

Metabolic Effects of Human Growth Hormone in Corticosteroid-Treated Children

HELEN G. MORRIS, JACQUELINE R. JORGENSEN, HAROLD ELRICK, and
RICHARD E. GOLDSMITH, with the technical assistance of VIBART L. SUBRYAN

*From the Department of Medicine, Veterans Administration Hospital,
University of Colorado School of Medicine, and Children's Asthma
Research Institute and Hospital, Denver, Colorado; Metabolic
Laboratories, Cincinnati General Hospital, Cincinnati, Ohio.*

ABSTRACT The effects of administered human growth hormone (HGH) were evaluated in dwarfed, prepubertal children who were receiving long-term corticosteroid therapy for a chronic disease. During 11 complete metabolic balance studies, the eight corticosteroid-treated children demonstrated impaired response to large doses of HGH with minimal nitrogen and no phosphorus retention. In contrast, two hypopituitary subjects and two asthmatic children not receiving corticosteroid responded to the same preparations of HGH with nitrogen, potassium, and phosphorus retention. Six corticosteroid-treated children were given large doses of HGH (40–120 mg/wk for 4 to 8 months and showed no improvement in their retarded rate of growth, whereas the hypopituitary subjects showed accelerated growth during administration of 10–15 mg of HGH/wk. It is concluded that dwarfism in steroid-treated children results from corticosteroid-induced antagonism of the effects of HGH at the peripheral tissue level.

INTRODUCTION

One of the more distressing features of long-term corticosteroid therapy of children is the resultant

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Address requests for reprints to Dr. Helen G. Morris, 1055 Clermont Street, Denver, Colo. 80220.

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inhibition of growth (1). The present study was undertaken to obtain further information about the relationship of human growth hormone (HGH) to this form of dwarfism. Response to HGH was evaluated during complete metabolic balance study and during prolonged administration to children who were receiving corticosteroids for a chronic disease and who exhibited growth retardation as a result of corticosteroid therapy (2–4).

METHODS

Patients. The corticosteroid-treated group consisted of eight children who were 2 or more standard deviations below normal in height. Most of the children showed minimal evidence of Cushing's syndrome other than growth retardation. Prepubertal subjects were selected so that any response to HGH would not be confused with an adolescent growth spurt. Six children were receiving corticosteroids for intractable asthma, one for rheumatoid arthritis, and one for the nephrotic syndrome. The asthmatic subjects were drawn from the patient population of the Children's Asthma Research Institute and Hospital where previous studies have shown that growth retardation is directly attributable to corticosteroid therapy, since steroid-treated children show more severe growth inhibition, despite better control of asthma, than the nonsteroid-treated children (3, 4). The metabolic effects of HGH during 11 studies of the corticosteroid-treated patients were compared with those of two children with panhypopituitarism and two asthmatic children not receiving corticosteroid. The pertinent clinical features are summarized in Table I.

Metabolic balance studies. During a prolonged pre-study observation period, and during both the acute balance and the long-term phases of the study, corticosteroid (prednisone) dosage was maintained at a constant level

TABLE I
Clinical Data on Subjects for Metabolic Balance Study

Patient	Sex	Age	Diagnosis	Height, deviation from mean	Steroid dose	Fasting HGH <i>μg/ml</i>
P. L.	M	12	Asthma	-2.2 SD	Prednisone, 5 mg b.i.d.	8.5
J. O'N.	M	12	Asthma	-2.6 SD	Prednisone, 5 mg q.i.d.	14
C. B.	F	12	Asthma	-4.4 SD	Study 1, no steroid Study 2, prednisone 2.5 mg t.i.d.	6
J. S.	M	12	Asthma	-3.7 SD	Prenisone, 2.5 mg t.i.d.	1.5
M. K.	F	12	Asthma	-3.4 SD	Prednisone, 5 mg b.i.d.	4.2
K. K.	M	13.5	Asthma	-4.0 SD	Prednisone, 5 mg t.i.d.	<1
M. P.	F	12	Rheumatoid arthritis	-5.5 SD	Prednisone, 5 mg t.i.d.	
C. W.	F	8	Nephrosis	-4.0 SD	Prednisone, 5 mg q.i.d.	10
E. L.J.	M	12	Asthma	-2.2 SD	None	5.0
D. H.	M	18	Panhypopituitarism		None	<1
J. M.	F	16	Panhypopituitarism		None	<1

and was the minimum required by each child at the beginning of the study for control of symptoms. Children were hospitalized in the Clinical Research Center of the University of Colorado Medical School for complete metabolic balance studies which were carried out by standard balance techniques. Each study consisted of an 8 day stabilization period, an 8 day pre-HGH control period, 8-12 days of HGH administration, and an 8 day post-HGH period. Throughout the study, urine was collected in 24-hr pools and stools in 96-hr pools. Children received a constant diet of their choice. Food was eaten under observation of the dietitian, and there were no returns or refusals (except by patient J. M. whose returns were analyzed and during study I by patient C. B. who managed to hide some food). Most of the balance studies were performed on two children simultaneously to provide an additional check on the technical aspects of the study.

HGH (Elrick) had an activity of 1.0 USP unit/mg (5, 6), as demonstrated by rat tibia bioassay. The hormone was dissolved with several drops of 0.1 N NaOH and diluted with normal saline; fresh solutions were prepared every 48 hr. HGH was administered daily by intramuscular injection in a volume of 1 ml preceded by 0.4 ml of 1% procaine hydrochloride given through the same needle (7). During the pre-HGH control period, children were given placebo injections of procaine followed by normal saline. HGH dosage for the children with hypopituitarism was 5 mg/day. Preliminary observations suggested that steroid-treated children were unresponsive to HGH doses of 10 mg/day. Therefore, steroid-treated children received several consecutive 4-day periods of HGH administration during which the dose was progressively increased from 10 to 30 mg/day in an attempt to achieve a dose of HGH which would be metabolically effective.

Methods of analysis. Specimens were analyzed for nitrogen by the micro-Kjeldahl method (8), calcium by

atomic absorption (9), phosphate by the method of Chen, Toribara, and Warner (10), sodium and potassium by the flame photometer, and chloride and creatinine by the AutoAnalyzer (11, 12). For some of the studies (M. P., E. L.J., D. H., J. M.) intake was determined by analysis. In the remaining studies intake was determined by calculation from standard food composition charts (13, 14). Studies in our laboratory have indicated excellent agreement between analyzed and calculated diet composition with the exception of phosphorus content where analysis consistently yields slightly higher values than those determined by calculation.¹

Metabolic balance was calculated for each substance and was compared with theoretic balance (15). The results of the balance studies are charted according to the method of Reifenstein, Albright, and Wells (16), with intake plotted down from the zero line and excretion plotted up from the intake line. Positive metabolic balance is indicated by a clear zone below the zero line and negative balance by excretion above the zero line. Nitrogen, phosphorus, and calcium balances are plotted on scale, according to their ratios in normal body composition; potassium balance is not on this scale.

Long-term effects of HGH. After completion of the metabolic balance studies, six steroid-treated children were given prolonged courses of HGH. Steroid dosage was maintained at a constant level, and HGH was administered intramuscularly 2 or 3 times a wk for 4-8 months at a total dose of 40-120 mg/wk. In contrast, the hypopituitary subjects received 10-15 mg of HGH/wk (in 1-2 injections). Initially, a week's supply of HGH was prepared at one time. Later each dose was dissolved immediately before injection. Children were seen weekly for measurement of height and weight and for observation of any untoward effects of the HGH or change in the pattern of their disease.

¹ Unpublished observations.

Assay of endogenous HGH concentration. Fasting plasma samples obtained during the control phase of the balance studies were stored in the freezer and later analyzed for endogenous HGH concentration by the Glick, Roth, Yalow, and Berson radioimmunoassay (17).

RESULTS

Metabolic balance studies. Fig. 1 illustrates the results of a metabolic balance study during which HGH (preparation E-54) was administered to a child with hypopituitarism at a dose of 5 mg/day. It can be seen that HGH resulted in nitrogen and potassium retention in association with marked phosphorus retention. The responses continued throughout the 12 day period of HGH administration and are similar to those reported in hypopituitary patients with other preparations of HGH (18-22). This study, published previously (7), is included here for comparison with the effects observed in steroid-treated children.

Fig. 2 illustrates the response observed when the same preparation of HGH (E-54) was administered in doses of 10 and 20 mg/day to an

asthmatic child (P. L.) who was receiving 10 mg of prednisone daily. Despite administration of HGH at 2 and 4 times the dose found to be metabolically effective in the child with hypopituitarism, the steroid-treated child showed minimal nitrogen or phosphate retention and rapid rebound excretion after termination of HGH. Detailed balance data are given in Table II A.

Fig. 3 demonstrates even less response when the same preparation of HGH (E-54) was administered simultaneously to another asthmatic child (J. O'N.) who was receiving 20 mg/day of prednisone. In this study (see Table II B) there was minimal response to HGH with return to control excretion during the short period of hormone administration. Despite a 1700 calorie diet containing 80 g of protein, the child was in negative metabolic balance. During a previous study, he received a higher calorie diet and maintained positive metabolic balance, but he showed a similar poor response to HGH.

Fig. 4 illustrates the response to a different

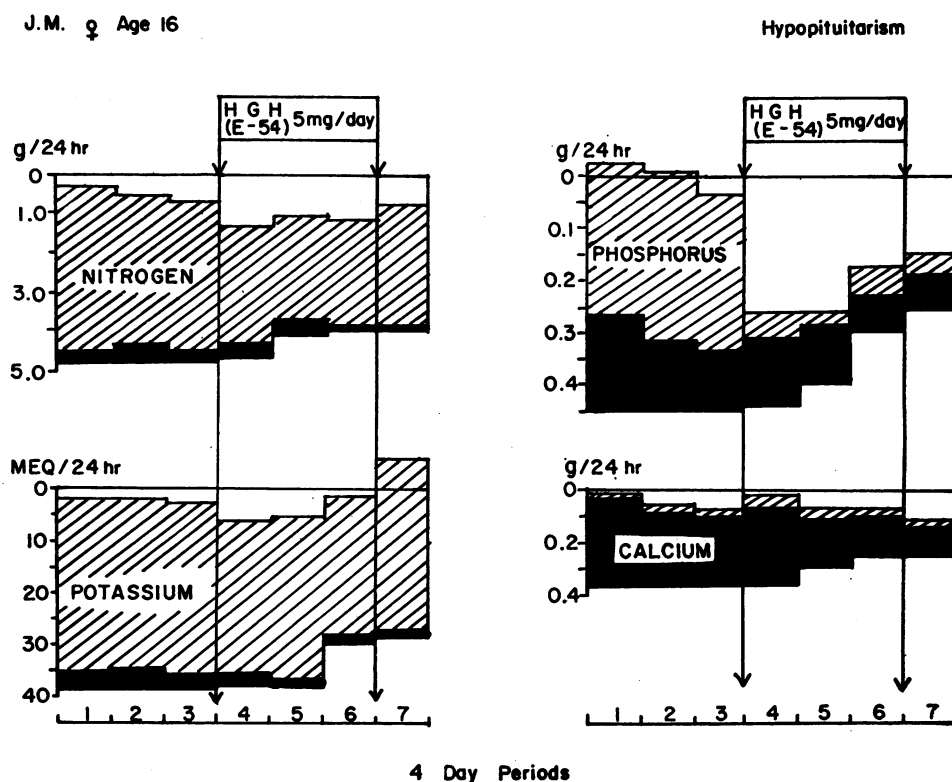


FIGURE 1 Metabolic effects of HGH (E-54) in a hypopituitary subject. In this study, as in all balance studies to be shown, results are plotted according to the method of Reifstein, Albright, and Wells (15).

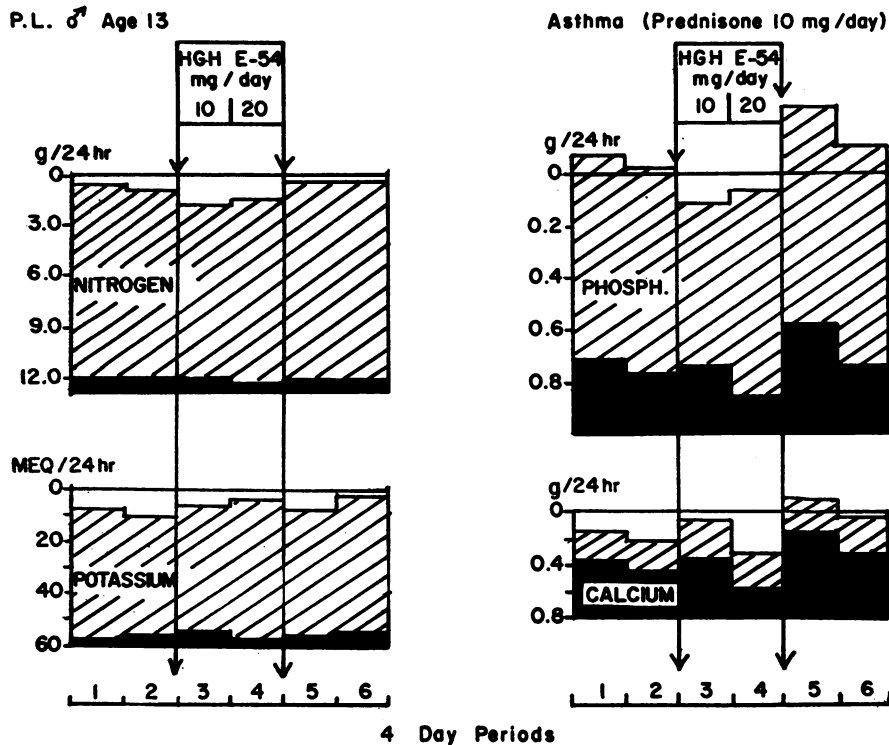


FIGURE 2 Metabolic effects of GHG (E-54) in an asthmatic child receiving 10 mg of prednisone daily. Note that because of the larger dietary intake, the scale used for plotting the balance results is different from that of Fig. 1. Analyzed phosphorus retention is slightly less than theoretic balance during the control period and equal to theoretic balance during first GHG period.

preparation of GHG (E2P2) when administered in doses of 10, 20, and 30 mg/day to a child (M. K.) receiving 10 mg of prednisone daily. The child was in positive metabolic balance during the control period. GHG produced an increase in nitrogen and potassium retention and in urinary calcium excretion. It can be seen, however, that the nitrogen and potassium retention were associated with paradoxical decrease in phosphorus retention, because of increase in both stool and urinary phosphorus. The negative calcium balance during GHG administration also resulted in part from paradoxical increase in stool excretion. The balance study carried out simultaneously in patient K. K. was similar to that shown in Fig. 4 and listed in Table II C.

The effect of steroid on calcium and phosphorus balance during GHG administration is further demonstrated by the responses of C. B. (Fig. 5). In the first study, shown on the left, the child was not receiving steroid and had severe asthma. This

study was not entirely satisfactory because of difficulties with food intake. The second study, shown on the right, was performed several months later while the child was receiving 7.5 mg of prednisone daily, and her asthma was well-controlled. In both studies, GHG caused retention of nitrogen and potassium but there was less retention during steroid administration. When the child was not receiving steroid, GHG administration resulted in phosphorus retention and growth during the course of the balance study. When she was receiving steroid, GHG administration resulted in decreased phosphorus retention, and growth did not occur. It can be seen from the figure that phosphorus intake was comparable during the two studies and that steroid therapy alone was associated with increased stool phosphorus. When the child was under the influence of GHG and steroid, there was a further marked increase in stool phosphorus and negative phosphorus balance. During steroid therapy, a similar paradoxical increase in

TABLE II
Effects of HGH on Metabolic Balance during Corticosteroid Treatment

	Dates	Treatment	Nitrogen			Phosphorus			Calcium			Potassium						
			Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
			g/day	mg/day	mg/day	g/day	mg/day	mg/day	g/day	mg/day	mg/day	g/day	mg/day	g/day	mg/day	mg/day	g/day	mg/day
A. P. L. age 13 M prednisone 10 mg/day	10/16-10/20	Control	12.5	11.2	0.7	+0.6	1010	798	281	-69	709	139	409	+161	62	51	2	+9
	10/20-10/24	Control		11.0	0.7	+0.8		780	244	-14		114	370	+225		47	3	+12
	10/24-10/28	HGH, 10 mg/day		10.1	0.7	+1.7		640	263	+107		161	484	+64		53	4	+5
	10/28-11/1	HGH, 20 mg/day		10.7	0.3	+1.5		800	145	+65		166	215	+328		57	1	+4
	11/1-11/5	Control		11.6	0.7	+0.2		863	422	-275		145	654	-90		51	3	+8
B. J. O'N. age 12 M prednisone 20 mg/day	11/5-11/9	Control		11.6	0.7	+0.2		846	256	-92		127	519	+63		56	4	+2
	10/16-10/20	Control	13.0	12.7	1.6	-1.3	1038	973	222	-157	603	303	343	-43	68	45	9	+14
	10/20-10/24	Control		11.7	1.8	-0.5		920	452	-334		229	488	-114		44	15	+9
	10/24-10/28	HGH, 10 mg/day		10.7	1.5	+0.8		738	259	+41		310	319	-26		41	8	+19
	10/28-11/1	HGH, 20 mg/day		12.0	1.2	-0.2		1000	241	-203		323	363	-83		60	7	+1
C. M. K. age 12 F prednisone 10 mg/day	11/1-11/5	Control		13.3	1.4	-1.7		1010	223	-195		286	330	-13		54	5	+9
	11/5-11/9	Control		11.9	1.4	-0.3		975	223	-160		310	330	-37		45	5	+18
	3/16-3/20	Control	15.7	13.3	0.6	+1.8	1602	930	551	+121	1300	159	917	+224	73	85	7	-19
	3/20-3/24	Control		13.5	0.7	+1.5		777	505	+320		162	779	+359		70	6	-3
	3/24-3/28	HGH, 10 mg/day		11.0	1.3	+3.4		855	651	+96		251	960	+89		48	7	+18
D. C. B. age 12 F study 2 prednisone 7.5 mg/day	3/28-4/1	HGH, 20 mg/day		10.6	0.5	+4.6		863	672	+67		293	1064	-57		55	2	+16
	4/1-4/5	HGH, 30 mg/day		10.1	0.9	+4.7		1030	658	-86		241	1126	-67		54	7	+12
	4/5-4/9	Control		12.1	0.8	+2.8		1017	666	-81		154	1036	+110		61	3	+9
	4/9-4/13	Control		13.3	0.8	+1.6		915	424	+263		91	658	+551		56	8	+9
	1/10-1/14	Control	13.1	11.0	0.5	+1.6	1576	485	672	+419	1611	137	1097	+377	71	61	6	+4
	1/14-1/18	Control		10.1	0.5	+2.5		539	596	+441		151	1132	+328		55	6	+10
	1/18-1/22	HGH, 10 mg/day		10.2	0.4	+2.5		361	1226	-11		186	1364	+61		52	7	+12
	1/22-1/26	HGH, 20 mg/day		10.1	0.5	+2.5		97	1224	+255		147	1493	-29		53	5	+13
	1/26-1/30	Control		11.1	0.6	+1.4		144	1095	+337		118	1297	+196		59	5	+7
	1/30-2/3	Control		11.6	0.6	+0.9		87	1075	+414		123	1331	+157		61	5	+5

J. O'N. ♂ Age 12

Asthma (Prednisone 20 mg /day)

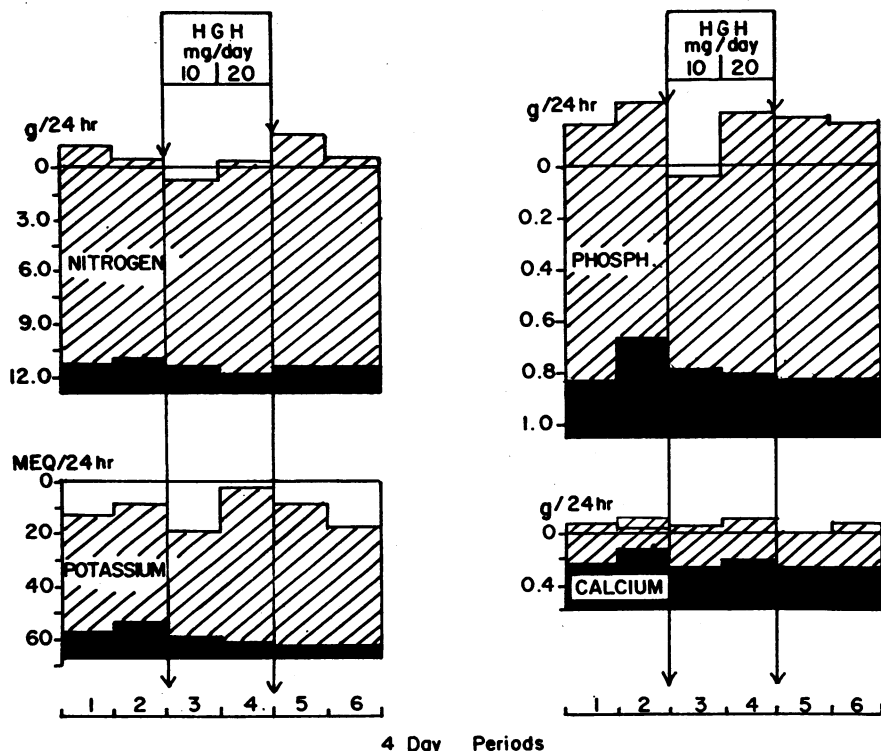


FIGURE 3 Metabolic effects of HGH (E-54) in an asthmatic child receiving 20 mg of prednisone daily. Analyzed phosphorus balance equals theoretic balance during the control period and the HGH period.

stool calcium resulted in negative calcium balance during the HGH period.

The data shown in Table II and illustrated in Figs. 2-5 are representative of the results observed during each of the balance studies in the steroid-treated children. Several children showed minimal response to HGH by every parameter tested. Three of these subjects (P. L., J. O'N., and J. S.) were studied during two balance periods separated by an interval of several months, and they showed minimal responses on both occasions. In some of the children, (M. K., K. K., and M. P.), HGH administration was associated with significant nitrogen retention, but even in these patients corresponding retention of phosphorus did not occur.

Table III lists the metabolic data obtained during HGH administration to two asthmatic children who were not receiving corticosteroid therapy. The markedly positive metabolic balance seen throughout study 1 of C. B. (Table III A) may

be partly related to defective intake; however, excretion of nitrogen, phosphorus, and potassium showed definite decrease during HGH administration and reverted toward control after termination of HGH. When the child was restudied after institution of prednisone therapy, (Table II D), HGH produced minimal change in nitrogen and potassium excretion and a marked increase in calcium and phosphorus excretion.

The responses of another nonsteroid-treated asthmatic child (E. L.J.) are shown in Fig. 6 and Table III B. In contrast to patient C. B., this patient had been symptom-free for a number of months and, except for small stature (as a result of previous corticosteroid therapy), he was essentially a normal child at the time of study. Retention of nitrogen observed during administration of 5 mg/day of HGH increased further when HGH was increased to 10 mg/day. Nitrogen retention was associated with slight retention of potassium and phosphorus (greatest at the 10 mg

dose of HGH). There was no significant change in calcium balance during HGH administration but after withdrawal calcium balance became markedly positive.

Long-term effects of HGH. Despite the poor responses to HGH which were observed during the metabolic balance periods, six of the steroid-treated children were given large doses of HGH for periods of 4–8 months. Table IV lists the heights and weights of each of the children before, during, and after the period of HGH administration and for comparison also shows the growth record of a patient with panhypopituitarism who received the same preparations of HGH. In contrast to the hypopituitary patient, none of the steroid-treated children showed any change in their retarded rate of growth during prolonged administration of HGH. While the children showed no change in height or bone age, several showed significant increase in weight during HGH administration. This weight increase may be partly

related to maintenance of corticosteroid at a constant level.

Fig. 7 graphically compares the growth response of one steroid-treated child (K. K.) with that of the hypopituitary patient (D. H.). The hypopituitary patient received 10–20 mg of HGH/wk and showed an increase in growth. The steroid-treated child received HGH for 8 months with doses of 120 mg/wk during the last 3 months and showed minimal growth. The figure further demonstrates that the growth retardation associated with corticosteroid therapy may be even more severe than that of hypopituitarism. Thus, D. H., who had panhypopituitarism secondary to craniopharyngioma (partially resected at age 5), grew 15 inches over a period of 13 yr with no endocrine replacement therapy. In contrast, K. K., the steroid-treated subject, grew normally until shortly after institution of high dose corticosteroids (15 mg of prednisone daily), after which he showed essentially no growth.

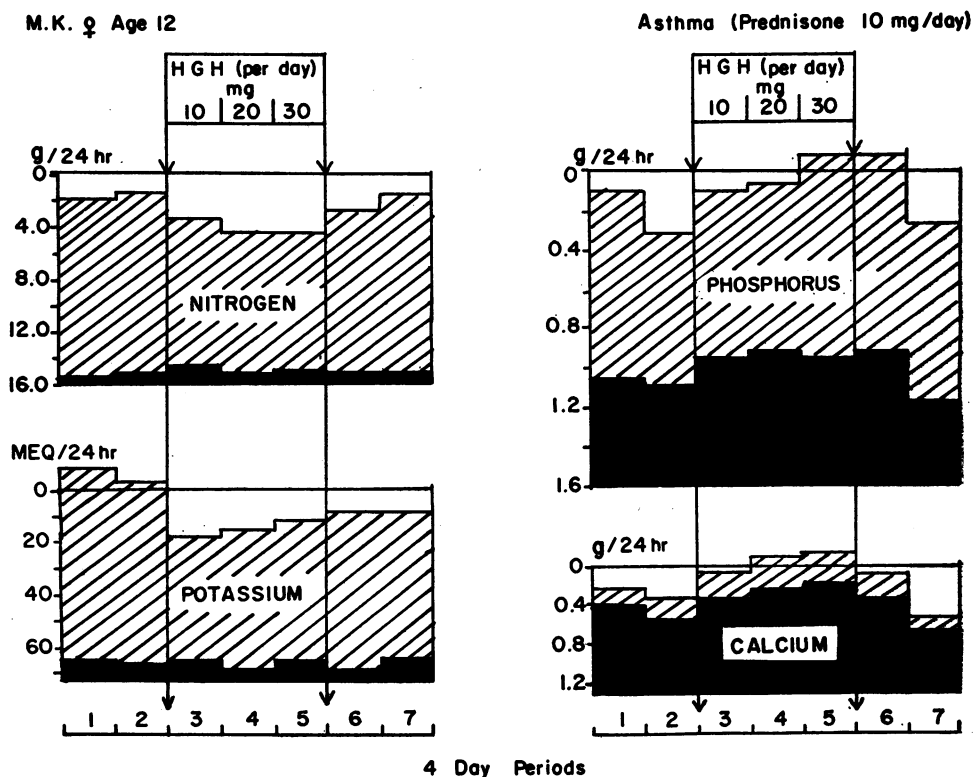


FIGURE 4 Metabolic effects of a different HGH preparation in an asthmatic child receiving 10 mg of prednisone daily. Analyzed nitrogen and phosphorus balance equals theoretic balance during the control period.

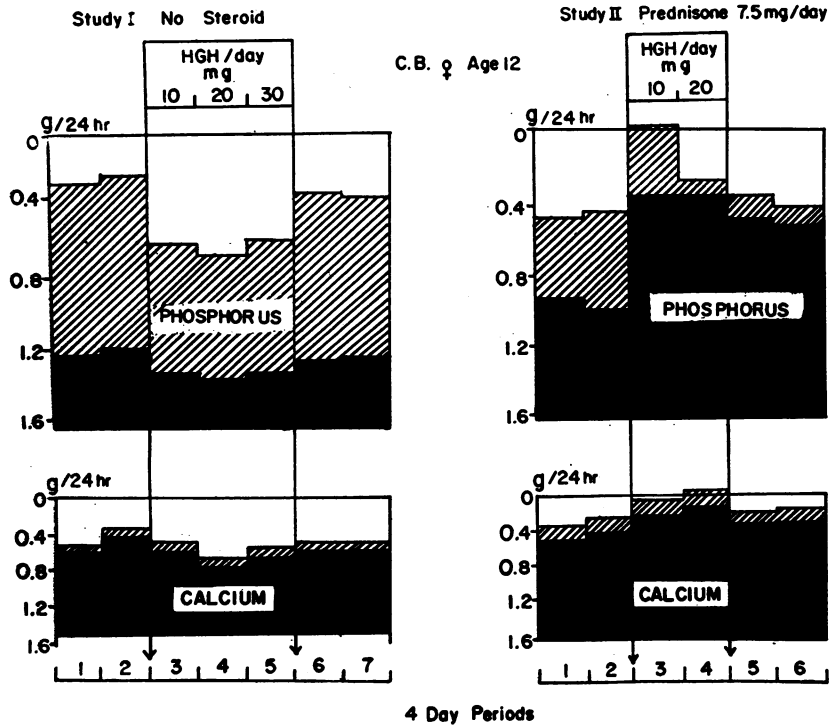


FIGURE 5 Comparison of the effects of HGH on phosphorus and calcium balance in an asthmatic child before and during treatment with 7.5 mg of prednisone daily.

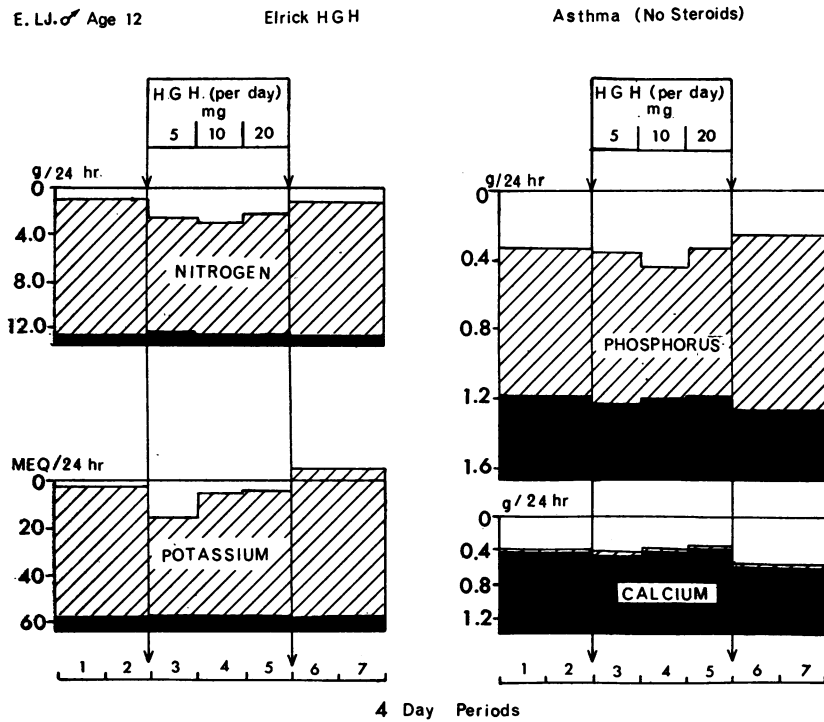


FIGURE 6 Metabolic effects of HGH in an asthmatic child not receiving corticosteroid therapy.

TABLE III
Metabolic Effects of HGH in Children Not Receiving Corticosteroids

	Dates	Treatment	Nitrogen			Phosphorus			Calcium			Potassium						
			Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
			g/day	g/day	g/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day	mg/day
A.																		
C. B. age 12 F	5/24-5/28	Control	16.3	9.7	0.3	+6.3	1652	955	422	+275	1467	48	918	+501	75	62	5	+8
study 1	5/28-6/1	Control		9.3	0.4	+6.6		975	450	+227		51	1070	+346		50	7	+18
no steroid	6/1-6/5	HGH, 10 mg/day		7.3	0.3	+8.7		724	307	+621		63	915	+489		63	5	+7
	6/5-6/9	HGH, 20 mg/day		6.7	0.2	+9.4		696	264	+692		69	738	+660		43	4	+28
	6/9-6/13	HGH, 30 mg/day		8.4	0.3	+7.6		782	300	+570		50	910	+507		51	4	+20
	6/13-6/17	Control		9.9	0.2	+6.2		909	365	+378		45	901	+521		43	5	+27
	6/17-6/21	Control		9.2	0.4	+6.7		882	365	+405		47	901	+519		40	5	+30
B.																		
E. I.J. age 12 M	2/9-2/13	Control	13.7	11.4	0.8	+1.5	1664	880	341	+443	1357	26	666	+665	67	57	4	+6
no steroid	2/13-2/17	Control		12.1	1.0	+0.6		809	636	+219		28	1217	+112		60	7	0
	2/17-2/21	HGH, 5 mg/day		10.0	1.2	+2.5		851	448	+365		42	898	+417		45	6	+16
	2/21-2/25	HGH, 10 mg/day		9.7	1.1	+2.9		764	463	+437		48	927	+382		55	6	+6
	2/25-3/1	HGH, 20 mg/day		10.5	1.0	+2.2		864	471	+329		48	978	+331		57	6	+6
	3/1-3/5	Control		11.0	1.0	+1.5		1029	461	+174		29	889	+439		64	6	-5
	3/5-3/9	Control		12.0	0.8	+0.9		999	338	+327		27	639	+691		69	3	-5

TABLE IV
Effect of Human Growth Hormone on Longitudinal Growth

Patient	Date	Age	Height		Weight	HGH
			In.	Lb.		
K. K. M asthma prednisone, 5 mg t.i.d.	2/63	12.5	51	75		
	12/63	13	52	81		
	3/64	13.5	52.25	87		Metabolic study (HGH 240 mg)
	5/64		52.25	88		HGH, 25 mg b.i.w.
	7/64		52.50	89		HGH, 40 mg b.i.w.
	8/64	14	52.75	91		HGH, 40 mg t.i.w.
	12/64		52.75	95		HGH discontinued
	2/65	14.5	53	97		
M. K. F asthma prednisone, 5 mg b.i.d.	11/63	11.5	51.5	72		
	3/64	12	51.5	75		Metabolic study (HGH 240 mg)
	5/64		51.5	77		HGH, 15 mg b.i.w.
	7/64		52	87		HGH, 25 mg b.i.w.
	8/64		52	85		HGH, 25 mg t.i.w.
	12/64	12.5	52	82		HGH discontinued
	2/65		52	83		
	intermittent steroid	4/65	13	52.5	82	
	6/65		53	85		
	8/65	13.5	54	84		
J. O'N. M asthma prednisone, 5 mg q.i.d.	7/64		52.5	79		Metabolic study 1 (HGH 240 mg)
	8/64	12	52.5	87		
	10/64		52.5	93		Metabolic study 2 (HGH 160 mg)
	12/64		52.5	99		HGH, 20 mg t.i.w.
	2/65	12.5	52.5	102		HGH, 20 mg t.i.w.
	4/65		52.5	103		HGH discontinued
	8/65	13	53	106		
P. L. M asthma prednisone, 5 mg b.i.d.	2/64	11.5	53.5	60		
	7/64	12	53.75	65		Metabolic study 1 (HGH 240 mg)
	9/64		53.75	71		
	10/64		53.75	72		Metabolic study 2 (HGH 160 mg)
	12/64		53.75	75		HGH 20 mg t.i.w.
	2/65	12.5	54.25	76		HGH 20 mg t.i.w.
	4/65		54.50	77		HGH discontinued
	7/65	13	55	81		
M. P. F rheumatoid arthritis prednisone, 5 mg t.i.d.	10/64	14	52.5	74		Metabolic study
	11/64		52.5	79		HGH, 35 mg b.i.w.
	1/65		52.5	81		HGH, 35 mg b.i.w.
	3/65		52.5	81		HGH discontinued
	10/65	15	52.5	81		
	8/66	16	52.25	78		
C. W. F nephrosis prednisone, 5 mg q.i.d.	2/63	7	41	56		
	8/63	7.5	42	59		
	10/63		42	56		Metabolic study (HGH 60 mg)
	11/63		42.25	58		HGH 20 mg b.i.w.
	1/64		42	64		HGH 20 mg b.i.w.
	2/64	8	42.25	63		HGH discontinued
D. H. M hypopituitarism no steroid	10/62	19	54.5	74		Metabolic study (HGH 30 mg)
	1/63		54.5	74		HGH 5 mg b.i.w.
	5/63	19.5	55.2	76		HGH 5 mg b.i.w.
	11/63	20	57.5	75		HGH 15 mg q wk
	7/64	20.5	59	89		HGH 15 mg q wk
	12/64	21	60	89.5		HGH 15 mg q wk
	5/65	22	61	98		HGH 20 mg q wk

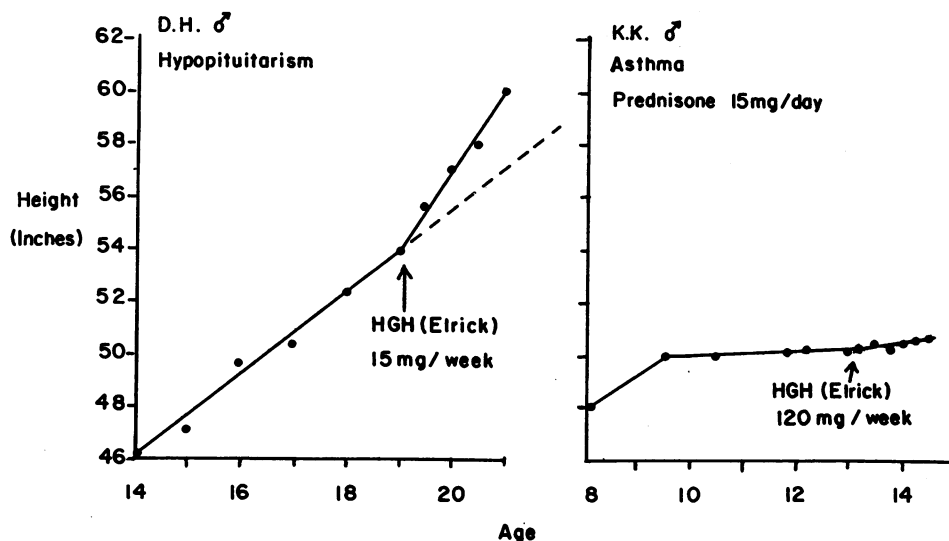


FIGURE 7 Growth response to human growth hormone. The hypopituitary subject showed acceleration of growth rate with small doses of HGH. The asthmatic child showed no improvement in his markedly retarded growth rate during treatment with large doses of HGH.

Most of the children tolerated the HGH well. C. B. whose asthma was poorly controlled when she was not receiving corticosteroid became more symptomatic during a period of marked fluid retention while receiving HGH. Local skin reactions characterized by redness, tenderness, and swelling occurred in K. K. after each injection of HGH. A minute amount of the same HGH preparation injected intracutaneously produced localized blanching for 15–20 min and suggested that the local reactions were an irritant rather than an allergic phenomenon. HGH administration caused no other change in the pattern or severity of the basic disease.

Endogenous GH concentrations. The concentrations of endogenous growth hormone in fasting plasma samples obtained during control periods of the balance study are shown in the last column of Table I. It can be seen that the steroid-treated children had fasting levels of GH which are similar to those reported in normal preadolescent children (23, 24). The hypopituitary subject had unmeasurable levels of growth hormone both during fasting and after induced hypoglycemia.

DISCUSSION

The metabolic effects of HGH have been described by a number of investigators. Subjects have included children with hypopituitarism (22),

gonadal dysgenesis (25, 26), constitutional dwarfism (27, 28), primordial dwarfism (22, 29), malnutrition (30), and infants (31, 32) and adults with a wide variety of diseases (18–21, 33), including Cushing's syndrome (21). In virtually all reports, the effects of small doses of HGH have been similar to those effects observed during the initial metabolic balance studies in 1958–60 (18–21), which demonstrated the effectiveness of HGH in man and showed that the response to acute administration of HGH is characterized by nitrogen, potassium, and phosphorus retention and increased urinary calcium excretion. The only exceptions to this response to HGH have been observed in children with primordial dwarfism (29). The acute metabolic responses to HGH are seen with such regularity that Wright, Brasel, Aceto, Finklestein, Kenny, Spaulding, and Blizzard (22), in reporting an extensive experience with HGH administration to children with various forms of dwarfism, indicated that the acute effects of administered HGH represent a pharmacologic response which is to be expected whenever an active preparation of HGH is administered; but acute metabolic effects, as judged by urinary excretion, are not necessarily indicative of improved growth rate during prolonged HGH administration.

In this study the effects of HGH were observed

during 11 complete metabolic balance studies of eight children who had significant growth retardation as a result of prolonged corticosteroid therapy. Results were compared with those observed in two children with hypopituitarism and in two children with asthma who were not receiving corticosteroids. The hypopituitary patients exhibited the greatest sensitivity to HGH in terms of magnitude and duration of response, a finding which is in agreement with other reports. The two children who were not receiving corticosteroid demonstrated less response than the hypopituitary patients, but both showed nitrogen retention in association with phosphorus and potassium retention, and one child (C. B.) grew during the period of HGH administration. In contrast, the steroid-treated children had impaired response to administered growth hormone. Although large doses of HGH were given, most of the steroid-treated children showed only minimal nitrogen retention. Phosphorus balance appeared to be an even more sensitive index of anabolic response since even when nitrogen was retained, none of the steroid-treated children retained phosphorus.

Some of the abnormalities demonstrated in the steroid-treated children would have been completely overlooked had stool analysis not been performed in addition to urinary excretion studies. The paradoxical decrease in net intestinal absorption of calcium and phosphorus during HGH administration to the steroid-treated children emphasizes the influence of the gastrointestinal tract on metabolic balance. In contrast to previous reports which have shown that HGH administration increases absorption of phosphorus (18, 25) and calcium (18, 34) from the gastrointestinal tract, in several steroid-treated children increased stool excretion was largely responsible for the negative phosphorus balance and contributed to the negative calcium balance during HGH administration (Figs. 4 and 5).

The repeated observation of absence of phosphorus retention during administration of HGH to the corticosteroid-treated children is of particular interest. Corticosteroids alone are known to cause profound effects on phosphorus balance with decreased phosphorus content of muscle (35-37) and increased phosphorus excretion in urine (38-41) and stool (37, 41). HGH alone also produces significant changes in phosphorus metabolism.

While the usual effect of administered HGH during balance study has been increased retention of phosphorus in parallel with the improved nitrogen retention (18, 20, 25) HGH is known to affect phosphorus balance in the opposite direction as well. In patients with acromegaly, the bone disease presumably due to excessive GH has been shown to be the result of marked increase in both bone accretion and resorption rates (42). Moreover, a number of patients with active acromegaly have shown negative phosphorus balance in conjunction with the negative calcium balance (42, 43). It thus appears that the over-all effect of HGH on external phosphorus balance is the result of two opposing forces, deposition and resorption. In our study there was increased excretion of phosphorus under the influence of corticosteroids alone. The further increase in excretion under the influence of HGH may be the result of increased mobilization of phosphorus which is not utilizable in the presence of excess corticosteroid. The consistent finding of diminished phosphorus retention during administration of HGH seems significant, because it is difficult to conceive of new tissue formation occurring without phosphorus retention.

Similarly, it is impossible to conceive of new tissue formation in the absence of nitrogen retention. In many studies nitrogen has been used as the major parameter of GH response. However, the magnitude of the nitrogen retention often observed during administration of HGH is difficult to explain because it is seen in adults as well as in children (18-21) and is far in excess of the amount of nitrogen retained by normal, actively growing children (44). Furthermore, it has been shown that the nitrogen retention may not be followed by growth during long-term HGH administration (22). Recently the concept that nitrogen "retention" is adequately reflected by the difference between dietary intake and urine and stool excretion has been challenged (45, 46). There is evidence that urine and stool excretion may not be the only sources of nitrogen loss from the body, since excess nitrogen or ammonia is also present in expired air (46-48).

While HGH is of proven effectiveness in the therapy of children with growth retardation secondary to hypopituitarism (22), prolonged administration of HGH to children with other forms

of dwarfism has yielded variable results. Some observers have reported significant improvement in growth rate during administration of HGH to children with gonadal dysgenesis (49) and constitutionally short stature (28), while others have reported minimal or no improvement in growth rate in children with dwarfism unrelated to pituitary disease (27, 50). In the present study, none of the corticosteroid-treated children demonstrated any improvement in their retarded rate of growth during prolonged therapy with large doses of HGH.

In contrast to our studies, some investigators have reported that even small doses of HGH can overcome effects of excessive corticosteroid. Bergenstal and Lipsett described reversal of the negative nitrogen balance with 5 mg/day of Raben growth hormone in a patient with Cushing's syndrome (21). Matiasевич and Gershberg (51) described marked improvement in growth rate during administration of 9 mg/wk of Wilhelmi HGH to two children who were receiving corticosteroid in doses similar to our patients. We have no explanation for these differences from our results.

It seems very unlikely that the responses observed in the present study are related to the specific preparations of HGH used (Elrick HGH). Each of the preparations was demonstrated by the rat tibia bioassay to have potent biologic activity (5, 6), and the hypopituitary subjects showed typical responses to HGH during both acute and long-term administration. It seems apparent that the altered effects observed in the steroid-treated children were related to altered ability to respond to the hormone.

Antagonism between growth hormone and corticosteroids has been suggested by reports of others. In 1952, Selye (52) demonstrated in intact rats that inhibition of linear growth during corticosteroid administration could be overcome by simultaneous administration of a crude beef growth hormone preparation and that larger amounts of growth hormone were required as steroid dosage was increased. Similar results were reported earlier with ACTH in intact (53) and hypophysectomized (54) rats and more recently with cortisone by Soyka and Crawford (55). Small doses of cortisone have also been shown to inhibit growth in children with hypopituitarism. Blodgett, Burgin, Iezzoni, Gribetz, and Talbot re-

ported cortisone-inhibition of the retarded growth rate in untreated patients (1), while Soyka and Crawford (55) showed that the improved growth rate during HGH administration was inhibited by steroids but could be restored by increasing the dose of HGH. In both studies, the dosage of cortisone was lower than that which permits normal growth in children with Addison's disease (1). These observations suggest that the antagonistic effects of growth hormone and corticosteroids are dose-related. In the present study, we were unable to demonstrate any difference in response to HGH during steroid therapy at doses ranging between 7.5 and 30 mg/day of prednisone. The deleterious effects of the steroid were not overcome by 30 mg/day of HGH during the acute balance study or by dosages up to 120 mg of HGH/wk during long-term studies. It is possible that during steroid therapy in the dose range encountered in this study, still larger doses of HGH would be required to overcome the effect of the steroid.

It has recently been reported that in adults corticosteroids inhibit pituitary release of growth hormone after hypoglycemia (56, 57), and it has been postulated that relative deficiency of endogenous growth hormone might in part explain the growth retardation of steroid-treated children (56). The results of the present study demonstrate that doses of HGH in the range of 8 times the amount shown to be growth promoting in a hypopituitary patient are ineffective in the steroid-treated children. Moreover, as indicated in Table I and as will be described further in a separate communication from this laboratory, plasma levels of endogenous HGH, both during the fasting state and after hypoglycemia, are similar in steroid-treated and nonsteroid-treated asthmatic children (58). Our results are in agreement with the thesis that the growth retardation is related to the "anti-anabolic effect" of corticosteroids (59) and may be associated with peripheral tissue inability to respond normally to available HGH.

Several lines of evidence indicate that deficiency of growth hormone is not the responsible mechanism for most forms of dwarfism. Most children with growth retardation have normal plasma levels of GH and show normal responsiveness to induced hypoglycemia (24, 60, 61). Furthermore, such children show little or no improvement in

growth rate during therapy with HGH (27, 50). These data suggest that the growth retardation may result from limited capacity of peripheral tissue to respond to available GH.

In certain forms of dwarfism such as gonadal dysgenesis and primordial dwarfism, the abnormality in responsiveness to HGH may be a genetic defect. In steroid-induced dwarfism, the abnormality results from the medication (3, 4) and is reversible if steroids can be discontinued (1). Other evidence which demonstrates the role of tissue responsiveness has been obtained in this laboratory where it has been observed that starving but otherwise normal individuals demonstrate a paradoxical response to HGH, with increased excretion of nitrogen, phosphorus, and sodium instead of the opposite effect seen during HGH administration to fed subjects (62). The requirements necessary for tissue responsiveness to HGH are unknown. However, if the mechanisms responsible for corticosteroid-induced dwarfism can be determined, these may point the way to mechanisms responsible for other forms of dwarfism.

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