Metabolic Studies in the African Pygmy

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A B S T R A C T Major metabolic effects of human growth hormone (HGH) were assessed in the African Babinga pygmy. Plasma free fatty acid (FFA) and glucose concentrations were measured in pygmies, HGH-deficient dwarfs, Bantu tribesmen, and Caucasian controls after each received 4 mg of HGH intravenously over a 20 min period. Pygmies had an early decrease of plasma FFA and glucose concentration, but did not exhibit a later lipolytic response.

In neighboring Bantu tribesmen, American controls, and HGH-deficient dwarfs, both the early and late responses to intravenous HGH were present. The failure of plasma FFA concentration to increase in the pygmy after intravenous HGH was not due to a generalized defect in lipolysis since a normal lipolytic response was obtained with epinephrine (2 μg/min for 20 min).

Pygmies, like HGH-deficient dwarfs, had significantly reduced insulin responses to both oral glucose and arginine. Insulin secretion was significantly reduced when compared with either Bantu tribesmen or American controls and was not altered by 2 wk of a high carbohydrate/high protein diet. HGH treatment in pygmies (5 mg b.i.d. for 5 days) failed to augment either glucose or arginine-induced insulin secretion. Glucagon consistently caused normal insulin secretion in HGH-deficient dwarfs and was, likewise, effective in each pygmy studied. In two offspring from different pygmy mothers and Bantu fathers, insulin responses to glucose were initially normal and increased in a normal manner after HGH treatment.

In previous studies, HGH failed to reduce serum urea nitrogen concentration in pygmies. Sulfation factor was found to be normal. A consideration of the data *in toto* is consistent with a hypothesis that the metabolic findings in the pygmy may result from partial nonresponsiveness to either HGH or to a factor generated by

HGH. This defect is not transmitted as either an autosomal or sex-linked dominant trait.

INTRODUCTION

Pygmy subjects have normal increases of plasma immunoassayable HGH after appropriate stimuli and normal concentration of sulfation factor. Thus, a deficiency of human growth hormone (HGH)[1] can be excluded as a cause of their short stature (1). There were in our initial studies, however, clinical and biochemical findings suggesting a similarity of pygmies and dwarfs with a monotropic deficiency of HGH (sexual ateliotic dwarfs) (1, 2). Both groups displayed (a) abnormally prolonged hypoglycemia after exogenous insulin and (b) insulinopenia after intravenous arginine and glucose.

Initial studies revealed, likewise, that plasma FFA concentrations did not increase in 19 pygmy subjects given HGH intravenously and that poor responsiveness was noted after 5 days of receiving HGH treatment. Effectiveness of HGH treatment was judged by comparing changes of insulin secretion and changes in serum urea nitrogen with those obtained in American controls and HGH-deficient dwarfs.

Although we interpreted our initial data to indicate end-organ unresponsiveness to HGH in the pygmy (2, 3), it was recognized that this hypothesis depended upon assumptions regarding the prior diet of these subjects and the suitability of the control population.

The present paper will focus upon four topics: (a) studies in pygmies both prepared and unprepared by special diets for 2 wk; (b) comparative responses of Bantu, American controls, HGH-deficient dwarfs, and pygmy subjects with special reference to lipolytic hormones other than HGH; (c) the possible site of the de-

TABLE I

		Glucose, mg/100 ml of plasma				
	Time	0	30	60	2 hr	3 hr
American controls (23)		82.9 ±4.1	140.9 ±3.2	139.3 ±5.8	100.5 ±6.2	90.3 ±5.6
Bantu (8)		89.5 ±3.0	129.0 ±9.3	113.0 ±6.3	86.1 ±9.0	91.7 ±4.9
HGH-deficient dwarfs (21)		79.4 ±7.1	155.0 ±9.9*	195.6 ±18.8*	189.0 ±21.8*	137.3 ±2.4*
Pygmies (no diet) (19)		79.5 ±4.1	123.8 ±8.3	145.5 ±8.8	95.6 ±3.9	
Pygmies (diet) (7)		78.4 ±2.2	113.2 ±5.5	131.0 ±6.6	109.5 ±9.4	84.7 ±6.8

All values are means ±SEM.

Plasma insulin responses of pygmies differ from Bantu and American controls at 30, 60, and 120 min, ($P < 0.01$). Glucose and insulin responses of pygmies fed a high carbohydrate/protein diet do not differ from pygmies unprepared by diet.

Insulin is given in microunits per milliliter.

* Indicates values are significantly > than in pygmies, $P < 0.01$).

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fect in the pygmy; (*d*) the inheritance of the "pygmy" trait.

METHODS

Studies in pygmies were conducted in three isolated villages in the Lobaye region of the Central African Republic—at Bagandou, Zomia, and Tobali. Pygmies studied at Bagandou were fed a diet composed of 400 g of carbohydrate and a minimum of 2 g of protein per kg of body weight daily divided into two meals. This diet was ingested completely for each of 14 days before any tests.

Sexual ateliotic dwarfs and normal controls were admitted to the Clinical Research Center for Boston University School of Medicine at Boston City Hospital. The diagnosis of sexual ateliosis (monotropic deficiency of HGH) was established previously by multiple tests of pituitary function (1).

Growth hormone infusions. Five of the pygmies received growth hormone infusions consisting of 4 mg of Wilhelmi HGH lot 1-C in 150 ml of saline given in an antecubital vein over a 20 min period. Plasma samples were collected every 10 min for 60 min and then every 30 min for an additional 1½ hr. Five Bantu from a nearby village received similar infusions; four were conducted as in the pygmies. One Bantu subject received, inadvertently, 4 mg of HGH in 8 min rather than the usual 20 min period. 10 normal American controls and 12 HGH-deficient dwarfs received similar infusions.

Glucose tolerance. Before controlling the diet and administering HGH, oral glucose tolerance tests were performed with 100 g of glucose. Subjects studied in this manner included 23 Caucasian controls, 8 Bantu, 21 HGH-deficient dwarfs, and 19 pygmies. Plasma samples were collected every 30 min. The American controls and HGH-deficient dwarfs had a carbohydrate intake of at least 150 g daily for 2 wk before testing. 11 of these pygmies, 6 of the Caucasian controls, and 6 of the sexual ateliotics had a second glucose tolerance test after receiving 5 mg of HGH intramuscularly for 5 days. Five pygmies receiving the special diet were studied after the administration of glucose, but only one was treated with HGH. Two subjects, each known to be the offspring of different pygmy mothers and Bantu fathers had similar glucose tolerance tests. Each was

then treated with 10 mg of HGH intramuscularly daily for 2 days and the glucose tolerance tests were repeated.

Glucagon infusion studies. Five pygmies received 1 mg of glucagon intravenously over a 20 min period. Six sexual ateliotics and seven normal controls were studied in a similar manner. To facilitate sampling at early time intervals, two intravenous infusions were used—one for infusion of glucagon, the second for sampling only. Samples were collected every 10 min for 60–90 min.

Epinephrine infusion studies. Five pygmies not prepared by diet were given epinephrine infusions at a rate of 2 µg/min for 60 min. Plasma samples were collected at − 15, 0, 20, 40, 60, and 90 min. No Bantu subjects were studied with epinephrine, but five studies were conducted in sexual ateliotic dwarfs. 10 American controls had been studied previously in this manner.

On a previous expedition the effects of HGH upon sulfation factor, arginine-induced insulin secretion, and serum urea nitrogen concentration were studied. These data will be summarized in the text.

Collection of samples and methods of analysis. Using a portable centrifuge, serum was separated after each collection period, transferred to vials, and submerged slowly in a storage container of liquid nitrogen. Control vials containing HGH and insulin standards were treated in a similar manner to be certain rapid freezing did not destroy the hormones present in serum. Samples collected in all tests were analyzed for insulin, HGH, FFA, and glucose. Glucose and FFA were measured by methods described previously in detail (3, 6). Plasma growth hormone and insulin were measured by a dextran-coated charcoal modification of the initial immunoassay procedures of Yalow and Berson, and Glick, Roth, Yalow, and Berson (4, 5). The insulin assay was accurate to within 5 µU/ml and the growth hormone assay to within 0.5 ng/ml of plasma. For each hormone measurement, samples were analyzed in triplicate. If the discrepancy between samples was greater than 10% they were reanalyzed.

RESULTS

Glucose tolerance test. The mean glucose and insulin concentrations in plasma of all groups studied before HGH treatment are compared at pertinent time intervals

Time	0	30	60	2 hr	3 hr
		Insulin, $\mu U/ml$ of plasma			
	14.2 ±1.4	76.9 ±11.3*	87.1 ±12.4*	64.6 ±5.5*	46.3 ±6.1*
	27.8 ±5.4*	57.8 ±10.0*	70.0 ±4.3*	33.6 ±3.9	28.0 ±4.6*
	16.1 ±1.5	27.4 ±4.0	37.4 ±4.2	43.3 ±5.8	30.8 ±7.1*
	15.4 ±2.1	21.0 ±2.7	25.3 ±3.9	22.2 ±5.0	
	13.8 ±4.5	17.2 ±3.5	28.8 ±5.6	23.0 ±6.3	12.8 ±2.2

after administration of glucose in Table I. The maximal glucose concentrations in plasma achieved after the ingestion of glucose were 140.9 ±3.2 mg/100 ml[a] in American controls, 129.0 ±9.3 mg/100 ml in Bantu subjects, 195.6 ±18.8 mg/100 ml in sexual ateliotics, and 131.0 ±6.6 mg/100 ml in pygmies prepared with the high carbohydrate/high protein diet. This latter figure was similar to that noted in pygmies not prepared with the special diet, (145.5 ±8.8 mg/100 ml of plasma). Unlike the sexual ateliotic, the pygmy did not exhibit glucose intolerance.

The insulin responses of Bantu subjects and American controls were significantly greater than in pygmies. The mean peak insulin response to glucose in Bantu was 70.0 ±4.2 $\mu U/ml$, in American controls, 87.1 ±12.4 $\mu U/ml$, and in 11 pygmies not prepared by diet, 25.3 ±3.9 $\mu U/ml$. That these responses of the pygmy were not related to the prior diet or to the control group chosen is emphasized in Fig. 1. The mean maximal insulin response obtained in pygmies prepared by diet was 28.8 ±5.6 $\mu U/ml$.

Fig. 2 compares the mean insulin responses with glucose before and after HGH treatment. Subjects studied are American controls, pygmies not prepared by diet, and HGH-deficient dwarfs. Similar responses of a single pygmy prepared by diet and two offspring of pygmy mothers and Bantu fathers are shown after a shorter course of HGH treatment in Fig. 3. The individual responses of 11 pygmies are also shown in Table II which indicates not only the initial level of response, but emphasizes the complete, uniform failure of the pygmy to respond to HGH.

Both American controls and HGH-deficient dwarfs had a striking augmentation of their insulin responses

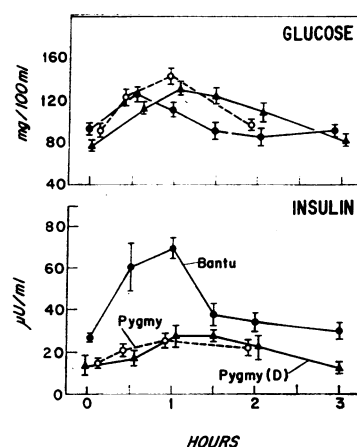[a] All mean and mean maximal values are given with standard errors of the mean.

FIGURE 1 Plasma glucose and insulin concentrations are shown for Bantu, pygmies unprepared by diet, and pygmies prepared by diet (D). 100 g of glucose was ingested at time 0. All points are means ±SEM. Peak insulin responses of both pygmy groups at 30 and 60 min are significantly different from Bantu.
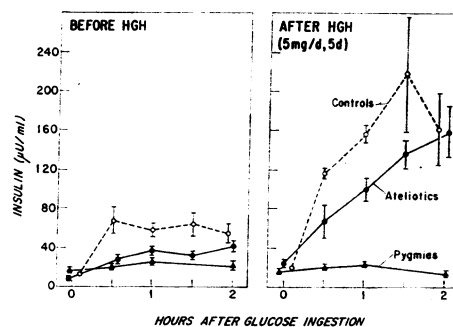

FIGURE 2 Plasma insulin concentrations after oral glucose (100 g) are shown before and after HGH treatment. All points are means ±SEM.
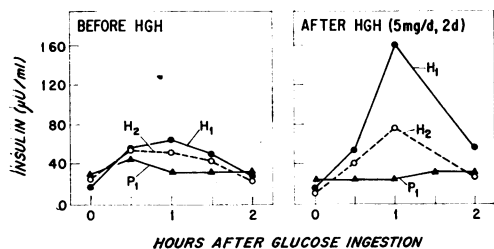
FIGURE 3 Plasma insulin concentrations after 100 g of glucose are shown before and after HGH treatment. H_1 and H_2 indicate offspring of pygmy mothers and Bantu fathers. P_1 is a pygmy prepared with a high protein-carbohydrate diet.

to glucose after receiving HGH for 5 days. The pygmy prepared by diet failed to increase his insulin response after receiving HGH for only 2 days, but two offspring of pygmy mothers and Bantu fathers (the *only* two studied) responded to this latter treatment with augmented insulin responses to glucose. The failure of the pygmy's insulin response to increase after HGH was noted previously after the infusion of arginine also. The mean data for this test are summarized in Table III.

Glucagon infusion. Unlike other stimuli for insulin secretion, the infusion of glucagon caused a similar increase of plasma insulin in both sexual ateliotics and pygmies—an increase which was similar with that seen in normal controls. The mean maximal response was 120.4 $\pm$12.8 μU/ml in pygmies, 102.8 $\pm$9.4 μU/ml in sexual ateliotics, and 101.6 $\pm$19.3 μU/ml in normal Caucasian controls.

Intravenous growth hormone and epinephrine. Mean basal concentrations of FFA were similar in each group studied. After the rapid infusion of 4 mg of HGH, plasma FFA concentrations and plasma glucose concentrations decreased. The time course of these early changes with the subsequent increase of FFA concentration in all groups except the pygmy are emphasized in Fig. 4. Since the timing of each FFA response was obviously variable from one individual to the next, mean minimal and maximal plasma concentrations and the percentage change from basal are given in detail in Table IV. There was not a statistically significant difference between any groups in the early decrease of FFA or glucose, but pygmies had a significantly smaller increase of FFA than any other group studied; (pyg-

TABLE II
Effect of HGH upon Insulin Response to Glucose

	Plasma insulin levels							
	Before treatment				After treatment			
	0	30	60	2 hr	0	30	60	2 hr
Pygmies								
Subject 1	20.0	14.0	14.0	14.0	15.0	14.0	36.0	15.0
Subject 2	16.0	26.0	46.0	34.0	14.0	36.0	38.0	—
Subject 3	11.0	11.0	15.0	10.0	12.0	14.0	14.0	12.0
Subject 4	24.0	33.0	—	12.0	13.0	22.0	16.0	9.0
Subject 5	18.0	18.0	24.0	24.0	14.0	24.0	16.0	12.0
Subject 6	30.0	38.0	—	—	13.0	28.0	32.0	22.0
Subject 7	8.0	26.0	24.0	20.0	13.0	13.0	22.0	18.0
Subject 8	9.0	14.0	12.0	14.0	12.0	22.0	26.0	14.0
Subject 9	10.0	22.0	39.0	20.0	16.0	34.0	30.0	18.0
Subject 10	10.0	11.0	22.0	12.0	14.0	14.0	14.0	18.0
Subject 11	13.0	18.0	32.0	62.0	10.0	28.0	34.0	12.0
Mean	15.3	21.0	25.3	22.2	13.3	22.6	24.7	15.0
SEM	2.2	2.7	3.9	4.9	0.48	2.5	2.7	1.3
Caucasian controls (8)								
Mean	11.3	68.5	57.0	51.5	19.5	119.0*	156.0*	160.0*
SEM	2.9	14.4	7.4	7.9	2.5	4.9	9.8	42.3
Sexual ateliotics (6)								
Mean	12.3	27.4	37.4	43.3	18.5	69.8	103.8*	158.2*
SEM	1.5	3.9	4.2	5.8	4.0	19.9	11.0	27.4

Insulin is given in microunits per milliliter.
* Indicates value is significantly > than pretreatment value.

TABLE III
*Effect of HGH upon Insulin Responses to Arginine**

| | Plasma insulin levels | | | | | | | | | |
| | Before treatment | | | | | After treatment | | | | |
	0	30	60	90	120	0	30	60	90	120
Pygmies	12.2	26.8	22.0	13.6	15.2	12.8	18.3	15.3	13.0	—
(19)	±1.9	±3.6	±3.9	±1.7	±2.2	±1.6	±1.2	±3.5	±1.7	—
Caucasian	21.5	81.5	49.2	28.0	27.7	23.0	290.0‡	101.0‡	33.0	—
Controls (8)	±4.5	±19.0	±0.5	±4.9	±7.6	±1.3	±65.0	±10.5	±1.7	—

* Insulin is given in microunits per milliliter. All values are mean ±SEM.
0.25 g of arginine per pound of body weight was given from time 0 to 30.
‡ Indicates value is significantly > than pretreatment value.

mies vs. Bantu $P < 0.01$, vs. normal $P < 0.05$, vs. HGH-deficient dwarfs $P < 0.01$).

The mean maximal FFA response to epinephrine was similar in growth hormone-deficient dwarfs and Babinga pygmies. Epinephrine caused an increase in plasma FFA concentration in each of these groups. The mean maximal increase of FFA over basal concentration was 150 ±20.5% in pygmies and 158 ±16.0% in HGH-deficient dwarfs. In a previous study, similar responses were noted in normal controls.

DISCUSSION

We have described previously two groups of dwarfs who have a monotropic deficiency of HGH, and Laron has described a type of dwarfism in which high basal values of immunoreactive HGH are found (7–9). The present study was undertaken to clarify the problems which arose in our earlier attempts to delineate the endocrine status of the African pygmy.

On previous expeditions to the Central African Republic, we established that Babinga pygmies do not have a deficiency of HGH, that their basal plasma HGH values are not elevated, and that several responses expected after HGH treatment were absent (1–3).

There were several problems which made it difficult to interpret the initial data. Although we had emphasized the poor insulin response of the pygmy to glucose after treatment with HGH, it seemed possible that this could be secondary to dietary peculiarities and not simply the result of resistance to HGH. Furthermore, we had compared the pygmy in all studies with American controls, but if neighboring Bantu resembled the pygmy, the comparisons would be invalid. We, likewise, emphasized the lack of a lipolytic response (i.e. a late rise in FFA level above basal) after intravenous HGH. This, however, could be nonspecific or, alternatively, might reflect a relatively greater physiologic effect of insulin in the pygmy. In addition to these problems, we

had no information which aided in determining the site of the defect and its manner of inheritance.

That the impoverished insulin response of the pygmy noted initially was not related to diet is evident from the data given in Table I and Fig. 1. Despite the fact that pygmies were prepared with a special diet for 2 wk, their plasma insulin responses to a glucose load remained attenuated and were almost identical with responses obtained in pygmies not treated with a high carbohydrate/protein diet. Insulin responses of Bantu to glucose were very similar to those of American controls. Glucagon, the only stimulus giving consistently a normal insulin response in HGH-deficient dwarfs, also gave a similar response in pygmies. This would seem to further support the fact that decreased insulin responses of the
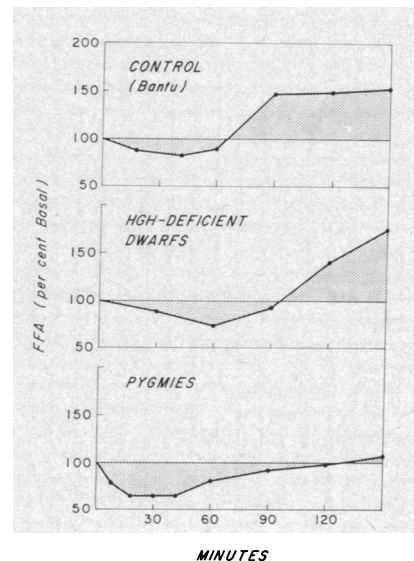

FIGURE 4 Free fatty acid concentration in plasma expressed as per cent of the basal FFA concentration is shown after 4 mg of intravenous HGH given over 20 min.

*Effect of HGH Infusion on Plasma Glucose and FFA Concentrations**

	Mean basal FFA concentration	Mean minimal FFA concentration		Mean maximal FFA concentration		Maximal decrease of plasma	
	μM/ml	μEq/ml	% of basal level	μEq/ml	% of basal level	mg/100 ml	% decrease from basal level
Pygmies (prepared by diet)	0.653 ±0.092	0.384 ±0.099* (59.0 ±9.4%)		708.0 ±0.074 (107.0 ±8.8%)		15.4 ±2.1* (17.5 ±1.9%)	
Bantu	0.652 ±0.084	0.394 ±0.090* (60.2 ±10.3%)		1.078 ±1.00* (165.0 ±21.0%)		20.5 ±6.6* (18.8 ±4.6%)	
HGH-deficient dwarfs	0.800 ±0.102	0.442 ±0.083* (55.0 ±12.0%)		1.402 ±0.126* (175.0 +16.3%)		16.9 ±4.3* (17.0 ±2.3%)	
American controls	0.608 ±0.062	0.394 ±0.070* (65.0 ±9.3%)		0.923 ±0.064* (151.0 ±7.8%)		—	

The initial decreases of FFA and glucose concentrations occurred within 40 min. All increases of plasma FFA concentrations occurred between 60 and 150 min.

* Indicates value differs significantly both from basal state and from maximum variation obtained in 12 control studies with the infusion of saline.

pygmy to glucose and arginine were somehow related to HGH. This finding, however, need not be overemphasized. Indeed, the insulin output of the pygmy to glucose may well be functionally appropriate. The point of major importance is not the appropriateness or inappropriateness of the pygmies initial insulin response to glucose, but the consistent failure of insulin secretion to increase after exogenous HGH was administered. In our experience, it remains striking and unique to find any group in which every individual studied failed to augment insulin secretion after HGH therapy.

The FFA responses after acute administration of HGH also support the view that HGH is at least partially ineffective in these individuals. As indicated in Fig. 4, the infusion of HGH failed to increase FFA levels in pygmies. Increases were readily detectable in control subjects, (including the Bantu) and in sexual ateliotics. As with insulin secretion, diet does not explain these results and our "control" studies appear suitable since Bantu from the same area do not show patterns similar to the pygmy. As with insulin output after HGH therapy, it remains possible that the impaired rise in FFA levels is related somehow to a greater physiologic activity of insulin in the pygmy. If so, it is an uniquely specific effect, since insulin did not alter the increase of FFA levels obtained with epinephrine.

The exact nature of the metabolic defect in the pygmy cannot be described with complete assurance, but the data seem to us most consistent with two possibilities: (a) An intracellular defect in HGH-mediated protein synthesis or (b) a similar, partial insensitivity to a

HGH-dependent substance such as sulfation factor. Although early responses to HGH (as we tested them) might well be pharmacologic effects, they are known to be independent of DNA-medicated protein synthesis (10, 11). The crucial metabolic reactions responsible for a normal growth rate, such as the over-all protein synthetic rate, are probably abnormal in the pygmy as indicated by the failure of HGH to increase lipolysis, augment insulin secretion, or reduce serum urea nitrogen concentration. These reactions are blocked readily by agents interfering with DNA-mediated protein synthesis (10–12). For example, the need for HGH to induce intracellular protein synthesis for its lipolytic action is fairly well documented (13, 14). Similarly, the ability of HGH to alter insulin secretion is clearly an effect requiring a minimum of hours and usually several days (15). There are normal basal levels of plasma HGH in the pygmy. If the above speculation is correct, this might indicate that neural centers controlling HGH secretion are not dependent upon a HGH-mediated protein synthetic process.

It cannot be determined at present whether the insensitivity noted is to HGH, per se, or to a substance generated by HGH. It is known that sulfation factor is normal in the pygmy, so one must consider the possibility that anabolic effects attributed to HGH are induced by an intermediary. It is not possible to speculate whether there is an unknown antagonist to the action of HGH or whether the HGH of the pygmy is anomalous, retaining immunoreactivity but lacking biological activity. With the present data, the latter possibility is highly unlikely. One would expect decreased responsiveness to

exogenous HGH only if the concentration of the anomalous hormone were increased.

Too few subjects were studied to state conclusively the manner in which the "pygmy" trait was inherited. Despite a considerable effort to locate such subjects, only two could be identified positively as the offspring of pygmy/Bantu parents. That the defect is not inherited as a dominant trait is apparent from studies conducted in these two hybrids. Fig. 2 shows the plasma insulin response to oral glucose before and after HGH treatment in controls, sexual ateliotics, and pygmies. Each of these subjects had received 5 mg of HGH daily for 5 days. Although the two hybrids were treated with HGH for 2 days only, each showed an increase of their plasma insulin response to glucose.

In summary, the pygmy has several defective responses to HGH. These probably involve actions of HGH dependent upon late protein synthetic processes. Offspring of pygmy mothers and Bantu fathers do not show abnormal insulin responses to glucose and readily augment their insulin responses to HGH treatment, indicating that the defect is not inherited as a dominant trait. Although isolated cases of insensitivity to a peptide hormone have been described, the defect in the pygmy appears unique in that it effects an entire race.

ACKNOWLEDGMENTS

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