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Hypophyseal Growth Hormone

II. Interaction with Other Hormones

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Growth hormone (GH) synthesis and release is controlled by hypothalamic GH releasing factor. Thyroid hormones, androgens and estrogens in physiologic concentrations enhance GH secretion but a controlling role for glucagon and vasopressin in GH release is not established. Under stress, ACTH directly facilitates GH release while the similar action of the catecholamines is mediated by the α -adrenergic receptors. Though physiologic doses of glucorticoids and progestins do not affect GH liberation, prolonged administration of medroxyprogesterone acetate or of glucocorticoids in high dosage will decrease blood levels or blunt GH responsiveness. GH enhances the release of insulin. A shift in adrenal steroid biosynthesis from the glucocorticoid to the androgenic pathway may also be an effect of GH administration. Prolonged elevated GH levels decrease serum thyroid binding globulin but increase the turnover of free thyroxine. Decreased thyroidal iodine uptake is probably secondary to these changes in thyroxine metabolism. In hypothyroidism and severe Cushing's syndrome GH release is blunted. In most cases of acromegaly as well as in hyperthyroidism GH is non-suppressible, while in diabetes its response to stimuli other than hypoglycemia is exaggerated.

In a previous article¹ we reviewed the functions of growth hormone (GH) as a stimulant to growth and as a factor regulating intermediary metabolism. Its secretion is influenced not only by physical, neuronal and metabolic activity, as previously discussed, but an important interplay also exists between GH and other hormones. These hormonal relationships are the subject of the present discussion.

Growth Hormone Releasing Factor (GHRF)

The synthesis and release of GH is under the direct influence of a hypothalamic neurohumor, growth hormone releasing factor (GHRF), which is se-

creted in or around the median eminence. It is transmitted through the hypothalamic-hypophyseal portal system to the anterior pituitary where it promotes synthesis and release of GH by the eosinophilic cells.

Low plasma GH levels and poor response to hypoglycemia have been observed in children with emotional deprivation and growth retardation. GH response to hypoglycemia became normal after a few days in a supportive environment and normal growth resumed. Powell et al² believe that deprivation of maternal love in some way reduces GH secretion in these children. The situation may be analogous to anorexia nervosa, in which GH deficiency has also been observed, in contrast to starvation in which GH levels are reportedly very high. Pre-

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sumably, alterations in GHRF are responsible for the GH changes characteristic of these clinical states.

Vasopressin

Gagliardino et al³ demonstrated a rise in plasma GH levels after administration of vasopressin to 15 normal men, women and children. The peak response occurred 30 minutes after intramuscular injection. Previously, others had demonstrated a GH stimulatory effect of lysine-vasopressin in two normal female subjects but not in males.⁴ Although vasopressin also stimulates ACTH and TSH release, both of which are under hypothalamic control, it is unlikely that this polypeptide plays a physiologic role in anterior lobe secretory activity.

Corticotrophin (ACTH)

Zahnd et al⁵ recently demonstrated that 1 mg of synthetic ACTH stimulated GH release in six normal subjects comparable to that which followed insulin-induced hypoglycemia. The time of peak response ranged from 15 to 90 minutes and the earliest, highest response occurred in the only female subject tested. The authors propose that ACTH is a possible mediator of stress-induced GH release.

Islet Cell Hormones

Although insulin and glucagon both stimulate GH secretion, the mechanisms of their action are somewhat different. Well-known are the opposing effects of these hormones on the level of glucose, the primary regulator of GH secretion. Insulin increases glucose utilization and lowers blood sugar, stimulating GH secretion. GH, in turn, tends to raise blood glucose by inter-

acting with its utilization, by increasing glycogenolysis and by accelerating gluconeogenesis.

Consequent to the rise in glucose and possibly by direct islet cell stimulation, growth hormone causes synthesis and release of insulin. With prolonged administration, persistently elevated blood sugar may result despite elevated insulin levels as seen in diabetes of acromegaly.⁶ Even with normal blood sugar levels, plasma insulin in acromegalics has been found three times greater than that of controls.⁷ Although increased islet cell stimulation secondary to GH effect on the blood sugar may account for the increased insulin secretion, a markedly increased insulin secretory capacity can also be demonstrated, for example, by tolbutamide testing in acromegalic patients.⁶ A similar priming effect on the beta cells is indicated by the exaggerated insulin response to tolbutamide administered to dogs treated with GH.⁸ This increased secretory reserve correlates with the islet cell hypertrophy demonstrated in acromegalic subjects by Recant⁹ as well as in various laboratory animals treated with growth hormone.¹⁰

The extraordinary insulin secretory capacity of acromegalic subjects can also be demonstrated by challenge with a glucocorticoid (eg, dexamethasone 8 mg/day for 2 days). Under these conditions, normal individuals exhibit a four- to fivefold increase in plasma insulin response to tolbutamide. Similar treatment of acromegalic subjects results in a tenfold increase in plasma insulin levels.¹¹

No significant change in plasma insulin was found by Daughaday and Kipnis⁶ in normal subjects 30 minutes

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after a single intravenous injection of 5 mg of GH. However, administration of 10 mg/day for 3-8 days to hypopituitary subjects produced a progressive increase in both blood sugar and insulin. Furthermore, carbohydrate tolerance was diminished despite a six-fold increase in plasma insulin response.

On the other hand, plasma GH in diabetics differs from that of normals in that diabetics are more sensitive to GH releasing stimuli other than hypoglycemia. This phenomenon does not correlate with the presence or absence of retinopathy.¹²

Recently, Mitchell et al¹³ demonstrated an elevation of plasma GH in 15 individuals within three hours of the subcutaneous injection of 1 mg of glucagon. Most often, the peak elevation occurred at two hours and changes in blood glucose alone could not explain the rise in GH. This observation is contrary to previous reports that glucagon does not stimulate GH release but the authors contend that the GH levels in earlier studies were not observed beyond 90 minutes. The exact mechanism of glucagon-induced stimulation of GH release is not known but the late falling glucose levels may contribute or may reflect merely a physiologic fluctuation of GH release.

Corticosteroids

Observations concerning the effects of glucocorticoids on GH release are conflicting. The absence of normal spontaneous GH peaks in two patients with Cushing's syndrome was demonstrated by Stiel et al,¹⁴ but this phenomenon was not reproduced in normal subjects treated with prednisone 15 mg daily. Both Hartog et al¹⁵ and

Frantz and Rabkin¹⁶ reported that in adults receiving corticosteroids, GH response to hypoglycemia is blunted. Morris et al¹⁷ failed to confirm this claim in children. Our study of growth hormone in 12 patients with Cushing's syndrome concludes that the suppression of GH response to hypoglycemia which occurs in the hypercortical state is proportional to the duration and severity of the adrenal hypersecretion. In these cases, impaired GH release did not depend upon glucose levels, and responsiveness was restored with remission of the Cushing's syndrome in all except one patient who had developed a pituitary tumor. In children and adolescents with Cushing's syndrome, growth had ceased despite normal GH response to hypoglycemic stimulus.¹⁸ These observations, consistent with the findings in prepubertal children receiving corticosteroid treatment, suggest that the impaired growth is the result of steroid-induced antagonism to GH at the tissue level.^{18,19}

Strauch et al²⁰ studied GH releasing mechanisms in Cushing's syndrome utilizing insulin, glucose and arginine. In nine patients who did not respond to falling glucose, arginine provoked a GH release in all but three, two of whom were male. The authors conclude that this "partial somatotrophin deficiency" in Cushing's syndrome is due to hypothalamic GHRF inhibition and that the pituitary GH secretory mechanism is intact. A similar mechanism may explain the exaggerated GH response in diabetics who also respond to stimuli other than hypoglycemia.

We have studied GH response to arginine in four patients with the adrenogenital syndrome, and have evaluated

Table I

EFFECT OF GLUCOCORTICOID THERAPY ON GROWTH HORMONE RESPONSE
TO ARGININE IN ADRENOGENITAL SYNDROME

Name	Age & Sex	State	Growth Hormone mUg/ml								P'triol Mg/24-hr
			0 Min.	30 Min.	45 Min.	60 Min.	75 Min.	90 Min.	120 Min.	150 Min.	
RC	17M	Untreated	12.4	15.4	16.8	6.0	3.8	2.0	13.6	12.4	32.6
		TRIAMCINOLONE	15.0	50	> 100	80	53	20	14.5	11.5	0.5
DC	13M	Untreated	1.4	10.0	18.4	12.0	3.4	1.8	7.6	19.8	30.0
		TRIAMCINOLONE	6.0	2.0	2.0	2.8	13.2	27.0	21.0	9.7	1.4
LP	19F	Untreated	3.0	—	14.0	54	30	11.6	44.0	7.0	30.5
		PREDNISONONE	13.4	60	74.0	68	54	44	7.8	4.8	2.3
CC	17F	Untreated	2.4	24	> 100	80	> 100	> 100	26.0	10.4	65.0
		PREDNISONONE	6.8	> 100	> 100	100	> 100	> 100	44.0	9.6	3.3

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RC and DC were given triamcinolone and GH response was tested four weeks later. In cases of LP and CC long-term prednisone treatment was discontinued a month before arginine stimulation. The higher GH response during treatment is not statistically different from untreated values. The very high levels in CC are unexplained.

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the effect of glucocorticoid therapy. Although there was no statistical difference in GH levels, adrenal suppression treatment tended to improve the GH response (Table I). In one patient (CC) GH levels were very high after arginine, and were not affected by corticoid therapy. The somewhat higher GH levels during corticosteroid administration were unexpected in view of the tendency of cortisol to reduce GH response in other patients. A possible explanation is suggested by the work of Lawrence and others who have studied the suppressive effect of medroxyprogesterone acetate on GH release.²¹ This drug is a methylated derivative of 17-hydroxyprogesterone which is secreted in high titer by untreated patients with the adrenogenital syndromes. Urinary pregnanetriol indicates the 17-hydroxyprogesterone secretion in our patients and the suppressive effect of treatment. Conceivably, this steroid or its metabolites account for the somewhat lower GH response observed during the untreated state. The extraordinary response of patient CC (Table I), unique to our experience, is unexplained.

At the present time there is no convincing evidence that the corticosteroids normally influence GH release. Although physiological doses of cortisol enhance GH production in tissue cultures of normal human pituitaries as well as eosinophilic adenomas,²² there is little doubt that pharmacological doses of these steroids can impair GH release and most assuredly antagonize the growth-promoting effects of the hormone.

Another subtle relationship may exist between GH and adrenocortical secretions. GH administration is capable

of altering the adrenal response to corticotropin. Rats treated with HGH and prolactin release less corticosteroid in response to ACTH than do control animals.²³ Similarly, basal 17-hydroxycorticoid secretion is reduced in dogs treated with HGH preparations and this response is dose-related.²⁴ In normal human subjects as well as in patients with Cushing's syndrome, GH reportedly lowers urinary 17-hydroxysteroids.²⁵ On the other hand, GH probably enhances adrenal androgen secretion, and hirsutism is a common clinical finding in acromegalic females. Reasoning from the characteristic elevation of urinary 17-ketosteroids in acromegaly, Lim and Dingman²⁶ postulated GH-induced activation of adrenal androgenic steroidogenesis. An acromegalic patient has been reported with non-suppressible adrenal function, virilization, high GH levels, moderately elevated urinary 17-ketosteroids but normal 17-hydroxysteroids, presumably the result of excess ACTH secretion in the presence of increased GH.²⁷

To evaluate the possible significance of this GH-adrenal cortex relationship to growth in childhood, we have studied adrenal function in eight GH-deficient children receiving HGH therapy. In eight-month courses of treatment, a small reduction in mean 17-hydroxycorticosteroids and cortisol secretion rate occurred in these subjects (Table II), while the urinary androgen metabolites, especially androsterone, increased (Table III). All children responded to therapy with accelerated growth.

Catecholamines

A role for epinephrine in the control of growth hormone secretion is also unsettled. Blackard and Heidingsfeld-

Table II

EFFECT OF EXOGENOUS GROWTH HORMONE ON URINARY
17-HYDROXYCORTICOSTEROIDS (17-OHCS) and CORTISOL SECRETION
RATES (CSR) IN 8 DWARF CHILDREN

Name	Age Sex &	CSR Mg/24-hr.		Urinary 17-OHCS Mg/24-hr.	
		Before Treatment	After Treatment	Before Treatment	After Treatment
RK	6M	9.4	4.0	2.4	1.6
DB	5M	12.8	4.7	2.4	3.0
BS	9M	10.3	6.6	2.4	2.7
WR	8M	10.7	6.0	2.0	1.1
GM	12M	5.8	3.9	3.4	1.4
TH	13M	5.6	6.9	2.4	2.7
RKu	15F	4.1	2.6	2.3	1.0
MR	12M	7.6	12.4	12.8	5.7
Mean		8.3	5.9	3.8	2.4

Two mg of human growth hormone three times weekly was administered for eight months. CSR fell in six of eight subjects and urinary 17-OHCS decreased in five. The mean values of both CSR and urinary 17-OHCS are lower after treatment but wide variation in the subjects precludes statistical analysis.

er²⁸ studied the effect of catecholamines on plasma GH under conditions of controlled glucose concentration. During α -adrenergic blockade, insulin-induced hypoglycemia produced a lesser elevation of growth hormone than that produced without blockade. Conversely, GH levels were higher with insulin-induced hypoglycemia during β -adre-

nergic blockade, but inhibition of cyclic 3'5-AMP phosphodiesterase activity with administration of theophylline had no detectable effect on plasma GH response. This study is interpreted to indicate a stimulatory effect by α -adrenergic receptors and an inhibitory effect by β -adrenergic receptors of growth hormone secretion, a pattern

Table III
EFFECT OF GROWTH HORMONE ON URINARY ANDROGENS

Name	Age & Sex	ANDROSTERONE in mg/day		ETIOCHOLANOLONE in mg/day		Total C ₁₉ O ₂ 17 - KS in mg/day	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
RK	6M	.006	.003	----	.010	.006	.013
DB	5M	.015	.019	.007	.013	.022	.032
BS	9M	.023	.035	----	.022	.023	.055
WR	8M	.060	.038	.030	.010	.100	.051
GM	12M	.112	.167	.130	.119	.242	.304
TH	13M	.830	1.161	.290	.274	1.150	1.435
RKu	15F	.030	.031	----	.008	.040	.039
MR	12M	.400	.689	----	----	1.065	1.375
Mean		.196	.268			.330	.413

HGH was administered 2 mg thrice weekly for eight months. In contrast to reduced cortisol secretion, androgen metabolites increased in six of the eight subjects after GH therapy.

opposite to the sympathetic mechanism controlling the release of insulin. Apparently, catecholamines released during hypoglycemia inhibit insulin secretion and assist in promoting a rise in GH. The observation that neither adrenergic blockade nor theophylline altered basal GH levels suggests that the sympathetic nervous system plays no role in the control of resting GH levels. However, Imura et al²⁹ earlier demonstrated an elevation of GH after propranolol administration without other stimulus. Their study also supported the role of sympathetic receptors in the control of GH release.

Thyroid

Accelerated growth is a well recognized feature of hyperthyroidism in childhood³⁰ while retarded growth is seen in juvenile myxedema.³¹ An effect of thyroid hormone on synthesis and secretion of GH is suggested by the decrease in the number of pituitary acidophils found in patients with myxedema³² and in rats after thyroidectomy.³³ In both children and adults with primary hypothyroidism GH release is impaired in response either to insulin-induced hypoglycemia or arginine.³⁴⁻³⁹ Responsiveness returns to normal after adequate treatment, but before thyroid therapy the impoverished GH response to hypoglycemia may suggest an erroneous diagnosis of hypopituitarism. The mechanism by which thyroid deficiency influences GH synthesis and release may involve GHRF secretion or GH synthesis and storage by pituitary cells or both. As stated previously, adrenergic receptors influence growth hormone secretion, and thyroxine may exert its effect through hypothalamic adrenergic receptors.⁴⁰

In studies of hyperthyroid patients, deficient GH release in response to insulin-induced hypoglycemia was reported by Burgess⁴¹ but others observed normal responses.⁴² On the other hand, GH suppressibility with glucose is impaired in hyperthyroidism and normal reactivity returns with restoration to the euthyroid state. The mechanism of this resistance is unknown.⁴³

Limited evidence indicates that GH may affect binding and transport of the thyroid hormones. In acromegaly, despite a low or normal free thyroxine level, an increased thyroxine turnover rate occurs which may partly explain the hypermetabolism of the disease.⁴⁴ Exogenous administration of GH slightly decreases the thyroxine binding globulin (TBG) after five days of administration and low TBG has been reported in long-standing acromegaly.⁴⁵ Administration of GH in five-day courses to normal volunteers also reduced thyroxine binding capacity.⁴⁵ The lower serum thyroxine levels secondary to reduced plasma binding may be mistakenly interpreted as TSH failure in subjects receiving GH therapy. Root et al⁴⁶ studied the effect of HGH therapy on thyroidal iodine uptake and serum PBI in 20 children with stunted growth from various causes. In nine patients a significant change in uptake and PBI was observed: in two iodine uptake increased and PBI increased in two; in six subjects, both PBI and uptake decreased. The authors interpret these data as indicating diminished TSH secretion induced by GH administration. Because exogenous GH has been shown to lower TBG levels, the data of Root et al do not permit, in our opinion, unequivocal interpretation as direct inhibition of TSH. Conceivably,

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reduced TBG with altered equilibrium between the free and bound thyroid hormones accounts both for the lowered PBI and the diminished TSH effect evidenced by lower iodine uptake. The authors reported TSH assays only in two patients who were already hypothyroid. The markedly elevated levels were somewhat reduced after five days of GH administration.

Gonadal Steroids

Accelerated growth at puberty, a universal physiological phenomenon, suggests the possibility of augmented growth hormone release in the presence of gonadal steroids. In support of this hypothesis, Martin et al⁴⁷ demonstrated increased GH response to hypoglycemia in a single patient after puberty compared with the prepubertal values, and in a dwarfed, prepubertal child they observed enhanced GH release after five days of testosterone administration. Deller and associates⁴⁸ studied a 12-year-old dwarfed, sexually infantile male who had negligible GH response to hypoglycemia. Twenty hours after a single 400 mg dose of testosterone, GH response rise to a similar stimulus was normal and during the next ten weeks the patient grew 5 cm. Illig and Prader⁴⁹ observed an improved GH response to hypoglycemia in four patients with anorchia and one with delayed puberty after two days of androgen administration. The response was more pronounced two to three months after treatment. Although basal plasma GH levels do not rise at puberty, the accelerated growth may well be secondary in part to enhanced stimulated GH levels.

GH levels during various phases of the menstrual cycle are comparable,⁵⁰

but there is evidence for slight increases during the preovulatory and premenstrual phases. Frantz and Rabkin⁵¹ demonstrated that estrogen administration increases ambulatory GH levels and Spellacy⁵² demonstrated similar effects in patients using the common combination type oral contraceptives. Furthermore, the greater GH response to hypoglycemia which occurs in patients receiving the sequential type of oral contraceptives is considered to be due to the estrogen content of the pill.⁵³ On the other hand, Schwartz⁵⁴ postulated antagonism between estrogen and GH at the cellular level, indicated by their opposite effect on urinary calcium and hydroxyproline and the serum phosphorus. That such an antagonism may be of clinical importance is suggested by our experience with a female acromegalic patient, age 58, who had undergone oophorectomy seven years before diagnosis of her pituitary eosinophilic adenoma. The patient has been treated with stilbestrol 5 mg daily with periodic interruptions for a period of three years. She reports regression of hand and foot size, shrinking of the gums and jaws, requiring new dentures, and relief of headache. GH levels were somewhat reduced after a month of treatment but returned to pretreatment values after six months. (Table IV)

Simon⁵⁵ demonstrated a blunting of GH release after hypoglycemia in four of five men who had received medroxyprogesterone acetate (MPA) 1 gm intramuscular 48 hours previously. Lawrence reported that this synthetic progestin administered orally had similar effects.²¹ In 9 of 11 normal volunteers and 11 of 12 acromegalics receiving oral MPA, GH response to arginine was negligible and in 10 acromegalics,

Table IV

GROWTH HORMONE LEVELS IN A FEMALE ACROMEGALIC
PATIENT RECEIVING STILBESTROL

Date	Condition	F	<u>GH (mug/ml)</u>
			2-hr. after glucose
4-14-66	Control	62	62
4-28-66	Stilbestrol (5 ml/day)	41	37
5-27-66	"	18	24
7-21-66	"	48	48
11-30-66	"	52	53
9-14-67	"	59	77

Although there is a decrease in both the fasting and post-glucose GH levels one month after beginning stilbestrol, GH values are the same as control after 17 months of stilbestrol therapy. The corresponding blood glucose values were not significantly changed. In all studies 100 gm of glucose was ingested after the control specimen was obtained. The patient reported objective improvement in her acromegalic features.

GH levels were strikingly reduced. Chronic therapy improved the appearance of two. Malaskey and Daughaday⁵⁶ recently recorded the 24-hour profile of GH secretion and the response to insulin and arginine infusion in five acromegalics with very high GH levels who were treated with 40 mgm MPA daily for six months. During the first two weeks, GH was elevated in four of five patients but thereafter levels fell significantly and clinical improvement occurred. We observed no effect from MPA given parentally, 100 mg/week to a post-menopausal female acromegalic subject. Headache seemed to improve after treatment but neither the

basal nor post-glucose GH values were improved and the blood sugar increased and hypoglycemic drug therapy was required. (Table V)

Discussion

The complex functional interrelationships of the hypophyseal polypeptide termed "growth hormone" are barely implied by this simple designation. Even after growth and maturation are completed the continuing GH secretion helps to regulate the supply and utilization of energy substrate while protecting the integrity of structural proteins. Throughout life, GH facilitates the incorporation of ingested pro-

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Table V

GROWTH HORMONE LEVELS IN AN ACROMEGALIC TREATED WITH MEDROXYPROGESTERONE ACETATE (MPA)

<u>Date</u>	<u>Condition</u>	<u>GH (mug/ml)</u>		<u>Blood Glucose (mg. %)</u>	
		<u>F</u>	<u>2-hr.</u>	<u>F</u>	<u>2-hr.</u>
5-17-69	Control	23	18	90	155
6-7-69	After MPA	30	22.5	95	230

MPA (200 mgm) was administered intramuscularly in three doses during the two weeks ending May 31, 1969. The two-hour blood sugar is increased after progestin treatment and GH values are slightly increased.

teins and amino acids into body tissues. These two broad areas of function, mobilization of energy substrate and maintenance of tissue, are represented by the two prominent GH release mechanisms, glucose deficiency and amino acid plethora.

The manifold interactions between GH and other hormones may also be interpreted in terms of regulating growth, preserving body structural integrity and providing readily accessible energy stores. In this regard, enhanced GH response to stimulation observed in the presence of androgens and estrogens may contribute to the accelerated growth of adolescence. Moreover, the synergistic anabolic activity of GH and androgens undoubtedly promotes pubertal growth. The observed peripheral antagonism between GH and estrogens is less clearly of utility to the body economy. It is possible that peripheral antagonism between GH and estrogens

contributes to fat deposition in the subcutaneous tissues of the females.

The suppressive effect of pharmacological doses of synthetic progestins on GH release has no known physiological significance. It may help interpret GH levels in our studies of patients with congenital adrenal hyperplasia who had a marked hypersecretion of 17-hydroxyprogesterone in the untreated state. During adrenal suppression by corticosteroid administration, GH levels were slightly increased.

Corticosteroids in high dosage impair GH release especially after prolonged administration or hypersecretion. To a less striking degree, administered GH may in turn diminish adrenal cortisol secretion. A prominent antagonism exists between GH and corticosteroids in their cellular effects and growth of children is markedly impaired by excess corticoids even without suppressed GH release. The

adrenal function studies in our GH-deficient children receiving physiologic doses of HGH also indicated a slight reduction of cortisol secretion, an effect which theoretically enhances the growth-promoting action of the administered hormone. At the same time, and very likely as a concomitant of the lowered cortisol secretion, urinary androgen metabolites increased. Adrenal androgen secretion normally increases progressively and disproportionately in the growing child, a phenomenon termed "adrenarche," and the androgen undoubtedly promotes the accelerating late childhood growth. That GH contributes to the adrenarche through its influence on adrenocortical secretion of corticoids and androgens seems a permissible speculation.

Insulin-deficient children do not grow normally even in the presence of GH and augmented insulin secretion is a predictable result of GH administration to normal subjects. Thus, GH and insulin are mutually stimulatory although the relationship depends on their opposing effect on plasma glucose, apparently the ultimate regulator of the secretion of both hormones. Whereas GH and insulin respond in opposite ways to glucose levels, aminoacidemia is stimulatory to the release of both polypeptides, presumably through a mechanism not involving glucose.

Growth failure in hypothyroidism is

in part due to GH failure. Similar impaired secretion has not been demonstrated for the other pituitary hormones in myxedema, and TSH is predictably elevated. Thyroid hormone corrects the impaired GH release. GH administration modifies plasma binding of the thyroid hormone and a fall in PBI may not necessarily reflect a decrease in TSH secretion. Impaired thyroid secretion as a result of GH action, if proved to be a physiologic fact, has no obvious biologic utility since thyroid hormone is required for optimal growth.

There is little evidence that interaction between GH and ACTH, vasopressin, the catecholamines, the glucocorticoids and glucagon are significant in everyday life. However, in conditions of physiologic stress in which ACTH and the catecholamines are liberated, subsequent release of GH provides a reparative, anabolic or anti-catabolic function. The reported GH stimulatory effects of ACTH and of the α -receptors of the sympathetic nervous system offer a mechanism for this reaction. Inasmuch as augmented GH levels are not sustained in stress states, the protective function of the hormone has limited significance.

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