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Diagnostic and Prognostic Value of Short-term Metabolic Response to Human Growth Hormone in Short Stature

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Clayton, B. E., Tanner, J. M., and Vince, F. P. (1971). *Archives of Disease in Childhood*, **46**, 405. **Diagnostic and prognostic value of short-term metabolic response to human growth hormone in short stature.** Metabolic tests of the response to three days of administration of human growth hormone (HGH) have been done on 55 patients aged 6·2 to 20·3 years. 22 had 'isolated' growth hormone deficiency (or hyposomatotrophic short stature, HS), 16 CNS tumours or multiple hormone deficiencies, 6 short stature associated with low birthweight, 3 psychosocial short stature, 4 Turner's syndrome, 1 hereditary short stature, and 3 uncertain diagnosis. Height was measured at 3-monthly intervals for a full year, then HGH was given for a full year and the difference in rate, that is the acceleration during the growth hormone year, was calculated. The height measurements were all done by one measurer in 45 of the patients.

In the metabolic test there were 5 baseline days followed by 3 days of a single injection of 10 IU HGH, then 2 final days. The means for urinary nitrogen excretion, blood urea, and urinary calcium excretion were calculated for the 5 baseline days and for the last 2 HGH days plus the one subsequent day. The difference between the means is given as a percentage of baseline values.

The children with isolated growth hormone (GH) deficiency had a greater decrease in nitrogen excretion ($33\pm3\%$) than the low birthweight cases and small children ($7\pm5\%$), but there was overlap between individuals in the isolated deficiency group (range 12 to 66%) and the rest (range -12% to 42%); 2 deficient children were below a dividing line of 20%, and 1 Turner's syndrome and 3 psychosocial short stature children were above it. The tumour and multiple deficiency patients had an average fall of $40\pm3\%$ and showed no overlap with the low birthweight group. Blood urea and calcium excretion gave a worse separation. Within the isolated deficiency and the tumour and multiple deficiency groups there was no relation between any metabolic parameter and the amount of growth acceleration in the first year of HGH treatment.

In the HS, though not in the tumour patients, there was a correlation ($-0\cdot60$) between the decrease in percentage nitrogen excretion and peak GH level on stimulation and between per cent decrease in urinary nitrogen excretion and per cent decrease in blood urea ($0\cdot76$).

We conclude that the differential diagnostic value of the short-term metabolic test is very limited now that we have tests of GH response; and that in cases of isolated GH or multiple pituitary hormone deficiency the result of the metabolic test does not predict at all the height acceleration obtained on HGH treatment.

The acute effects of human growth hormone (HGH) on nitrogen retention in growth hormone-deficient patients were reported by Beck *et al.* (1958) and made into a systematic test for growth hormone deficiency in children by Prader and his colleagues (1964, 1968). The test is a short-term one, made under metabolic balance conditions, with one injection given daily for 3 to 6 days (depending

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on the various investigators). Metabolic balance studies in children, however, are difficult, expensive, and somewhat painful, and entail a hospital stay of about 3 weeks. Now that blood levels of growth hormone can be estimated directly the metabolic test should be avoided unless it really gives some useful additional information. The question therefore is whether the test helps in the differential diagnosis of children with short stature, and whether its results in a given child enable one to predict the long-term effect on growth of administration of HGH.

We present metabolic test data on 55 children and young people who have taken part in the Medical Research Council Clinical Trial of HGH. We conclude that the value of the test in differential diagnosis is very limited, and the value in prognosis within a specified diagnostic category is negligible.

Material and Methods

Results from 55 children and young people are presented in Table I. All patients have been treated for a year or more with HGH as part of the trial being carried out by the Medical Research Council Sub-Committee on Human Pituitary Hormones. Until recently it was a condition of the trial that patients had to have a metabolic balance before beginning treatment. In all, about 75 balances were done but a number have had to be excluded because of incomplete biochemical or growth data. From the methodological point of view, the 55 patients are divisible into three groups: 30 were studied by uniform methods at The Hospital for Sick Children, the growth hormone estimates and balances being done in the Department of Chemical Pathology and the growth measurements being made by one anthropometrist, Mr. R. H. Whitehouse. Since these patients constitute a methodologically homogeneous group they are placed separately in each section of Table I. Their case numbers, which are the same as those in the detailed report on their growth responses to HGH (Tanner *et al.*, 1971), are preceded by A (e.g. Case A1.1). The second group consists of 15 patients who were also all measured by Mr. Whitehouse, but who had their metabolic and growth hormone estimations done in several different hospitals throughout the United Kingdom. These are designated B in Table I, followed by their case number in the growth response paper. The third group consists of 10 patients, all of whom were measured and had balances at different hospitals; these are designated C1 to C10 in Table I.

From the point of view of diagnosis, 22 children had 'isolated' growth hormone (GH) deficiency or hyposomatotrophic (HS) short stature; all these were prepubertal throughout the period of study. 16 patients ('tumour' group) had either had craniopharyngiomas with a variety of pituitary deficiencies as a result (see replacement treatment in Table I) or had multiple pituitary deficiencies for other, usually unknown, reasons. 6 patients had low birthweight dwarfism, 4 Turner's syndrome, 3 psychosocial and 1 hereditary short stature, and 3 were of uncertain classification.

The blood GH levels in response to insulin hypoglycaemia (the blood sugar falling to less than 50% of fasting level and below 50 mg/100 ml) or to Bovril are given in Table I.

Growth response to HGH. Each patient was measured every 3 months for a minimum of a year before being given HGH. The average rate of growth over the pretreatment year was obtained by fitting a straight line to the five quarterly points (see Tanner *et al.*, 1971). Each patient was then treated with Raben-type HGH for one year, the dose varying from 12 to 24 IU/week given in two i.m. injections per week; most received between 18 and 24 IU/week. Quarterly measurements were made during the year, and average treatment velocity calculated as before. A year without hormone followed (incomplete in 20 cases). The height response is measured by the acceleration, calculated as the rate during treatment year less the rate during the pretreatment year. (This is a legitimate procedure, since at the ages, or more correctly at the bone ages, represented by our patients the normal velocity is dropping only very slightly.) An acceleration of 2·0 cm/yr (per yr) is a response significant at 2·5%; that is to say, only 2·5% of normal children of this range of bone ages have accelerations of this amount.

Ratings of sexual development were made, using the Tanner (1969) scales. In the patients who showed some degree of development the velocities have been placed in brackets in Table I and the ratings of genitalia or breast, and of pubic hair (2 beginning, 5 adult status) at the end of the year concerned have been printed above them.

Antibodies. Patients in Groups A and B had their blood tested for antibodies every three months as reported by Chalkley and Tanner (1971). Patients in Group C, as well as some in A and B, were tested by Dr. W. M. Hunter to whom our thanks are due. None of the patients reported here developed antibodies to a degree sufficient to interfere with growth response (see Chalkley and Tanner, 1971).

Metabolic balance: Group A. All metabolic balances were done shortly before the year's treatment began, the greatest interval being 3 months. With the assistance of the patient's mother, a diet was prepared similar to that which the child had been having at home. It often took several days before the optimum diet acceptable to the child was found, and this was used for at least 3 days before the balance began. Generally there were two menus which were used on alternate days and provided the same quantities of calcium, nitrogen, and calories. The diet was prepared in bulk and deep frozen before the balance began. The child

was encouraged to eat all the diet but there were occasional rejects which were returned to the diet kitchen. The daily intakes of calcium and protein were calculated taking into account the rejects.

Twenty-four-hour urine specimens were collected during a baseline period of 5 days, during 3 days on growth hormone, and for 2 days after the hormone. HGH was administered as a single dose of 10 to 12 IU intramuscularly at 10.00 a.m. on three consecutive days.

Blood or plasma urea was determined by a urease method on capillary samples obtained by finger-prick at 11.30 a.m. each day, the child last having had food at 8 a.m. Nitrogen was estimated by the standard micro-Kjeldahl procedure. Calcium was determined by flame photometry following dry ashing. Urine creatinine was determined by a standard picric acid procedure.

The mean values of blood urea, urinary nitrogen excretion, and urinary calcium excretion were calculated for the five days of baseline (a) and for the second and third day of HGH plus the first day after HGH (b). The percentage increase or decrease was calculated as the difference in percentage of the baseline figure, that is (b−a)/a.

In addition the mean excretions have been calculated for the 5 days consisting of the 3 days of HGH plus the next 2 days thereafter. The percentage increase or decrease over the baseline was again calculated. The results from these calculations were very close in all cases to those from the 3-day method and the conclusions from the two methods were identical.

Metabolic balance: Groups B and C. The balance procedure and methods of analysis in Groups B and C were generally the same as for Group A except that bloods for urea were taken fasting rather than after breakfast. In some diets calcium was artificially added and the intake was higher than for Group A. The chemical methods used were not uniform. Urinary nitrogen was determined by the Kjeldahl procedure usually manually but automated (Jacobs, 1968) for patients C6 and C9: for patients C4 and C7 a semi-automated method (Brown, Stimmler, and Lines, 1967) was used. Methods for calcium were diverse.

Results

The detailed results are shown in Table I, and the means for the three major groups of cases in Table II.

Height acceleration and metabolic results. All 22 HS children accelerated by over 2·0 cm/yr (per yr) on HGH and so did all tumour patients when we exclude those 4 who showed signs of puberty and who were nearing the end of their period of possible growth. The mean acceleration was 5·0±0·4 cm/yr (per yr) in the HS patients and 3·5±0·3 cm/yr (per yr) in the tumour patients. The extent of the first-year responses to HGH, however, could not be predicted from any of the three metabolic indices in either sets of cases (Fig. 1 to 3). The regressions of height acceleration

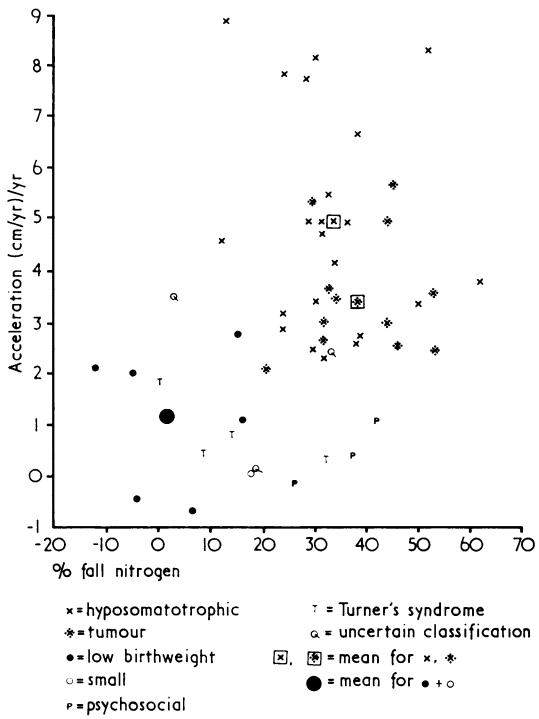

FIG. 1.—*Percentage decrease in the excretion of urinary nitrogen in response to HGH for three days compared with height acceleration during one year's treatment.*

were 0·00±0·03 and −0·02±0·03 on percentage decrease in nitrogen excretion, and −0·01±0·02 and 0·00±0·03 on percentage decrease in urea for the HS and tumour cases, respectively.

The peak GH value was no better a predictor of height acceleration either, the regression of acceleration on peak value in the HS patients being −0·08 ±0·15. In the pooled HS and tumour cases the regression was −0·07±0·14. However, the acceleration was significantly related to the pre-treatment velocity, the regressions being −1·00± 0·33 and −0·32±0·22 in HS and tumour groups.

Group differences of metabolic variables. The mean values for percentage fall of nitrogen excretion in the HS children (33±3) and the tumour patients (40±3) are significantly higher than the mean for the low birthweight and small stature (LBW) (7±5). The differences between the means of the HS and tumours do not quite reach significance (t = 1·7). There is a degree of over-

No.	Sex	Age When Therapy Began	Weight (kg)	Height (cm)	GH (I) (ng/ml)	Mean Daily Intake		Blood or Plasma Urea (mg/100 ml)	
						Calcium (mg/kg)	Protein (g/kg)	Base (II)	% fall
Hyposomatotrophic									
A1.4	M	6·2	12·9	95·7	3	59	2·5	37	32
A1.6	M	6·4	11·7	93·0	7	28	2·6	46	41
A1.9	M	7·3	14·8	91·1	6*	38	2·2	37	24
A1.10	M	7·7	12·6	91·9	3*	44	2·7	51	31
A1.12	M	8·2	13·6	107·8	—	47	2·2	39	41
A1.13	M	8·3	15·2	99·8	3	31	2·0	31	35
A1.14	F	8·5	14·1	98·3	6*	24	2·0	37	30
A1.16	M	8·9	14·8	101·9	6	65	3·2	41	41
A1.18	M	10·9	25·1	124·9	13, 11*	38	1·7	33	45
A1.22	F	12·2	17·4	110·9	6*	23	2·4	39	31
A1.24	F	12·6	25·0	116·4	5	31	1·7	42	38
A1.27	M	15·4	24·1	123·5	4	?16	?1·5	—	—
A1.28	M	15·8	20·0	110·6	9	25	2·7	—	—
B1.7	M	7·2	16·4	93·5	1	—	2·1	39	27
C1	M	10·6	15·0	103·0	7	—	4·0	22	27
C2	F	11·0	34·4	93·0	1	—	1·2	51	68
B1.20	M	11·7	20·0	119·2	6	—	2·6	36	28
C3	M	12·3	23·0	118·8	<2	—	2·2	—	—
C4	M	12·6	36·6	126·2	6	—	1·3	23	34
C5	F	13·2	15·0	102·3	3	32	2·6	34	56
C6	M	15·8	33·5	129·1	<1	—	1·9	45	51
B1.30	M	19·7	54·2	144·1	1	—	0·8	29	69
Craniopharyngioma (C) and other panhypopituitarism									
A2.8 (C)	F	16·1	36·6	145·4	6	15	0·8	24	50
A3.2	F	16·2	27·7	128·8	—	42	0·8	19	47
C7	F	10·5	21·4	106·7	—	—	2·3	—	—
B4.2	M	13·7	30·0	137·5	3	—	1·9	27	29
B2.4 (C)	M	14·3	28·0	133·9	<2	—	2·3	32	41
C8 (C)	M	14·7	27·5	130·2	<1	—	2·2	32	34
C9 (C)	F	14·8	36·0	139·0	<2	—	2·3	45	58
B2.7 (C)	M	15·4	29·8	126·6	1	—	2·0	—	—
B2.9 (C)	M	16·5	31·4	128·7	—	—	1·9	—	—
B2.10 (C)	F	16·9	39·5	144·7	—	—	1·9	22	36
B2.11 (C)	M	17·3	53·0	150·8	1	—	1·1	25	48
B2.14 (C)	M	17·9	41·8	144·5	<4	—	1·6	44	45
B2.15 (C)	F	18·2	39·2	146·3	6	—	2·1	29	52
B4.3	M	19·4	26·7	132·9	2	—	2·2	33	43
B4.4	F	20·1	30·5	143·0	<1	—	1·4	38	60
C10	M	20·3	39·0	140·8	<2	—	1·6	30	50
Low birthweight									
A5.5	F	5·8	10·6	94·8	>32	54	2·6	33	51
A5.7	F	7·3	16·1	104·3	31	22	1·9	32	25
A5.11	M	8·9	17·7	114·5	32	34	2·1	38	29
A5.15	M	12·3	22·8	128·1	34*	36	2·3	35	14
A5.17	M	13·7	26·5	133·0	>40	30	2·9	27	−14
B5.14	M	11·2	20·0	122·3	41	—	3·4	42	35
Small/Delay									
A8.1	M	6·2	16·3	101·7	32*; 16	53	2·5	42	26
Psychosocial short stature									
A8.2	F	7·8	12·5	92·5	37*	42	2·5	29	14
A8.3	M	13·1	21·4	119·3	32*	28	2·6	33	30
A8.4	M	13·3	12·5	106·4	37*	60	3·3	19	10
Turner's syndrome									
A10.1	F	7·6	15·9	103·2	40	50	3·1	33	57
A10.3	F	13·5	23·8	129·2	—	34	2·4	30	23
A10.4	F	15·5	26·4	119·4	—	16	1·5	21	9
B10.5	F	16·6	33·3	133·5	14	—	2·1	29	27
Uncertain classification									
A7.1	M	5·5	10·6	81·2	121	33	1·7	48	22
A9.1	M	7·3	14·0	100·3	23, 14	45	2·4	43	11
A9.2	F	7·9	11·2	102·3	32	51	2·3	21	19

(I) Blood growth hormone peak response (ng/ml) to insulin hypoglycaemia or *Bovril. (II) Mean excretion on 5 baseline days.
+ Metabolic balance done at 15·2 years. — Unknown, or, in 'other treatment' column, nil.
2,3,4,5, secondary sex character ratings (see text).

Urine Nitrogen (g/24 hr)		Urine Calcium (mg/24 hr)		Height Velocity (cm/yr)			Acceleration (cm/yr/yr) (e–d)	Other Treatment
Base (II)	% fall	Base (II)	% Incr.	Pre-HGH (d)	HGH (e)	Post-HGH (f)		
3·7	38	13	77	4·6	7·2	2·7	2·6	—
4·8	29	63	22	4·6	9·6	1·9	5·0	—
3·9	13	55	78	1·9	10·8	2·2	8·9	—
4·4	30	27	70	2·9	11·1	1·9	8·2	—
3·3	24	14	143	4·8	7·7	2·4	2·9	—
4·2	36	54	20	2·5	8·4	—	5·9	—
3·3	12	41	58	3·2	7·7	1·7	4·5	—
5·2	31	69	42	4·7	7·2	—	2·5	—
5·0	24	45	69	4·5	7·7	—	3·2	—
5·1	31	68	70	3·9	8·9	3·8	5·0	—
4·9	36	37	218	5·3	9·2	2·3	3·9	—
4·9	38	79	65	2·0	8·7	1·0	6·7	—
4·9	28	56	220	3·6	11·4	3·7	7·8	—
2·3	30	94	42	3·1	8·4	—	5·3	—
3·9	28	60	82	2·8	5·8	—	3·0	—
2·4	50	22	−18	2·5	10·9	—	8·4	—
8·0	30	126	27	3·1	7·9	—	4·8	—
3·3	51	95	31	4·2	7·6	—	3·4	—
5·5	31	—	—	5·7	9·1	—	3·4	—
4·1	24	36	67	1·5	9·4	—	7·9	—
8·3	36	83	69	2·1	6·2	—	4·1	—
8·7	66	148	85	2·8	6·5	1·2	3·7	—
4·3	53	19	68	1·6	4·1	—	2·5	T4
3·7	46	27	100	1·1	3·6	1·2	2·5	—
5·2	31	59	51	3·6	7·3	—	3·7	T4
5·7	29	44	100	3·1	8·4	2·5	5·3	T4 + cortisone
7·0	30	100	91	4·1	6·9	1·2	2·8	T4 + cortisone
2·6	57	83	44	2·2	5·7	—	3·5	—
10·1	47	71	100	1·5	4·5	—	3·0	T4 + cortisone
6·2	43	99	101	0·3	5·8	—	5·5	T4 + cortisone
4·5	48	96	112	$(6·4)^{2,2}$	$(8·5)^{4,4}$	$(3·0)^{4,4}$	$(2·1)^{4,4}$	T4 + cortisone
9·2	57	193	−26	$(1·8)^{3,4}$	$(1·0)^{3,4}$	$(0·6)^{4,4}$	$(-0·8)^{3,4}$	T4
6·8	21	210	68	3·7	5·7	—	2·0	T4 + cortisone
11·5	36	—	—	4·2	7·7	—	3·5	T4 + cortisone
6·7	29	194	30	$(0·1)^{5,5}$	$(0·9)^{5,5}$	$(0·2)^{5,5}$	$(0·8)^{5,5}$	T4
7·5	31	146	37	$(4·9)^{2,2}$	$(10·4)^{3,3}$	—	$(5·5)^{3,3}$	T4
5·7	42	61	130	0·4	5·4	—	5·0	Vasopressin
8·8	32	271	48	1·6	4·6	—	3·0	Vasopressin
4·4	15	41	32	5·5	8·3	5·1	2·8	—
4·0	−5	33	36	5·2	4·8	4·5	−0·4	—
5·3	7	29	41	6·0	5·4	5·2	−0·6	—
6·2	16	39	54	4·2	5·3	4·4	1·1	—
7·7	−5	79	−29	3·8	5·8	$(7·7)^{3,3}$	2·0	—
7·5	0	160	97	2·7	4·7	2·8	2·0	—
3·9	18	26	92	6·1	6·2	4·1	0·1	—
5·0	42	53	−17	4·2	5·3	—	1·1	—
6·9	37	24	83	4·0	4·3	2·4	0·3	—
3·8	26	83	16	3·4	3·3	1·4	−0·1	—
2·5	0	8	37	4·5	6·4	2·6	1·9	—
6·9	14	35	17	2·8	3·7	3·1	0·9	—
5·0	32	40	172	2·0	2·4	0·2	0·4	—
8·1	9	187	30	1·9	2·4	0·7	0·5	—
3·9	18	39	25	2·4	2·5	2·7	0·1	—
4·9	6	20	20	3·7	7·4	3·3	3·7	—
2·4	33	34	−15	3·7	5·8	2·1	2·1	—

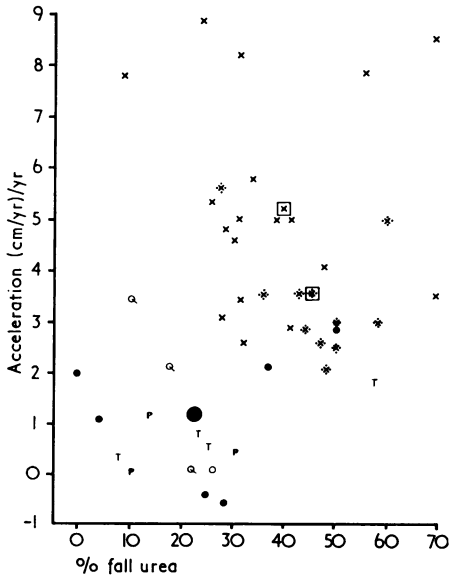

FIG. 2.—*Percentage decrease in blood or plasma urea in response to HGH for three days compared with height acceleration during one year's treatment.*

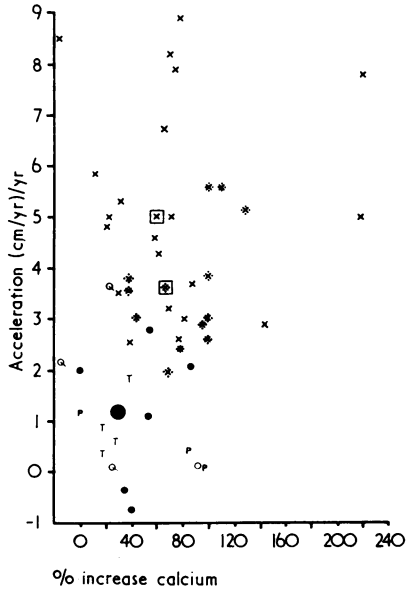

FIG. 3.—*Percentage increase in the excretion of urinary calcium in response to HGH for three days compared with height acceleration during one year's treatment.*

lap in the distributions of HS and LBWs; at the optimal dividing line of 20%, 2 HS children are misclassified. Both showed an excellent height response. At the same line, however, no tumour cases are misclassified, all having a fall of nitrogen excretion of over 20%. Tumour cases on cortisone (5 to 20 mg per day or equivalent) did not differ in nitrogen (or other) response from the remainder.

The means for percentage fall of blood urea are also significantly higher in the HS and tumour groups than in the LBWs. The tumour cases had a mean fall of 46% compared with HS mean of 39%, but this difference (which has $t = 1 \cdot 7$) may be due to nearly all the tumour cases having the basal values taken in the fasting state, while two-thirds of the HS were taken after breakfast. The mean fall of the 8 HS patients with fasting ureas (Groups B and C) was 45% compared with a mean fall of 35% for the non-fasting (Group A). The degree of overlap between HS and LBW groups is greater for urea than for nitrogen, and there are 2 subjects who overlap well into the tumour group range. Though the HS and tumour groups had a greater increase in calcium excretion than the LBW group, the differences failed to reach statistically significant levels, due to the very wide dispersion of values, especially in the tumour group, where the diets and metabolic procedures varied.

The three patients with psychosocial short stature had been in hospital a week or more before they were tested, which may account for their high levels. They retained as much nitrogen as the HS patients on the short-term test, but failed to grow much in height during the year of HGH treatment, perhaps because they returned home during that time.

Three of the 4 patients with Turner's syndrome showed little response in the metabolic test, and 3 (but not the same 3) had height accelerations under 1·0 cm/yr (per yr). The patient A6.1 suspected of lack of sulphation factor, had a nitrogen response of below 20% and patient A6.2, of unknown

TABLE II

Mean (+SE) of Metabolic Responses

	Hyposomatotrophic (22)	Tumours plus Multiple Deficiency (16)	Low Birthweight plus Small (7)
% fall nitrogen excretion	33±3	40±3	7±4
% fall urea	39±3	46±2	24±8
% increase calcium excretion	74±13	71±10	46±16
Acceleration of height growth (cm/yr (per yr))	5·0±0·4	3·5*±0·3	1·0±0·5

*Excluding 4 patients showing signs of puberty.

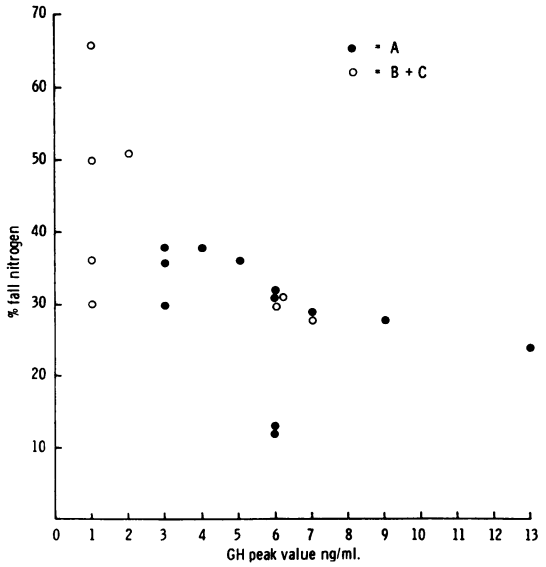

FIG. 4.—*Relation between percentage decrease in nitrogen excretion on metabolic test and peak GH level on stimulation: HS children: Group A solid dots, Groups B and C open circles.*

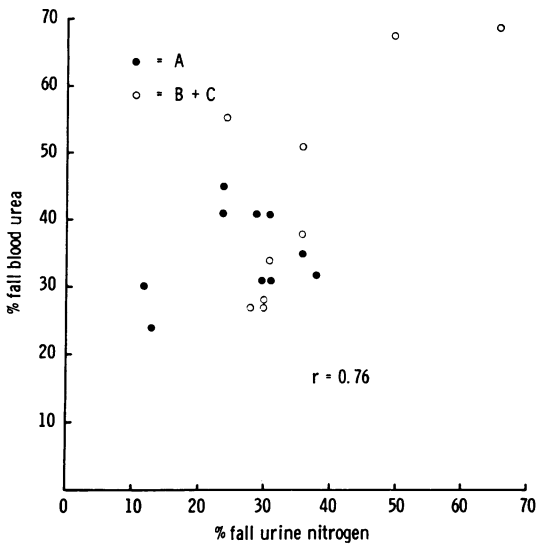

FIG. 5.—*Relation between percentage decrease in nitrogen excretion and percentage decrease in blood urea: HS children: Group A solid dots, Groups B and C open circles.*

diagnosis, showed no metabolic response, but did accelerate in height.

Relation between test variables. Within the HS group there was a considerable negative correlation between the peak GH values and the percentage nitrogen decrease ($r = -0{\cdot}60$, $b = -2{\cdot}38 \pm 0{\cdot}74$, nitrogen on GH) (Fig. 4). This presumably reflects the fact that some of these patients are really more deficient than others. In the tumour group no such correlation existed ($b = -0{\cdot}33 \pm 1{\cdot}8$) either because the GH values are all so low (in the calculation the <2 and <1 values have been taken as 1), or because the estimations have the disadvantage of being made in a number of different laboratories.

Within the HS group there was also a positive relation between the urea and the nitrogen values ($r = 0{\cdot}76$, $b = 0{\cdot}71 \pm 0{\cdot}14$, nitrogen on urea). In those 7 HS cases whose urea was taken fasting, the correlation was 0·91, which on the small numbers available is insignificantly different from 0·76 (Fig. 5). In the tumour cases, however, the correlation was negligible being $-0{\cdot}13$ with $b = -0{\cdot}16 \pm 0{\cdot}40$.

There is, however, no significant relation between pretreatment velocity and level of GH or percentage decrease of nitrogen excretion. There was no correlation between percentage calcium increase and the other two variables in any of the diagnostic groups. No correlation was apparent, either, between protein intake, expressed as g per kg/body weight and percentage decrease in nitrogen excretion within any diagnostic group. To exclude the possibility that a threshold effect might have occurred in patients with the lowest protein intake we examined the 7 patients (HS and tumours) with intakes of less than 1·5 g/kg. These had nitrogen decreases of 21, 42, 46, 50, 51, 53, and 66%; thus there is no evidence that variations in the diet affected the metabolic responses.

Discussion

The acute metabolic response is a laborious, expensive, and somewhat traumatic test. It was introduced as an aid to the differential diagnosis of children with short stature before the blood GH responses to stimulation by insulin hypoglycaemia, arginine, and Bovril were available. Some investigators also thought that it might be a guide to prognosis, and might indicate the degree to which the patient would respond in growth when given long-term treatment with HGH. We have to discuss these two uses separately.

Use in diagnosis. Prader *et al.* (1968), giving 5 days of 2 mg/m^2 Raben HGH, found that 17

hypopituitary children (3 with operated craniopharyngiomas and 14 with isloated GH or multiple hormone deficiencies) averaged a 38% decrease in nitrogen excretion compared with 16% for children with normal stature or short stature of non-endocrine origin. There was a small overlap in the distribution, however, 2 children being misclassified on this criterion. Brown *et al.* (1967), using 5 days of 10 IU Raben HGH, obtained separation between 10 children with 'clinical and biochemical evidence of hypopituitarism', who averaged 46% fall in nitrogen excretion (range 35%–52%) and 12 children with low birthweight or other non-endocrine cause of short stature, who averaged (counting two negatives as zero) 10% fall (range 0 to 23%). Melvin *et al.* (1967) had a small overlap on a 6-day test between similar groups of patients, and the figures of Wright *et al.* (1965) also show a little overlap.

Our own values agree closely with Prader's; the range in fall of nitrogen excretion in our 22 HS children was 12% to 66%, overlapping with the range of −5% to +18% given by one small and 5 low birthweight children. A division at the optimum of 20% gives 2 of the first group wrongly classified. The range in our 16 tumour and multiple deficiency patients was 21% to 57%. In short, the results of the metabolic test add nothing to the results of the GH determinations; in only occasional instances of confusion over diagnosis, e.g. our psychosocial cases, are they likely to be of any value.

Our finding that the peak GH response is fairly well correlated with the decrease in percentage nitrogen excretion in HS children seems to be a new and in a sense satisfying one, as in the high correlation between the acute responses in blood urea and in nitrogen. In the tumour cases these relationships no longer hold, perhaps because of the diversity and complexity of the patients and their other treatments. The degree of metabolic and GH response is not significantly related to height velocity before treatment in either HS or tumour patients.

The differential diagnosis of children with small stature still presents a problem, as Youlton, Kaplan, and Grumbach (1969) have most clearly shown. In 60 patients on whom both insulin hypoglycaemia and arginine stimulation tests were done, 23 had either equivocal values on both tests (3 to 7 ng/ml peak) or else disagreement between the tests. These investigators write, 'Some short children who exhibit limited growth hormone response to both insulin-induced hypoglycaemia and arginine may have partial growth hormone deficiency and exhibit a good therapeutic response to treatment with HGH.' Our experience (Tanner *et al.*, 1971) seems to confirm this. They also write that these perhaps partially GH-deficient children, 'can be distinguished by their growth response to long-term HGH administration but the short-term nitrogen retention test is of little value' (i.e. in individual diagnosis). The findings reported in the present paper support this opinion.

Use in prognosis. In discussing prognosis we have to consider the relation between first-year height response and nitrogen retention among children all with the same diagnosis. If we mix up diagnoses, then of course the low birthweight children with little decrease in nitrogen excretion grow less than the HS and panhypopituitary patients with a greater decrease in nitrogen excretion, and a correlation is established simply because of confounding the groups; not all authors have realized this.

Our own data show no significant relation between first-year acceleration and any of the metabolic parameters, either for the HS or tumour patients or the children with low birthweight. Again, our experience agrees with that of Prader *et al.* (1967) who, concerning 9 HS children, wrote, 'The N-retention measured in the metabolic HGH test has no prognostic value . . .'. Wright *et al.* (1965) found the same.

This is not really surprising. The immediate response, even in growth rate, may be great at first, but subsequently reduced by whatever factors underlie the 'catch-up' growth phenomenon. Some children will have a growth curve which rises very steeply but soon levels off; others a curve which rises less steeply, but levels off less abruptly. Henneman *et al.* (1960) in one of the first papers on the metabolic effects of HGH, showed that nitrogen retention was maximal on the third to sixth day of administration and by the end of 30 days' administration it was very small. Prader *et al.* (1968) make the same point. We must conclude that the time scales of the conventional metabolic test and the therapeutic trial response are too different for one to throw light on the other.

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