty. Of the 10 HS patients
who have so far reached a bone age at which puberty
should have started, 6 have developed secondary
sex characteristics and 4 have not. (In terms of
chronological age puberty may occur late in the HS
patient, but that is only to be expected, since
maturational age is delayed.)

No less than 13 of our 35 HS boys had an
abnormally small penis and ill-developed scrotum,
something that has previously been remarked by
Laron and Sarel (1970) who found it in an even
higher proportion of cases. Goodman *et al*.
found it in only 4 out of 22 of their isolated plus
multiple deficiencies, and Prader, Trygstad, and
Soyka do not remark on its occurrence. We
suppose that the maldevelopment is due to lack of
androgen stimulation *in utero*, not of GH stimulation,
as Laron supposes. Why this should so often
occur in GH deficiency is not clear; perhaps there
is failure of gonadotrophin secretion also at this
time. It will be interesting to see what proportion

of maldeveloped patients have failure of pubertal development; so far 1 boy with small genitalia has developed a spontaneous puberty and 1 failed, while 4 with normal genitalia have entered puberty and 1 failed.

The predominance of boys over girls requires an explanation. In our HS cases the ratio of boys to girls was 29/6; in Prader's 11/4, in Trygstad's 14/8, in Soyka's 8/6, and in Grumbach and Kaplan's (1971) 62/28 (isolated 35/19 plus multiple 27/9). The average ratio is 2·3, but the variation between series is considerable. No adequate explanation of the difference has been proposed; it seems greater than could be accounted for by a generally higher male susceptibility to fetal and natal traumata.

In our 35 HS patients we had 2 children with affected sibs, but our total HS material comprises an additional 22 cases and in these there are 2 more sib pairs. Thus in all we had 6 children with affected sibs among a total of 57 children (10%). Among Trygstad's (1969) cases 8 out of 22 (36%), and in Soyka's (1970) 2 out of 14 (14%) had affected sibs, in Prader *et al.*'s (1967) 3 out of 15 (20%) had affected sibs or cousins, in Grumbach and Kaplan's (1971) 6 out of 54 (11%). The average incidence to date is thus about 15%. 4 of our HS patients had one parent below the 1st centile for height; the only one we tested in insulin hypoglycaemia had a normal GH level. Parental consanguinity was conspicuous by its absence, being remarked in only one of the sib pairs (Seip, van der Hagen, and Trygstad, 1968). Isolated GH deficiency in a parent and offspring has been described (Butenandt and Knorr, 1970; Tyson *et al.*, 1970) but is uncommon.

Prader *et al.* (1967) consider that birth trauma may play a considerable part in the aetiology of the non-familial cases. We have no evidence that it does so in our cases, though we must emphasize that our histories of pregnancy and labour are not good ones.

GH stimulation tests: partial and total GH deficiency. The GH stimulation tests distinguish the HS patients from the great majority of the others. The agreement between Bovril and insulin tests is as good as or rather better than that reported between insulin and arginine stimulation by Youlton, Kaplan, and Grumbach (1969) and others (Parker and Daughaday, 1968; Hillman and Colle, 1969; Root *et al.*, 1969). Youlton *et al.* reported 9 patients with normal arginine responses in whom little rise occurred after insulin, but the insulin tests of 6 of these failed to meet the criteria for blood sugar decrease that we exact. All our LBW patients tested reached peak values of over 32 μU/ml on insulin stimulation: we consider 20 μU/ml the lower limit for a normal response.

In HS patients there is a relatively high correlation of 0·64 between peak GH level after insulin and pretreatment height velocity SDS (calculated over a period of a whole year). A combination of the two measurements allows us, we think, to define a category of *partial GH deficiency*. Patients with this diagnosis have GH peak responses between 7 and 20 μU/ml inclusive, and height velocity SDS between −1·0 and −2·0. 'Total' GH deficiency patients have peak GH responses between 1 and 6 μU/ml inclusive and height velocity of < −2·0 SDS. The short-term metabolic response, though differing on average between partial and total groups, is less useful in discriminating individuals (Clayton *et al.*, 1971).

The diagnosis of partial deficiency was at first not accepted by workers in this field. Parker and Daughaday (1968) noted that patients they described as partially deficient accelerated on treatment significantly, but less than the totally deficient patients. We found the same; the first-year acceleration averaged 3·2 cm/yr per yr in comparison with 5·8 cm/yr per yr. Acceleration is strongly negatively related to pretreatment velocity and the partials' acceleration is simply in accordance with this regression (Fig. 13); their pretreatment velocity averaged 4·5 cm/yr compared with the total HS average of 3·0 cm/yr. Grumbach's group were very positive about partial deficiencies, saying that 'some short children who exhibit limited GH response . . . may have partial GH deficiency and exhibit a good therapeutic response to treatment with HGH' (Youlton *et al.*, 1969). Our results make us agree with this statement. Though a careful study of the year's pretreatment height velocity is an added help in diagnosis and prognosis, short children with GH responses between 7 and 20 μU/ml in principle merit a year's therapuetic trial with HGH.

We should not forget, also, that a child may be capable of producing GH on laboratory stimulation, but incapable of producing it during the normal course of his life. Such a child could in principle be made to grow by HGH. Our patient No. 9.1 may be one of these; on first testing he produced GH levels of 23 μU/ml to both insulin and Bovril, but grew at 7·4 cm/yr on treatment, as opposed to 3·7 cm/yr during the year before. There was no evidence of emotional disturbance and he was treated in the same environment.

Catch-up response to treatment; pretreatment and treatment height velocities. The shape of the height velocity curve in response to

treatment shows the familiar 'catch-up' phenome-
non (Prader, Tanner, and Von Harnack, 1963).
This is shown in Fig. 12 for the first year, and in
Fig. 19 for successive years of treatment.

One might imagine that the catch-up velocity,
or treatment acceleration, would be greater at
younger than at older ages. Such is the case, but
the correlation is very low (r = −0·25). The
treatment acceleration is much more closely
related to velocity before treatment (r = 0·58).
Presumably the slowest-growing children have the
least capacity to secrete GH; as the results of the
GH stimulation test indicate.

The craniopharyngioma patients had a pre-
treatment velocity at the level of the 'total' HS
patients (2·7 cm/yr, compared with 2·9 cm/yr).
They showed the same relation between pretreat-
ment and treatment velocities, but their absolute
response was less by an average of 2 cm/yr than
that of HS patients of similar pretreatment velocity.
Possibly this reflects limitations of cortisone or
thyroxine dosage, or some regulation factor not yet
understood. The tissue responses, of fat and
muscle, were also smaller.

Regulatory deceleration after treatment.
Children whose growth has been stimulated by
these relatively high doses of HGH may sink back
in the posttreatment year to levels of height
velocity below pretreatment, or at least to levels
below that expected if no treatment had taken
place. We have some evidence, not at present
conclusive, that this occurs.

There are 14 HS patients with pretreatment,
treatment, and posttreatment years completed,
and who showed no signs of puberty during the 3
years. (The 11 pure longitudinal cases of Fig. 15
plus 3 others absent at one or other visit.) Their
average velocities were 3·40 cm/yr before treatment,
8·09 cm/yr on treatment, and 2·20 cm/yr after
treatment. Thus the posttreatment velocity is
1·20 cm/yr below the pretreatment. Some de-
crease would have been expected however (see
methods), and with a pretreatment velocity of
3·40 cm/yr at the ages with which we are concerned
this may be estimated as about 0·5 cm over the
two years. Thus the 'regulatory deceleration'
might average about 1·20 less 0·5, that is 0·70
cm/yr.

There are 7 similar LBW patients, with velocities
averaging 6·23 cm/yr, 6·90 cm/yr, and 5·13 cm/yr
in the 3 years, giving a difference of 1·0 cm/yr
between pretreatment and posttreatment rates.
In this case the expected decrease is greater, both
because of the higher pretreatment velocities and

because the children are younger. It amounts to
about 0·60 over the 2 years, giving a regulatory
deceleration of 1·10 − 0·60 = 0·50 cm/yr.

We might suppose that the deceleration comes
about because endogenous GH production is
suppressed when exogenous GH is given, and
takes time to restart, as does steroid secretion in
patients treated with exogenous steroids. If so,
then the height velocity would be less in the first
6 months of the posttreatment year than in the
second 6 months. We can examine this in 10
non-pubescent HS patients; the mean velocities
are 1·95 cm/yr in the first 6 months and 2·18
cm/yr in the second. Though in the expected
direction the difference is not significant. In the 7
LBW patients the two means were 4·86 and 5·33
cm/yr, a difference of 0·45 ± 0·29. In 6 HS long-
term patients whose year off treatment followed not
one but four to seven years on continuous HGH,
the means were 0·07 cm/yr in the first 6 months off
treatment and 0·53 cm/yr in the second. In all
these 6-month comparisons seasonal effects are
minimal, the two periods concerned having on
average approximately the same height velocity
expectation.

It does seem, therefore, that a degree of regulatory
deceleration does occur, particularly in those child-
ren who are capable of secreting their own GH to
normal levels before being given exogenous GH.
Probably by the end of 6 months (and perhaps
earlier, we cannot say) the effect has worn off.

**Height response and bone age: influence on
adult height.** In treating short children with
anabolic steroids, or hypothyroid children with
thyroxine, one runs the risk of stimulating bone age
increase faster than height increase, and thus
ultimately stunting the child. We have no evi-
dence of this happening in any patient on HGH.
The ratio *height velocity in % expected/bone age
velocity in % expected* averaged 0·8 before treat-
ment in the HS patients, 1·7 during treatment, and
0·7 in the control year after treatment. In no
instance did bone age advance to be greater than
chronological age. Though bone age should
certainly be estimated at least annually during
HGH treatment, undue advance does not seem to
be a danger.

Muscle and fat response to HGH. The loss
of subcutaneous fat in HS patients given HGH has
been described by several authors. The very
considerable gain of muscle size, followed by loss
when HGH is withdrawn, is a newer and striking
finding, and confirms the results of Cheek *et al.*
(1966) who described an HGH-induced increase

in muscle by biopsy in a few HS patients. The gain is expected from much animal work, though the loss is more surprising. It seems that a steady secretion of GH is necessary to maintain muscle at a normal level of development, in the same way that exercise, and, in the male, testosterone are required.

We are investigating the possibility of making the radiographic estimate of muscle gain and fat loss into a short-term test for the effectiveness of HGH; it appears likely that a month of HGH should produce measurable changes.

GH and testosterone. It is said that GH and testosterone are both necessary for the normal male adolescent growth spurt to occur, and that their effects are either simply additive, or even multiplicatory (Prader *et al.*, 1964). Zachmann and Prader (1970) considered GH might not only be necessary for testosterone to produce a proper growth spurt but even for it to produce proper development of secondary sex characters. Illig and Prader (1970) suggested that testosterone might actually increase GH secretion, since the GH response to insulin hypoglycaemia was clearly greater in 6 testosterone-lacking patients after they had been given intramuscular testosterone for two days (see also Deller *et al.*, 1970; Eastman *et al.*, 1971).

We have at present only a small amount of evidence bearing on this point. We have given testosterone oenanthate 250 mg IM every 2 weeks from age 20·0 (BA 14·4) to 21·3 (BA 16·2) to patient 1A.35 who lacked GH. His growth rate averaged 6·2 cm/yr over this period, distributed 8·4, 11·9, 5·0, 3·0 cm/yr. His puberty ratings went from 1,1 to 5,5 and his bone age increased at 1·4 'years'/yr. This height response has the shape of a normal adolescent spurt, but is smallish in total. The pretreatment velocity was only 2·4 cm/yr however, and had it been at the normal level of about 4·4 cm/yr the spurt velocity should have been near average. This case thus favours the idea that GH and testosterone are indeed simply additive.

Another patient No. 1A.34, HS with antibody development, underwent a spontaneous puberty while on no treatment. In four successive years his height velocities were 7·8, 5·7, 3·8, and 1·7 cm/yr. This also is below average as an adolescent spurt.

A craniopharyngioma patient (2.9), not on substitution therapy, was given HGH when the adolescent spurt had just started, spontaneously (bone age 13·4, testes 8/8). During the ensuing year

his growth rate was 8·5 cm/yr with progression to bone age 14·5, testes 12/12. This is a perfectly normal spurt. During the subsequent year HGH was stopped and his velocity fell to 2·9 cm/yr which is less than expected even in a declining spurt. HGH was then again given, and during the subsequent year the growth rate rose again to 4·8 cm/yr, restoring the normal diminishing-spurt velocity. This case also points to the effects of GH and testosterone being additive.

Another craniopharyngioma patient (2·14), on 0·2 mg thyroxine and 12·5 mg cortisone daily, was given long-acting testosterone I.M. for a year from age 20·9 (bone age 13·1 and no sexual development). He had previously been on HGH for a year and grown at 7·4 cm/yr, compared with a control year of 2·8 cm/yr. During the first quarter of the testosterone year he was off HGH and grew at 3·2 cm/yr; in the second quarter he was on HGH and grew at 9·3 cm/yr; third quarter, off HGH and grew 2·6 cm/yr; fourth quarter, on HGH and grew 10·0 cm/yr. It seems that GH indeed was necessary in this patient for testosterone to produce a full growth effect.

It has been suggested that the administration of HGH may trigger the secretion of gonadotrophin (Goodman *et al.*, 1968) but the evidence for this is simply that adolescence in some cases began soon after HGH was first administered. A more likely explanation is that HGH caused completion of the preadolescent growth phase, and that at the usual bone age adolescence began normally.

Our results seem to indicate that in truly isolated GH deficiency HGH brings the patient to within normal height limits at the bone age (more truly, the real developmental point of which bone age is a fallible measure) characteristic of take-off for the adolescent spurt. A normal adolescent spurt then proceeds provided HGH is continued. In cases of added gonadotrophin deficiency, catch-up is the same until the take-off point has been reached, after which growth proceeds very slowly. Gonadotrophin or sex hormone should then be given, in conjection with the HGH. A final increase of around 10–12 cm in girls and 15–18 cm in boys may then be expected.

Developmental maturity and inability to respond to HGH. The data given above, plus those on the 2 HS patients, 1.30 and 1.31, who had relatively advanced bone ages at the beginning of treatment, give us some information, however regrettably insufficient, on the degree of developmental maturity at which patients run out of capacity to respond to HGH.

There are 2 girls with bone ages over 14·0 years (coupled with puberty ratings of 3,4 and 5,5) and both failed to respond. There are also 2 girls with bone ages of 13·7 (ratings 3,2) and 13·8 (ratings 1,1) who responded with treatment velocities of 6·3 and 5·2 cm/yr. The second, however, showed a considerable drop of velocity in her second treatment year. It seems that after a bone age of about 14·0 'years', a girl's ability to respond diminishes, probably rapidly. This is probably so whether or not she has developed breasts and pubic hair.

In boys there is clearly a bone age beyond which only androgens can induce further growth, but we have insufficient evidence to say what it is, or whether advance in puberty development is important or not; by analogy with the girls it should be 16·0 'years'.

Advanced chronological age in itself is no bar to response, for 2 longterm patients responded at ages 20·0 and 21·2 years, having bone ages of 12·6 and 12·7 'years'. Certainly the achievement or near-achievement of normal centile height status diminishes the response, and this even when the height being asymptotically approached is the preadolescent rather than the adult one.

HGH results in patients other than HS and craniopharyngioma. HGH seems to be without useful effect in LBW patients, with a few possible exceptions (see Fig. 22 for one). Since all our LBW patients produced high levels of GH on stimulation, one would expect this result. The doses of HGH we used did produce an 'acute' effect; they stimulated loss of fat, increase of muscle, and slightly increased height velocity during a period of 3 to 6 months. The effect had died away by the end of the treatment year, and was usually 'compensated' by a regulatory deceleration on the way.

Turner's syndrome patients also behave in this way, if they are affected at all.

The psychosocial patients are highly interesting in that they showed very little acceleration, despite being given HGH. Unlike the LBW and small/delay patients they were growing at HS rates; furthermore the most usual view for their lack of growth is that they switch off secretion of GH for emotional reasons. (The fact that often the GH response on test is normal, as in our patients, is explained by it being done in hospital, where the patients have switched on again.) If that were so, however, one would expect the exogenous hormone to produce results.

The one high resting HGH, low somatomedin child that we have seems a classical case (Laron, Pertzelan, and Mannheimer, 1966), though his parents are not related, nor are they Jewish. At first it was thought (Laron, Pertzelan, and Karp, 1968) that at least some of these patients grew in response to exogenous HGH, as well as showing an acute metabolic response, so it was supposed that they had an altered GH molecule. However our patient, while showing a loss of skinfold thickness, failed entirely to accelerate in height.

Dosage of HGH. The dose of HGH we usually used, 20 IU/wk, was about double that of other investigators and we have not varied it according to body size. Prader's (1967) group used 5 mg/m² surface area twice weekly, which amounts to about 6 IU/wk in an 8-year-old HS patient and 10 IU/wk in a 12-year-old HS. Trygstad used 4 IU/wk or 8 IU/wk according to weight, the change-over corresponding to an HS patient of around 10 years. Grumbach's group gave about 8 IU/wk and Soyka's 6 or 12 IU/wk. We used 2 injections per week, Prader 2, Trygstad 1 or 2, Grumbach and Soyka 3. The height responses obtained by these other investigators are equal to or slightly less than ours.

Six long term HS patients had their dose doubled to 40 IU/wk for 6 months at a time when their growth velocity had dropped to within normal limits. The average increase in velocity compared with that of the previous 6 months was 0·5 cm/yr. Such a comparison is rather fallacious for the reasons set out in 'methods', above; but it suffices to assure us that no great increase in velocity can be achieved by increasing the dose to above the 20 IU/wk we use at present.

We have little evidence yet with regard to the smaller dose of 10 IU/wk, but what we have suggests that it does induce a lower velocity than 20 IU/wk. The lowering is not by as much as half however, so the cost-effectiveness of the dose of 10 IU/wk might be greater. At present we are treating alternating patients with 10 and 20 IU/wk.

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Appendix: Case Histories

No. 6.1 presents a difficult *diagnostic problem.* Her photograph and growth chart are shown in Fig. A1. She is the fourth child of unrelated parents; the first- and third-born sibs are normal but the second-born, a boy, had a birthweight of 1·53 kg at 34 weeks' gestation and at age 8 was at 3rd centile for height. Mother had toxaemia during Linda's pregnancy and entered hospital at 34 weeks, where Linda was born by spontaneous breech delivery at 36 weeks with a birthweight −0·8 SDS, about 25th centile. Progress thereafter was good, except for smallness.

When seen at age 2·2 years her height SDS was −5·0, bone age SDS −4·7, skinfold SDS −1·1. She had a bossed forehead, snub nose with forward-facing nostrils, shark mouth, bushy eyebrows, and somewhat hypoplastic mandible. The right side of her thorax was larger than the left and the fifth fingers were incurved though not short. Her appearance somewhat suggested Turner's syndrome, and a radiologist looking at the skeletal survey noted, independently, that there were some features that suggested this diagnosis (incurving of radius, ulna, and fibula shafts, cone-shape epiphyses in the metacarpals). The karyotype from blood and skin however was 46XX. Her appearance and her skinfolds would also be consistent with LBW short stature, and there is evidence in the history of possible intrauterine damage. She may indeed be a child who, had she remained *in utero* to be born at 40 weeks, would have been clearly classifiable then as low birthweight. Her growth progress certainly resembles that of the LBW's. Her skinfolds have remained low, and were scarcely altered by treatment.

On the other hand, her GH response to a very adequate insulin hypoglycaemia was only 11 μU/ml and to Bovril 17 μU/ml, which should indicate she is a partial HS. Her pretreatment height velocity of +0·1 SDS is against this (the range starts at −0·9) and so is her skinfold value and her small response to treatment (Fig. A1). Her treatment velocity SDS is 2·5 (absolute acceleration of 1·8 cm/yr per yr): the partial HS range includes 2 patients with lower treatment SDS and in our LBW's are 2 patients with higher ones. A metabolic test failed because she was enuretic at age 6 (though not at age 8). She is normally intelligent. Her relation with her parents and sibs seems good, and she is not apparently depressed or anxious.

We have thus the following possible diagnoses: partial HS, intrauterine damage (a sort of 'failed LBW'), delayed growth, Turner's syndrome mosaic, psychosocial short stature. The last two seem unlikely. Probably a simple growth delay is the best single diagnosis, but it may be coupled with some degree of unresponsiveness to GH-releasing stimuli, and both may possibly be related to her intrauterine development. Her prognosis for final adult height is good; only further studies can show whether administration of GH will make it better.

Four psychological short stature patients. Patient No. 8.1 was little delayed in bone age, either at
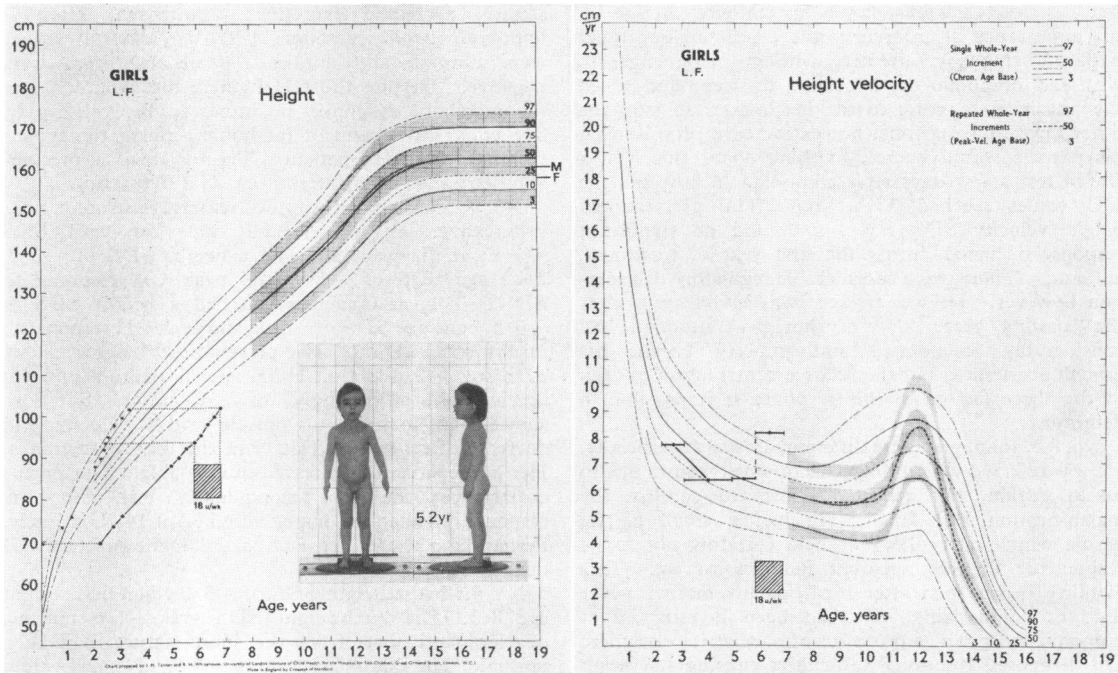
A1.—*Growth and response to HGH of Linda, of questionable diagnosis small/delay.*

diagnosis or beginning of treatment. His parents were relatively small, but he still had a height SDS of $-3 \cdot 2$ when this was allowed for. His skinfold SDS was $+0 \cdot 4$ and his pretreatment velocity SDS $-0 \cdot 7$. His skeletal survey was unremarkable and he had no signs or symptoms of malabsorbtion. His GH stimulation was done only in the coasting year, after treatment, and after two or three days in hospital. An insulin test, with a very satisfactory drop of blood sugar, produced a peak of 19 μU/ml, and Bovril 28 μU/ml. His nitrogen excretion decreased relatively little in the metabolic test. This boy's home situation is somewhat difficult. His mother complained that her husband 'doesn't care about children' and when the boy was aged $5 \cdot 3$ the husband left home. The child guidance clinic psychologist who saw John aged $8 \cdot 3$, with symptoms of aggressive behaviour and school failure, found him lacking in confidence and in need of treatment. On HGH, while at home, John's growth was hardly at all stimulated, the acceleration being $0 \cdot 1$ cm/yr, or, if allowance is made for the normal drop, about $0 \cdot 6$ cm/yr. It appears that he had a definite regulatory slow-down in his posttreatment year however. His diagnosis is in doubt, but probably he represents short stature from psychosocial causes. (In our previous paper, Clayton *et al.*, 1971, we had him classified as *small*; but he does have the same case number there.)

Patient No. 8.2, Teresa, was an adopted child. Her adoptive mother said she wanted a 'little doll' and kept Teresa babyish as much as she possibly could, by invent-

ing a weakness of the legs which prevented her walking upstairs to the toilet, for example, and a weakness of the arms which prevented her playing normally. When she was attending the clinic at age $8 \cdot 8$, she was still in nappies 'in case she wet herself' (she didn't). Teresa's 'mother' was aggressive, obsessional, and fussy, and barely hid a considerable dissatisfaction with Teresa under a cloak of maternal overprotection. 'Funny you get a child like this' she remarked in her presence, and later: 'she won't use school toilets or have school food'. Teresa never showed signs of being battered, but we would not have been surprised had she done so. She was one of the smallest for her age of all out subjects (height SDS $-6 \cdot 1$) with a considerable bone age delay also. Though her skinfold SDS was $-0 \cdot 3$, we thought she was a HS patient at first, but her insulin and Bovril GH responses done a few days after hospital admission, were 37 and 25 μU/ml. Her pretreatment height velocity SDS was $-1 \cdot 9$, and on treatment, while still in her home environment, her height velocity SDS was only $-0 \cdot 3$; the height acceleration was $1 \cdot 1$ cm/yr, or allowing for the expected drop of velocity about $1 \cdot 5$ cm/yr. She had a small decrease of skinfolds, however.

No. 8.3, Philip, also passed unrecognized as a psychosocial problem at first diagnosis, aged $9 \cdot 6$. He was then $-4 \cdot 6$ SDS in height for CA with a bone age SDS of $-5 \cdot 0$ and skinfolds SDS of $+0 \cdot 2$. He was noted to be small aged about 3; at 10, he had diarrhoea associated with Giardia infection but x-rays and tests for malabsorption were negative. He did well at school,

but was clearly anxious, as was his mother. At age 12, his appearance at interview was characteristic; quiet without being shy, attentive without being engaged, with sad immobile eyes. Alone, he wept and asked the physician to write to the headmaster to stop the other boys bullying him; but extracted a promise that his parents would be told nothing about this. In a Bovril test a few days after admission to hospital, the GH values reached 32 μU/mg. The pretreatment height velocity SDS was $-2\cdot0$, and no significant response occurred during the first year of treatment, at home. There was a considerable regulatory deceleration however. He was treated with HGH again after the coasting year. The psychological situation had considerably ameliorated and puberty began; his growth accelerated but the relative contribution of each of the three factors to this response is impossible to determine.

No. 8.4, John, was quite different, at least superficially. He was referred with a diagnosis of small stature due to malabsorption, but repeated efforts to confirm the malabsorption had failed. He had a small gastric hernia which our colleagues held certainly not to be responsible for his apparent inability to eat. This inability began soon after birth, as his mother never tired of emphasizing. He had been investigated at numerous hospitals: a professor of paediatrics elsewhere had diagnosed emotional difficulties causing starvation and short stature at age 5, but his psychiatric colleagues had believed the emotional difficulties to be the result and not the cause of the short stature. While this was still unknown to us, we diagnosed anorexia nervosa and sent the child for expert psychiatric help at the University Clinic near his home. Two psychiatrists both said the mother and child were stable and coping admirably with their difficult growth problem. On our repeated interviews the mother appeared aggressive almost to the point of being paranoid, and was at first very opposed to the idea of psychogenic causation. The child had something of the same depressed look as Philip and said little, even when alone. Aged 12·3 when first seen, he had a height SDS of $-6\cdot2$, a bone age SDS of $-2\cdot9$, the lowest skinfold SDS ($-2\cdot7$) we have ever recorded and a normal GH response to Bovril, following hospitalization. His pretreatment height velocity SDS was $-2\cdot5$ for BA and his treatment acceleration was nil. He is certainly suffering from starvation, though why is not clear.

Three cases of uncertain diagnosis. No. 9.1, with a birthweight SDS of $-1\cdot2$, had a height SDS of $-3\cdot7$, bone age SDS $-1\cdot7$, and skinfold SDS $-0\cdot6$. He was an only child, but the family seemed emotionally coherent. His pretreatment height velocity SDS was $-2\cdot4$. His GH response was 23 μU/ml to both insulin and Bovril on the initial occasion; and on a repeat during the coasting year 14 μU/ml and 16 μU/ml. In the metabolic test HGH caused only a very

slightly decreased excretion of nitrogen. His 17-hydroxycorticoid excretion, PBI, and skeletal survey were normal, and studies for malabsorption were negative. Despite the GH figures, the skinfolds, and the metabolic response, he increased his velocity by 3·7 cm/yr on treatment (at home), giving the typical response of an HS patient. The diagnosis is presumably partial or even intermittent GH deficiency.

No. 9.2 had known scapulo-humeral dystrophy, non-progressive. Her birthweight was low with SDS $-1\cdot4$; at diagnosis she had a height SDS of $-3\cdot5$, bone age SDS of $-1\cdot9$, and peak GH response to SDS $-1\cdot4$; at diagnosis she had a height SDS of $-3\cdot5$, bone age SDS of $-1\cdot9$, and peak GH response to insulin of 23 μU/ml. Her pretreatment height velocity SDS was $-2\cdot4$ and on HGH she showed a significant acceleration, surprisingly, of 2·1 cm/yr. She also showed an increase of muscle width velocity and decrease of fat width velocity in the limb radiographs. Her home situation appeared quite stable. During the coasting year she had a second insulin test, with peak response (on adequate hypoglycaemia) of 14 μU/ml only. Perhaps she also is a case of partial or intermittent GH deficiency.

No. 9.3 had a height SDS of $-5\cdot0$ when first seen at age 8·5. His birthweight SDS was $-1\cdot6$ but his development, apart from the short stature, had been normal. His skinfold SDS was $-0\cdot8$. No GH values were available. His pretreatment height velocity SDS was $-3\cdot1$, and his acceleration on treatment was 1·0 cm/yr, or, allowing for the natural decrease in velocity, about 1·5 cm/yr. Later, during puberty, he developed considerable bowing of the legs, resembling the situation seen in hereditary hypophosphataemia. However, his blood phosphorus had always been normal and there was no family history of short stature. Skeletal survey showed slight nonspecific deviations from normal and the radiologist reported some form of uncatalogued chondrodystrophy.

Appendix Table

The Appendix Table contains the following data for each individual patient: age, bone age, height, weight, height SDS, sitting height SDS, and skinfold SDS at initial diagnosis; birthweight, birthweight SDS, parents' height centiles and midparent height SDS, information on pregnancy and sib number; some clinical details; peak GH in insulin hypoglycaemia and Bovril, 17-hydroxycorticoid excretion, PBI; age and bone age at beginning of treatment, height velocity in pretreatment, treatment, and posttreatment years, both absolute and as SDS for chronological and for bone age, bone age velocities, and skinfold SDS at beginning and end of treatment. The complete table is available from the authors.

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