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Research Article

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Nearly half of the diabetics (16 of 38) had significant pathological abnormalities of the retina, but these changes were conspicuously absent in HGH-deficient dwarfs. No retinal lesions were detected in any HGH-deficient dwarf.

Diabetes Mellitus and Sexual Ateliotic Dwarfism: a Comparative Study

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ABSTRACT The incidence of diabetic retinopathy was determined in 38 diabetics and 31 sexual ateliotic dwarfs deficient only in human growth hormone (HGH). The age and sex distribution were approximately the same in each group. The incidence and pattern of glucose intolerance were similar in diabetics and HGH-deficient dwarfs. The majority of diabetics (21 of 38) and HGH-deficient dwarfs (26 of 31) exhibited insulinopenia after glucose, mixed glucose-beef meals, and the infusion of l-arginine. A smaller number of HGH-deficient dwarfs (5 of 31) and diabetics (8 of 38) had normal or augmented absolute insulin responses to these same provocative stimuli. Hypercholesterolemia and hypertriglyceridemia occurred with greater frequency in both diabetics and HGH-deficient dwarfs than in normal controls. 8 of 21 diabetics and 6 of 21 sexual ateliotics exhibited significant hypertriglyceridemia. Five diabetics and six sexual ateliotics had significantly greater than normal serum cholesterol levels.

Nearly half of the diabetics (16 of 38) had significant pathological abnormalities of the retina, but these changes were conspicuously absent in HGH-deficient dwarfs. No retinal lesions were detected in any HGH-deficient dwarf.

INTRODUCTION

In 1966 it was reported that sexual ateliotic dwarfs have a monotropic deficiency of human growth hormone (HGH) (1) and that a relatively high incidence of gross glucose intolerance occurs in this group. Studies carried out in a greater number of these dwarfs confirmed our initial impression that glucose intolerance was commonly associated with HGH deficiency and revealed, in addition, two patterns of insulin secretion. Most of these dwarfs exhibited insulinopenia after provocative stimuli for the secretion of insulin, and inherited dwarfism as an autosomal recessive trait. A smaller number of sexual ateliotics (5 of 31) had augmented insulin responses to provocative stimuli, and usually inherited dwarfism as an autosomal dominant trait (2, 3). These dwarfs thus appeared to resemble subjects with diabetes mellitus, who are reported to have characteristic patterns of insulin secretion: grossly decreased, as in juvenile diabetes, or less markedly decreased to normal, as in adult onset diabetes (4).

The general aim of this study was twofold: first, to document more systematically the pertinent metabolic and hormonal similarities of diabetics and sexual ateliotic dwarfs, and second, to determine if microangiopathic changes, specifically diabetic retinopathy, occurred in both groups.

In brief, the results indicate that sexual ateliotic dwarfs do not show pathological changes in the retina of any type, despite patterns of carbohydrate intolerance, insulin secretion, and blood lipid profiles similar to those of subjects with diabetes mellitus. Nearly half of the diabetic group showed pathological changes of the retina. The evidence suggests a supportive role of growth hormone in the pathogenesis of these lesions.

METHODS

31 sexual ateliotic dwarfs, 38 diabetics, and 52 normal healthy controls were studied. Each of the dwarfs had been previously shown to lack immunoassayable HGH after arginine infusion and insulin-induced hypoglycemia. Other conventional tests of pituitary function were normal in this group. These included radioactive iodine uptake, protein-bound iodine, urinary FSH (mouse units) and urinary 17-hydroxycorticoids and 17-ketosteroids before and after metapyrone (3, 5). On the basis of insulin responses to arginine and glucose and sensitivity to exogenous insulin on initial testing, two groups of sexual ateliotics were clearly delineated. Most (26 of 31) had significantly lower than

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TABLE I

Major Characteristics of Sexual Ateliotics and Diabetics Studied

	Characteristics	Comments
Sexual ateliotics		
Group 1 (No. = 26)	1. HGH less than 0.5 mμg/ml after arginine infusion or insulin-induced hypoglycemia. 2. Hypersensitive to exogenous insulin 3. Insulin responses to glucose and to arginine challenge less than mean control response, never greater.	1. Autosomal recessive inheritance or sporadic. 2. Five subjects between 10 and 20% greater than ideal body weight.
Group II (No. = 5)	1. HGH less than 5 mμg/ml after arginine infusion or insulin-induced hypoglycemia. 2. Not hypersensitive to exogenous insulin. 3. Insulin responses to glucose and to arginine at least two standard deviations greater than normal mean response.	1. Autosomal dominant inheritance or sporadic 2. Two subjects obese.
Diabetics		
Group I (No. = 23)	1. Insulin responses to glucose and to arginine challenge less than in controls (as for ateliotics of Group 1).	1. Six had received insulin 2–4 yr before testing. 2. 12 patients treated with sulfonylureas before tests. 3. Five patients treated with diet alone 3–8 yr; three subjects obese.
Group II (No. = 8)	1. Insulin responses to glucose and to arginine greater than normal (as for ateliotics of Group II).	1. Adult onset in all eight cases. 2. Two subjects 10–20% greater than ideal body weight.
Not classified (No. = 7)	1. Insulin antibodies prevented measurement of insulin.	1. Six cases with onset before age 25; two subjects obese. 2. Average duration of diabetes equals 15.0 yr.

normal to low-normal insulin responses to exogenous arginine and glucose. One group of sexual ateliotic dwarfs (5 of 31 studied) had significantly higher insulin output and may represent a distinct genetic type or a group with concomitant diabetes mellitus and HGH deficiency. Methods of selecting these groups have been reported extensively elsewhere (3).

Diabetic subjects were selected to match the sexual ateliotics in age and sex. The mean duration of diabetes was 12.4 yr in the diabetic subjects compared to the estimated duration of glucose intolerance in the dwarf group of 14.6 yr. With the exception of seven diabetics in whom insulin antibodies precluded an accurate measurement of insulin, the diabetics were grouped on the basis of their insulin response to oral glucose. The glucose and insulin data from diabetics with insulin antibodies are not used in this paper. The major characteristic of all groups are summarized in Table I.

Procedure. All studies were performed after an overnight fast and before ambulation. Glucose tolerance tests and arginine infusions were carried out in each subject. Glucose, 1.5 g/lb. of body weight, was given orally after each subject received at least 200 g of carbohydrate daily for 5 days. Arginine, 0.25 g/lb. of body weight, was infused into an antecubital vein of each patient over a 30 min period, and plasma samples collected every 15 min for 2 hr. To prevent repeated venipunctures, a saline infusion was allowed to "bleed" spontaneously 1–2 min before the collection of each sample. Randomly selected individuals from each group received combined glucose-beef meals (glucose 1.5 g/lb. of body weight and 300-350 g of beef tenderloin).

Basal levels of glucose, cholesterol, and triglycerides in blood were measured in the majority of subjects. The final values of cholesterol and triglyceride concentrations for each patient represent the mean of three early morning fasting specimens to avoid spuriously low or elevated levels of a single determination. If three adequate samples were not available, the subject was not included in the comparison of serum lipids.

Glucose was measured by a glucose oxidase method, serum triglycerides by the method of Van Handel and Zilversmit (6), and cholesterol by the method of Carr and Drekter (7). Plasma HGH and insulin were measured by a charcoal modification of the initial immunoassay procedure of Yalow and Berson (8) and Glick, Roth, Yalow, and Berson (9). The insulin assay was accurate to within 5.0 μU/ml and the HGH assay to within 0.5 mμg/ml of plasma. For each hormone, samples were analyzed in triplicate and if the discrepancy between samples was greater than 10%, they were reanalyzed.

Two ophthalmologists evaluated the eyes of each subject using both direct and indirect ophthalmoscopic methods with

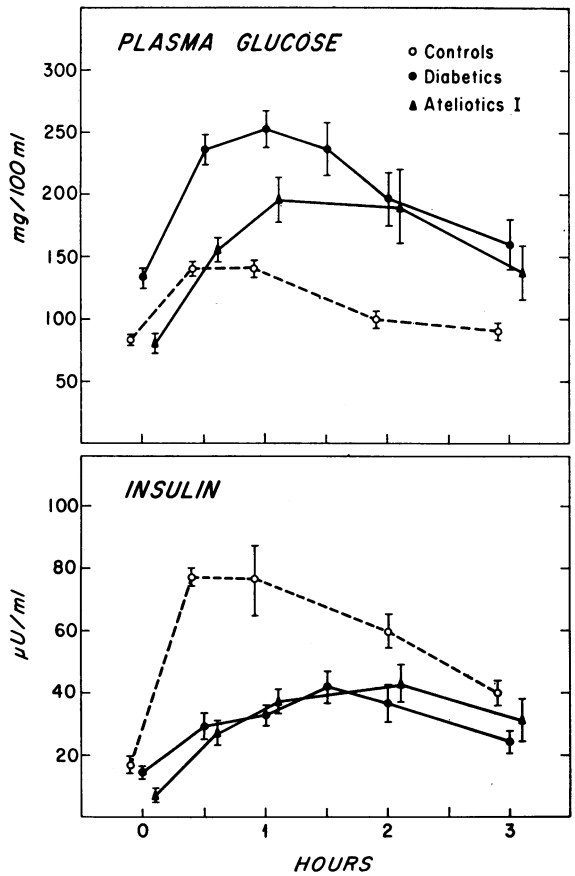

FIGURE 1 Plasma concentrations of glucose and insulin after 100 g of glucose orally are given for controls, diabetics, and sexual ateliotics with low absolute insulin concentrations noted on initial testing. Points are means ±SEM.

the pupils of each subject fully dilated. The ophthalmologists were not aware which subjects were normal or diabetics. Fundi were sketched, and, if necessary, photographed. The diagnosis of diabetic retinopathy depended upon the presence of multiple microaneurysms with or without significant angiopathic or proliferative changes.

RESULTS

Glucose tolerance. The mean glucose and insulin concentrations in plasma of all groups studied during an oral glucose tolerance test are compared at pertinent time intervals in Figs. 1 and 2.

The maximal glucose concentrations in plasma achieved after the ingestion of glucose were 140 ±3.2 mg/100 ml[1] in normals, 253.6 ±14.2 mg/100 ml in diabetics, and 195.6 ±18.8 mg/100 ml in sexual ateliotics. Plasma glucose was consistently elevated above basal concentration in dwarfs and diabetics 2 hr after ingestion of the glucose load. There was thus similar hyperglycemia and degree of glucose intolerance in the dwarfs and diabetics. (Figs. 1 and 2).

Of 38 diabetics, insulin could be measured in 31. 23 of 31 diabetics with measurable plasma insulin exhibited insulinopenia or low-normal insulin responses after ingestion of glucose. The mean maximal insulin response to glucose in this group of diabetics was 41.8 ±4.6 μU/ml compared with 77.3 ±2.9 μU/ml in controls. Type I sexual ateliotics exhibiting insulinopenia had mean maximal insulin responses after glucose of 43.3 ±5.8 μU/ml, a figure similar to that seen in the diabetics exhibiting low insulin output.

Five sexual ateliotic dwarfs and eight diabetics had significantly greater than normal absolute plasma insulin concentrations after oral glucose (See Table I). The mean maximal insulin concentration in plasma in the former group was 153 ±29 μU/ml, and in the latter, 157.7 ±12.4 μU-ml. These responses differ significantly from normals and the group of dwarfs and diabetics with low insulin output (Fig. 2).

Glucose-beef meal. Randomly selected individuals from each group were restudied after combined beef and

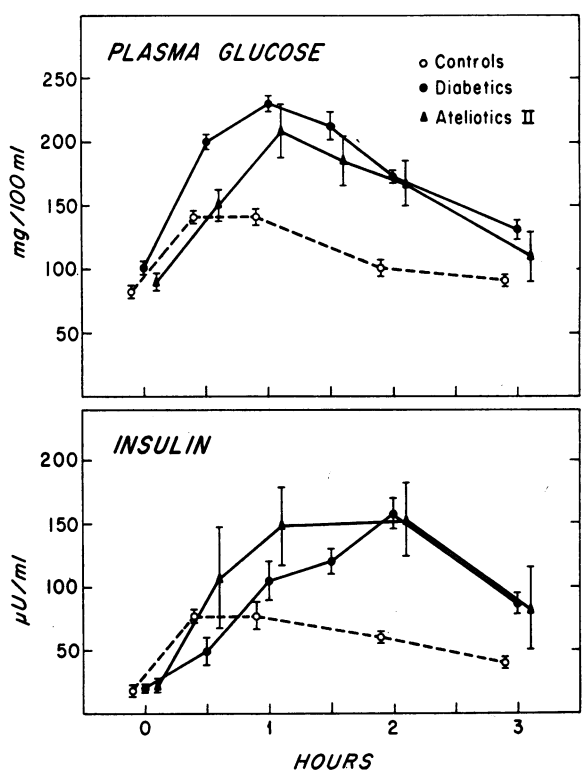

FIGURE 2 Plasma concentrations of glucose and insulin after 100 g of glucose orally are given for controls, diabetics, and sexual ateliotics with greater than normal absolute insulin concentrations during initial testing. Points are means ±SEM.

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

TABLE II

Plasma Concentrations of Glucose and Insulin Following Glucose-Beef Meals

	Glucose						Insulin					
	0	30	60	90	2 hr	3 hr	0	30	60	90	2 hr	3 hr
Normals (10)	84.7 ±3.3	165.5 ±20.5	144.6 ±11.5	112.0 ±8.7	96.2 ±8.9	68.5 ±3.6	21.6 ±3.5	116.2 ±50.7	166.5 ±28.0	140.0 ±21.4	95.8 ±16.0	68.5 ±6.0
Diabetics (7) Low output	109.3* ±1.6	176.0 ±13.2	268.3* ±30.1	— —	235.4* ±21.6	189.3* ±38.0	17.9 ±5.0	26.0 ±8.4	48.2 ±6.3	— —	54.3 ±9.3	43.0 ±8.5
Group I ateliotics (10) Low output	82.5 ±4.1	170.8 ±8.2	201.0* ±13.9	— —	123.0* ±33.0	105.0* ±26.2	8.2 ±2.7	43.6* ±12.9	57.8* ±8.5	— —	32.2* ±3.1	27.8* ±5.6
Diabetics (5) High output	118.9* ±8.9	182.0 ±8.4	220.0* ±19.5	210.0* ±28.0	184.0* ±10.2	161.2* ±21.3	15.6 ±6.0	68.4* ±17.3	96.0* ±11.0	137.0 ±18.0	140.0* ±6.8	94.0 ±6.3
Group III ateliotics (5) High output	90.5 ±4.5	156.7 ±6.8	187.2* ±21.4	171.5* ±29.7	141.9* ±31.4	126.0 ±11.0	18.4 ±5.5	127.2 ±35.0	159.0 ±37.0	159.0 ±40.6	147.0 ±40.7	122.0 ±41.7

The meal consisted of 100 g of glucose and 350 g of beef tenderloin ingested within 10 min. Glucose is given in mg/100 ml. Insulin is given in μU/ml. Starred values differ significantly from control values ($P < 0.01$).

glucose meals. In 10 normal controls, the mean maximal insulin response was 166 ±28 μU/ml. In 10 type I sexual ateliotics, and seven diabetics with low insulin output after glucose, the mean maximal insulin concentration after a mixed meal measured 57.8 ±8.5 and 54.3 ±9.3 μU/ml respectively. These concentrations differ from controls at the 1% significance level but are not significantly different from each other. In diabetics with normal to increased insulin responses to glucose, the mean maximal insulin concentration in plasma after the mixed meal measured 140 ±6.8 μU/ml. All five of the sexual ateliotics with greater than normal insulin output after glucose received the combined beef meal. The mean maximal concentration of insulin in plasma for this group after the mixed meal was 159 ±37.5 μU/ml. Using the unpaired *t* test, plasma insulin concentrations in normals differed significantly at most time intervals from both groups of diabetics and ateliotics. From the low output diabetics these times were 30–180 min ($P < 0.01$ at each interval), from the type I ateliotics at time 60–180 min ($P < 0.01$ at all intervals), and from normal or increased insulin output diabetics, all sampling intervals except 30 and 90 min, ($P < 0.01$ at 60, 120, and 180 min). Insulin output was not significantly different from normal in the high insulin output ateliotics except at 180 min ($P < 0.01$).

The increase in plasma concentration of glucose after the mixed meal was significantly greater than normal in both groups of ateliotics and diabetics, i.e. all groups regardless of their insulin responses showed significant hyperglycemia compared to controls, although this was more pronounced in diabetics. Plasma glucose levels differed significantly from the controls in all groups from 60 to 180 min. Basal concentrations of glucose were significantly greater than normal in both groups of diabetics, but not in ateliotics. These data are summarized in Table II and Fig. 3.

Arginine infusion. The mean maximal insulin concentration after arginine in normal controls was 90.4 ±8.6 μU/ml. Sexual ateliotic dwarfs who had shown significant insulinopenia after glucose had a mean maximal insulin response to arginine of 29.3 ±5.5 μU/ml. The diabetics with low insulin output after glucose had a mean maximal plasma concentration of insulin following arginine of 46.5 ±9.1 μU/ml. The plasma insulin concentrations of these groups at the selected time intervals after the infusion of arginine are shown in Fig. 4. All five type II ateliotics were studied after arginine. Their maximal insulin responses were 180, 200, 196, 65, and 115 μU/ml. Only five of the diabetics with increased or normal insulin responses to glucose were studied after the infusion of arginine. Their maximal insulin responses measured 79, 124, 50, 160, and 102 μU/ml.

Serum or plasma concentrations of cholesterol and triglyceride. The plasma or serum cholesterol and tri-

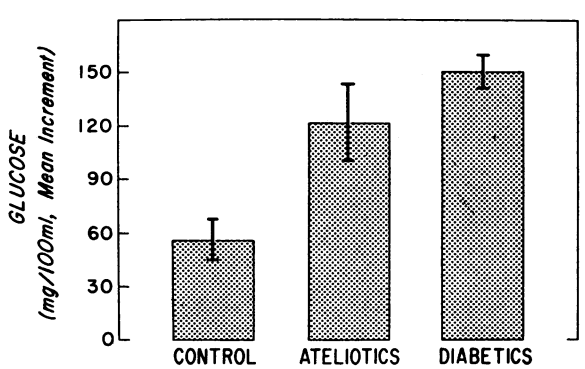

FIGURE 3 The mean maximal increase of plasma glucose from the basal fasting glucose concentration is given after 350 g of beef tenderloin and 100 g of glucose were ingested over a 10 min period. Standard errors of the mean are indicated.

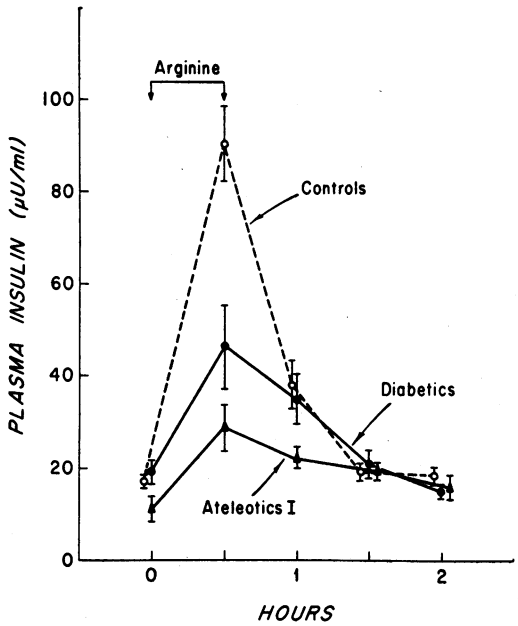

FIGURE 4 Plasma concentrations of insulin are shown after infusion of 0.25 g of orginine per lb. of body weight. Diabetics and sexual ateliotics with low insulin output to glucose only are illustrated. For others, see text.

glycerides are plotted for each individual studied in Fig. 5 and 6. Since normal values for these lipids change with age, for the normal mean and variation from the mean, we have used the extensive age-corrected data of Albrink, Meigs, and Man (10). The methods for cholesterol and triglycerides used in our laboratory give normal values comparable to those of Albrink (6, 7, 10). Of the 52 normal controls in our own study, only two were not within this range. One had an elevated serum cholesterol and one exhibited both elevated serum cholesterol and triglyceride levels. Both dwarfs and diabetics showed a significantly increased incidence of hypercholesterolemia and hypertriglyceridemia in the fasting state. 13 diabetics and 15 dwarfs had serum triglyceride levels within the normal range, but 8 diabetics and 6 dwarfs had hypertriglyceridemia, 5 diabetics and 6 dwarfs had cholesterol levels significantly greater than normal. Since these abnormalities did not appear related to the insulin responses shown after either arginine or glucose, nor to basal insulin concentration in plasma, the data has been combined.

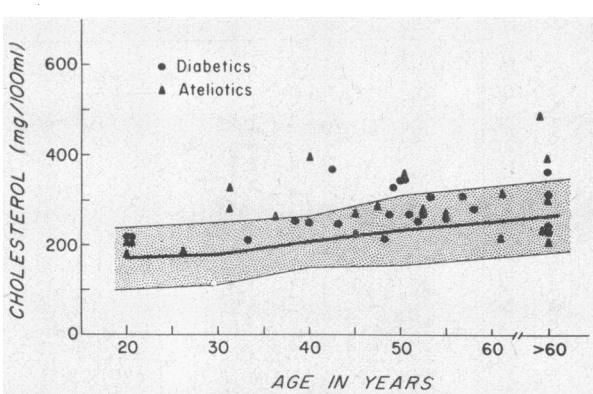

FIGURE 5 Serum concentrations of cholesterol are shown for diabetics and sexual ateliotics. Each point is a mean of three determinations. The mean normal concentration of cholesterol and two standard deviations from the mean are shown at pertinent age levels (8).

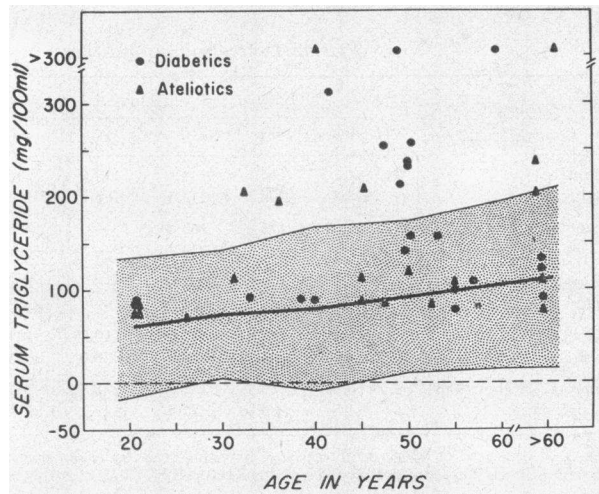

FIGURE 6 Serum concentrations of triglycerides are shown for diabetics and sexual ateliotics. Each point is a mean of three determinations. The mean normal concentration of triglycerides and two standard deviations from the mean are shown at pertinent age levels (8).

Ophthalmoscopic examination. The pupils of each eye were fully dilated and examined by two ophthalmologists. When retinal pathology was detected, sketches were made of the fundus and fundic photographs taken.

41% of the total diabetic group showed pathological changes classical of diabetic retinopathy. 16 of the 38 diabetics had multiple microaneursyms. Of these 16, 7 had exudates and 4 with exudates had detectable hemorrhages. Proliferative changes in the retina were noted in four diabetics. We could not correlate the presence or absence of retinopathy with any of the metabolic parameters measured. Pathological changes of the retina were not detected in a single dwarf, most of whom were examined on a minimum of two separate occasions over a 4 yr period.

DISCUSSION

The suspicion that growth hormone might be involved in the retinal pathology of diabetes mellitus dates from the publication of Poulsen's classic case and from re-

ports that exogenous growth hormone has a diabetogenic action (11–13). While it is true that hypophysectomy can result in improvement in diabetic retinopathy, this improvement can occur independently of alterations in plasma growth hormone levels (14).

The role carbohydrate intolerance and associated abnormalities of insulin secretion play in the development of diabetic retinopathy is not known. Since a very high incidence of carbohydrate intolerance and lipid abnormalities occur in sexual ateliotic dwarfs, and these individuals are deficient in HGH, it seemed reasonable to us that we might assess more fully in these individuals both the role of HGH and the significance of at least two pertinent metabolic abnormalities to the pathogenesis of diabetic retinopathy.

The data show clearly that diabetics and sexual ateliotics do have striking similarities of carbohydrate intolerance, blood lipid profiles, and insulin secretion. Both normal, decreased, and greater than normal insulin responses were seen in these two groups after glucose, glucose-beef meals, and after infusion of arginine. Changes of plasma glucose after each stimulus were simliar in diabetics and sexual ateliotic dwarfs; an exaggerated hyperglycemia occurred in both groups after the ingestion of glucose and after glucose-beef meals.

There were two points of divergence. Basal glucose concentration was more often greater than normal in diabetics than in sexual ateliotics. The mean basal glucose concentration, however, did not exceed 120 mg/100 ml, even in the diabetic group. Neither group of diabetics significantly augmented insulin responses to a mixed meal. In all controls and sexual ateliotics with low insulin responses to arginine or glucose, plasma insulin concentrations were greater after glucose-protein meals than after either glucose alone or the infusion of arginine. Although we have no explanation for the diabetic's failure to augment insulin responses to a mixed meal, it may reflect, as reported by others, a lack of insulin reserve in this group (15).

We were unable to characterize completely the lipid profiles in blood, but dwarfs and diabetics had a remarkably similar incidence of hypertriglyceridemia and hypercholesterolemia. Overall, the metabolic data can be summarized by stating that we could not distinguish between HGH-deficient dwarfs and diabetics on the basis of their insulin responses to several stimuli, the degree of their carbohydrate intolerance, or their lipid profiles in serum.

The funduscopic differences between these groups stand in marked contrast to the metabolic similarities. Whereas nearly half (41%) of the diabetics in our study exhibited significant pathological changes of the retina, no retinal changes of any type were noted in a HGH-deficient dwarf. The incidence of retinopathy in the diabetics of this study was in agreement with previously published figures. In studies summarized by Leopold, the incidence of retinopathy in diabetics examined varied from 8% in early studies in the 1940's to well over 40% in most series conducted since 1950 (16).

Although diabetic retinopathy occurs in patients with acromegaly and in patients with chronic pancreatitis who exhibit carbohydrate intolerance, it does so quite rarely. The conclusion that HGH plays at least some supportive role in the pathogenesis of these lesions is thus suggested, but cannot be substantiated by our studies. It might be that an unknown factor from the pituitary is likewise deficient in the type of dwarfs studied, but this, of course, cannot be determined. What does seem apparent is that carbohydrate intolerance and serum lipid abnormalities per se, regardless of the pattern of insulin secretion, are relatively impotent as causative factors of retinopathy in the chronic absence of HGH. It might be that the evolution of diabetic retinopathy occurs when the metabolic abnormalities of diabetes mellitus coexist with the ability to secrete HGH.

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