Familial Combined Hyperlipoproteinemia

EVIDENCE FOR A ROLE OF GROWTH HORMONE DEFICIENCY IN EFFECTING ITS MANIFESTATION

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ABSTRACT Hyperlipidemia associated with an isolated deficiency of growth hormone was investigated in 10 subjects with hypercholesterolemia consistently present over a 10-yr period. 8 of these 10 had serum triglyceride concentrations >185 mg/dl. 13 growth hormone-deficient patients with normal serum lipids, 28 age-matched controls, and 6 families possessing both growth hormone-deficient and hormonally normal members were also studied.

Hyperlipidemia occurred with growth hormone deficiency only in families in which hormonally normal subjects likewise exhibited hyperlipidemia. However the elevation of serum lipids, particularly cholesterol, was invariably greater in the growth hormone-deficient members of these families. Studies were most consistent with the classification of this trait as familial combined hyperlipoproteinemia.

Basal serum concentrations of insulin, glucose, and free fatty acids were similar in all groups. After oral glucose (1.5 g/kg of body wt) both hyperlipidemic and normolipidemic dwarfs exhibited a similar degree of glucose intolerance associated with insulinopenia. Sensitivity to insulin, assessed after the intravenous injection of insulin (0.05 U/kg of body wt), increased and was virtually identical in the two dwarf groups. Administration of 5 mg of human growth hormone twice a day for 1 wk to five subjects did not alter serum lipid patterns.

The data provide no conclusive evidence concerning a direct effect of growth hormone deficiency on hyperlipoproteinemia. We postulate that in some individuals growth hormone deficiency may unmask an underlying defect in lipoprotein metabolism.

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INTRODUCTION

From dwarfs with an isolated deficiency of growth hormone followed during a 10-yr period, 10 were identified who consistently exhibited serum cholesterols in excess of 300 mg/dl; 8 of these 10 had serum triglyceride concentrations in excess of 185 mg/dl. The cause of this hyperlipidemic state was not clear from the original data. From electrophoretic studies and from the isolation of serum lipoproteins by ultracentrifugation, the majority of dwarfs with elevated lipids had what appeared to be a type II-B lipoprotein pattern. High density lipoprotein, low density lipoprotein (LDL),[1] and very low density lipoprotein (VLDL) were found immunologically similar in hyperlipidemic and normolipidemic dwarfs, and the proteins did not differ from those isolated from normal controls (1–4).

Since all dwarfs did not have elevated serum lipids, it seemed reasonable that at least a partial solution to the problem might be found by comparing the hyperlipidemic and normolipidemic dwarfs. First to be considered was the possibility that the lipid status of the dwarf might reflect differences within the group in glucose tolerance, insulin secretion, and/or insulin sensitivity. A more systematic investigation of this was required. Secondly, it seemed plausible that growth hormone deficiency might not of itself cause hyperlipidemia but that it would merely unmask an independently inherited tendency for hyperlipidemia. To demonstrate such an effect would require characterization of serum lipids in multiple family members that had both hormone-deficient and nongrowth hor-

[1] *Abbreviations used in this paper*: LDL, low density lipoprotein; VLDL, very low density lipoprotein.

mone-deficient members. As we will show subsequently, the results of this investigation were most consistent with the second possibility.

METHODS

23 dwarfs deficient only in growth hormone were the subjects of this study. Previous studies had established in each subject the absence of immunoreactive growth hormone after both insulin-induced hypoglycemia and the infusion of L-arginine. Radioactive iodine uptake, protein-bound iodine, urinary gonadotropins, and urinary 17-hydroxycorticoids and 17-ketosteroids before and after metapyrone were normal in each of these patients (1–4). 10 dwarfs were noted to be consistently hypercholesterolemic. A group of 13 consistently normolipidemic dwarfs of comparable sex and age were selected for the purposes of this study. Control subjects (28) were similar in age and sex distribution. For lipid and lipoprotein analysis, blood samples were collected from each subject in disodium EDTA, 1 mg/ml, after 12–14 h overnight fast, and the plasma was separated from the erythrocytes by centrifugation at 2,400 rpm for 30 min at 4°C and processed within a 48–60-h period. These studies were performed at least twice during the follow-up period. The lipoproteins were separated by differential-density ultracentrifugation by the method of Havel et al. (5). For separation of chylomicrons, the plasma was left standing overnight and spun at 9,800 *g* for 10 min. The other lipoprotein fractions were isolated by centrifuging the plasma at 10°C in a Spinco model L ultracentrifuge (Beckman Instruments, Inc., Spinco Div., Palo Alto, Calif.) using a 40 rotor head at 105,000 *g* for 22 h. The plasma VLDL and LDL were isolated at solvent densities of 1.006 and 1.063, respectively. The isolated lipoprotein fractions were centrifuged twice more in salt solutions at each separation density to remove contaminants. All fractions were dialyzed at 4°C against 0.15 sodium chloride that contained 0.001 M EDTA at pH 7. Plasma cholesterol and triglyceride were measured by standard methods (6, 7). Plasma lipoprotein patterns were determined by paper and agar electrophoresis as described by Nobel (8).

The serum lipid profile described above was measured in two families with multiple members deficient in growth hormone. Serum cholesterol and triglycerides only were measured in members of four additional families. Details regarding these subjects are presented in Table II and Fig. 1.

For comparing hyperlipidemic and normolipidemic dwarfs the following tests were run in both groups:

Basal measurements. Serum concentrations of insulin and free fatty acids were measured after an overnight fast on at least three occasions. The means of these values are used in this paper for each individual. Hemoglobin (Hb) A_{Ic}, a measure of overall glycemia, was determined by column chromatography through the courtesy of Doctor Kenneth Gabbay (Boston Childrens Hospital, Harvard Medical School).

Carbohydrate tolerance. Both groups of dwarfs received a glucose tolerance test on at least two occasions. Glucose, 1.5 g/kg of body wt was given orally, and serum samples were collected every 30 min for 3 h. All sera were subsequently analyzed for glucose and immunoinsulin in the same assay. Studies were done both at the beginning of this study period and 10 yr later.

Sensitivity to insulin. Insulin tolerance tests were conducted with 0.05 U insulin/kg body wt i.v. Glucose measurements were made on samples collected every 15–20 min for 90–120 min.

Glucose, insulin, and free fatty acids were measured by methods previously reported in detail (9–12). Statistical analysis of data used the Student's *t* test; the sign test was used for paired analysis.

RESULTS

Table I summarizes the major characteristics of the plasma lipids in the hyperlipidemic dwarfs as analyzed by paper and agar electrophoresis; ultracentrifugation was also performed. A strongly staining beta band was demonstrable by electrophoresis in all 10 hyperlipidemic patients at the time of initial examination. With three exceptions (subjects 6, 7, and 9), the patients also showed a prominent prebeta band, which stained

TABLE I
Serum Lipids at Two Periods in Hyperlipidemic Growth Hormone-deficient Dwarfs

Subject	Sex	Age*	Study period I 1968–1969		Study period II 1977–1978	
			Cholesterol	Triglyceride	Cholesterol	Triglyceride
		yr	*mg/dl*	*mg/dl*	*mg/dl*	*mg/dl*
Normal	—	—	<280	<150		
1. R.S.	M	74	555	510	500	460
2. E.S.	F	76	520	453	590	480
3. D.T.	M	48	312	331	390	165
4. M.A.	F	55	329	396	410	502
5. J.M.	M	32	363	578	320	450
6. J.A.	M	44	462	163	390	170
7. F.B.	F	54	392	170	380	192
8. A.K.	M	40	285	461	302	410
9. M.K.	F	38	310	163	346	155
10. O.R.	M	44	360	410	410	400

* Age, when studied initially in 1968–1969. With the exception of subject 3 (D.T.), lipid patterns were comparable in subsequent evaluations.

less intensely. In two patients with the highest cholesterol (subjects 1 and 2), a double prebeta band was found by agar electrophoresis. Plasma LDL and VLDL were elevated in patients exhibiting both hypertriglyceridemia and hypercholesterolemia.

Patient No. 3 differed in the type of lipemia shown on the first and the second characterization. On initial examination, both cholesterol and triglyceride were elevated; on the second examination (9 yr later) only cholesterol was abnormally increased.

Pedigree studies

The pedigrees of six families in whom it was possible to characterize serum lipids in 37 subjects are shown in Fig. 1. In families A–C, no growth hormone-deficient subject had a cholesterol level exceeding 220 mg/dl nor a triglyceride concentration greater than 105 mg/dl. A total of 10 growth hormone-deficient subjects were studied. Multiple members of these families with normal stature also had normal serum concentrations of cholesterol and triglyceride. Family A is particularly noteworthy. There were six growth hormone-deficient dwarfs evaluated in this family and it was possible to study three generations.

In families D–F, pedigrees are illustrated for growth hormone-deficient subjects demonstrated to have a persistent hyperlipidemia. In the families of each of these dwarfs, a high incidence of hyperlipidemia was noted in members with normal stature (Fig. 1, Table II). In family D, a husband and wife (patients 1 and 2 in Table I) had serum cholesterol concentrations ranging between 450 and 650 mg/dl with a concomitant elevation of serum triglyceride concentration. A brother of the husband with normal stature had serum cholesterol concentrations between 310 and 340 mg/dl on four separate occasions with serum triglycerides within a normal range (patient 3, Fig. 1D). One offspring of normal size in this family exhibited a type IIA and another a type IV lipoprotein pattern. In families D–F, considered *in toto*, there were seven growth hormone-deficient dwarfs, six of whom exhibited a type IIB pattern and one of whom showed a type IIA pattern. In these same families, a total of 11 nongrowth hormone-deficient subjects were studied, four of whom exhibited a type IIA, two of whom exhibited a type IV, and five of whom had normal lipids. A type IIB pattern was not seen in this group. In a seventh family, not illustrated, incomplete studies were obtained (subject

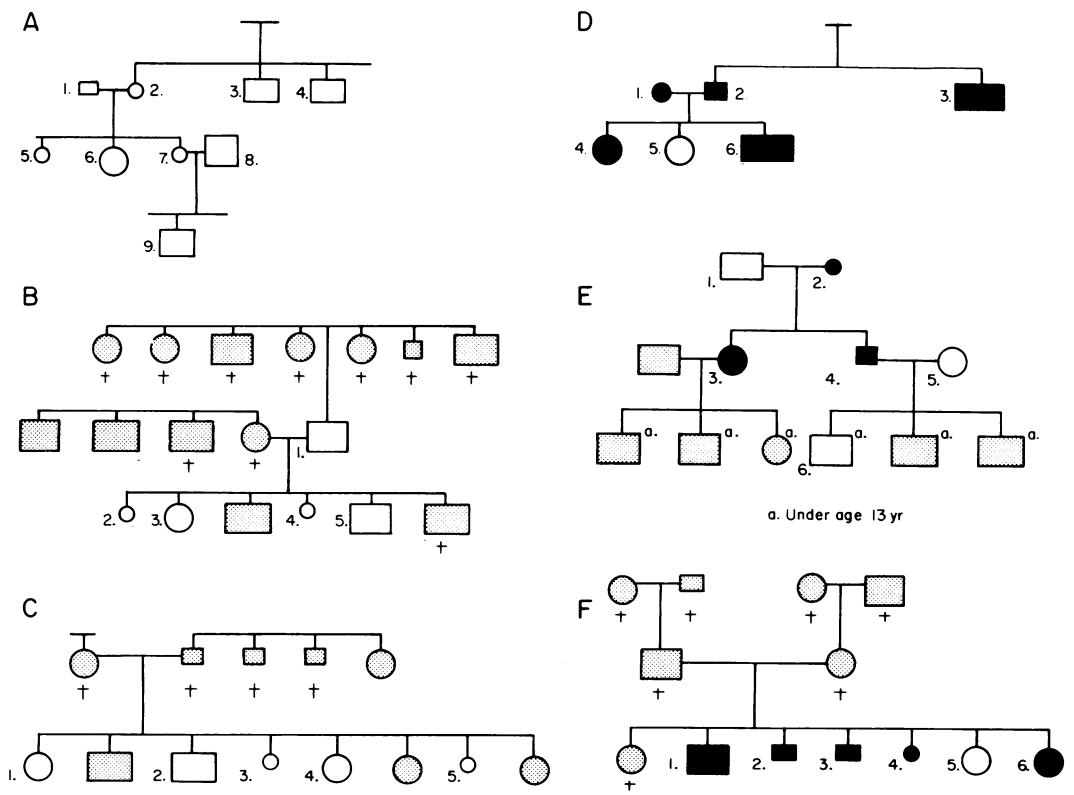

FIGURE 1 Pedigrees of six families with an hereditary deficiency of growth hormone are shown. Symbols indicate lipid findings and absence or presence of normal stature. Lightly shaded symbols indicate patients not available for study. Black indicates hyperlipidemia; unshaded, normolipidemia. Numbers refer to patients listed in Table II.

TABLE II
Serum Lipids in Six Families

	Cholesterol	Triglyceride	Phenotype
	mg/dl	*mg/dl*	
Family A			
1*	135	80	Normal
2*	160	110	Normal
3*	145	70	Normal
4*	230	128	Normal
5*	180	110	Normal
6	200	90	Normal
7*	205	95	Normal
8	186	103	Normal
9	170	102	Normal
Family B			
1	220	100	Normal
2*	195	107	Normal
3	240	125	Normal
4*	190	105	Normal
5	220	138	Normal
Family C			
1	168	90	Normal
2	225	86	Normal
3*	210	95	Normal
4	180	75	Normal
5*	219	132	Normal
Family D			
1*	520	454	Type IIB
2*	505	510	Type IIB
3	320	160	Type IIA
4	255	272	Type IV
5	206	90	Normal
6	313	112	Type IIA
Family E			
1	195	105	Normal
2*	380	115	Type IIA
3	305	130	Type IIA
4*	445	265	Type IIB
5	160	82	Normal
6 (age 11)	210	110	?
Family F			
1	238	310	Type IV
2*	380	260	Type IIB
3*	386	290	Type IIB
4*	336	200	Type IIB
5	240	142	Normal
6	310	180	Type IIA

Patient numbers refer to subjects in Fig. 1.
* Indicates growth hormone deficiency.

3, Table I). Subject 3 had a type IIB pattern on initial examination and a type IIA on a later examination. A maternal aunt had a type IV pattern on two occasions (only triglycerides increased).

In each of the hyperlipidemic families (Table II), lipid abnormalities tended to be quantitatively greater in the growth hormone-deficient members.

Metabolic comparison of dwarf groups

Basal studies. Fasting serum glucose concentrations were similar in hyperlipidemic and normolipidemic dwarfs, i.e., 79.8±5.7 mg/dl in hyperlipidemic, 82±3.8 mg/dl in nonhyperlipidemic dwarfs, and 80.1 ±2.9 mg/dl in controls. The mean fasting insulin concentrations were virtually identical in these groups; 14.7±1.4, 14.8±1.3, and 13.6 μU/ml, respectively. The mean basal free fatty acid concentrations in hyperlipidemic and normolipidemic dwarfs were 0.792±0.58 and 0.760±0.42 vs. 0.712±0.40 mM in controls (P = NS).

Basal serum concentrations of insulin and free fatty acids are shown for each individual at both time intervals of the study in Figs. 2 and 3. As with mean data, rank analysis of individual data also failed to show a significant difference between the groups compared.

Carbohydrate tolerance

Growth hormone-deficient dwarfs characteristically have glucose intolerance that is severe and undistinguishable from that noted in diabetics. These data have been presented in detail in a comprehensive study of the entire group of 31 dwarfs (2, 3). In comparing carbohydrate tolerance in dwarfs with and without hyperlipidemia, no difference could be seen between the two groups. The mean 2-h postprandial level was 190±11.2 mg/dl in hyperlipidemic dwarfs and 186 ±17.0 mg/dl in dwarfs with normal serum lipids. Both values were higher than in controls, 102±6.4 mg/dl ($P > 0.1$). 3 h after ingestion of glucose, glucose concentrations in serum remained elevated in both dwarf groups. Carbohydrate intolerance was associated with an insulinopenia state in both groups of dwarfs. (Mean peak insulin: controls, 83±14 μU/ml; lipemic

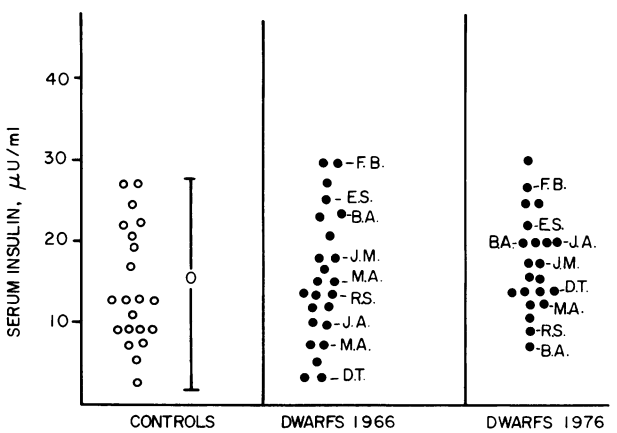

FIGURE 2 Basal serum concentrations of insulin are given for 21 control subjects and 24 and 22 growth hormone-deficient dwarfs studied in 1966 and 1976, respectively. The serum insulin concentrations in nine dwarfs with consistent hyperlipidemia are indicated by patient's initials.

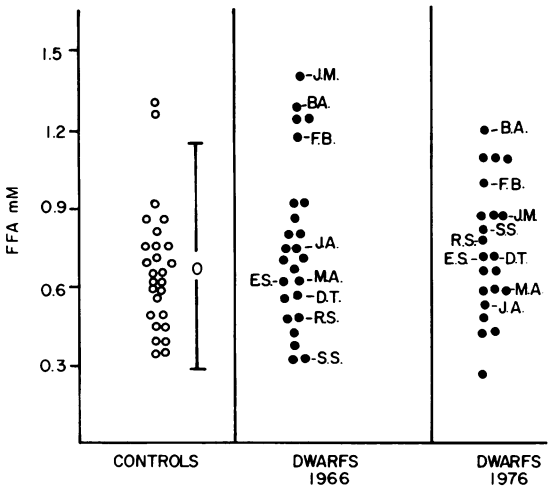

FIGURE 3 Basal serum concentrations of free fatty acid (FFA) concentrations are given for 27 control subjects and 25 and 22 growth hormone-deficient dwarfs studied in 1966 and 1976, respectively. The free fatty acid concentrations in nine dwarfs with consistent hyperlipidemia are indicated by patient's initials.

dwarfs, 38±6.9 μU/ml; nonlipemic dwarfs, 35±7.3 μU/ml [Fig. 4]).

Glycemic status

Although both groups of growth hormone-deficient subjects had gross CHO intolerance as compared to control subjects, HbA_{Ic} values were normal. The percent glycosylated HbA_{Ia+b+c} was 7.0% (range, 5–9%) in controls, 7.64% (range, 6.7–8.9%) in normolipidemic subjects, and 7.20% (range, 6.6–8.4%) in hyperlipidemic dwarfs.

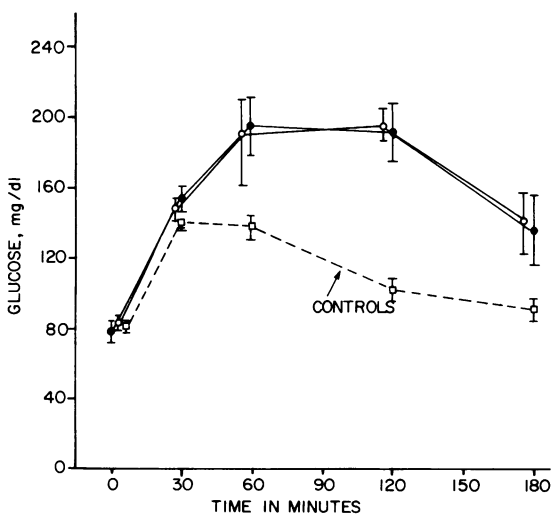

FIGURE 4 The plasma concentrations of glucose are given for hyperlipidemic (closed circles) and normolipidemic (open circles) subjects, and controls after ingestion of glucose (See Methods). Points are mean±SEM. Both groups of dwarfs differed at the 1% level from controls at 60, 120, and 180 min.

Sensitivity to insulin

Fig. 5 illustrates the glucose concentrations in serum after the injection of 0.05 U insulin/kg body wt. Both groups of dwarfs had a comparable decline in serum glucose concentration, usually reaching its lowest concentration within 15–30 min after injection. There was delayed return to basal level; serum glucose concentration 60 min after insulin was <45 mg/dl in both groups of dwarfs. In control subjects (not illustrated), glucose values at 60 min were ≥65 mg/dl.

Lipids and growth hormone treatment

Five growth hormone-deficient dwarfs with increased cholesterols and three hypercholesterolemic individuals of normal stature were given 2.5 mg of human growth hormone twice daily for 5 d. No significant change of serum cholesterol occurred (Fig. 6).

DISCUSSION

In a previous study we noted the high incidence of hyperlipidemia in dwarfs with an isolated deficiency of growth hormone (2, 3, 13, 14). More recently we completed lipid studies in nonhormone-deficient mem-

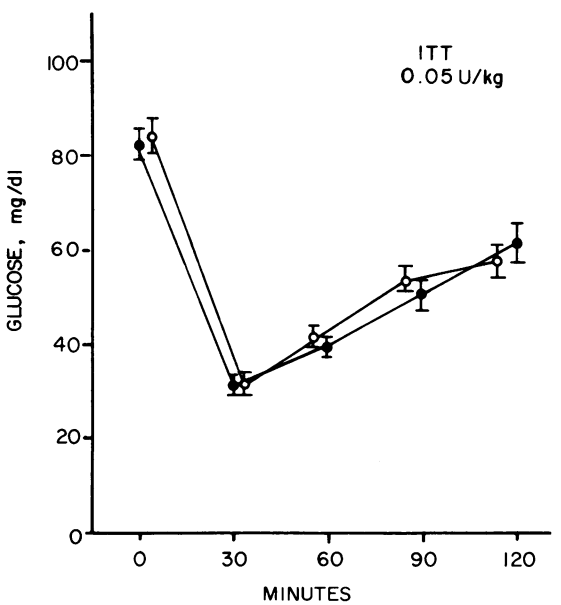

FIGURE 5 The similarity of sensitivity to exogenous insulin is shown for hyperlipidemic and normolipidemic growth hormone-deficient subjects. Hyperlipidemic dwarfs are shown with closed circles; normolipidemic with open circles. No significant differences were noted between these two groups. ITT, insulin tolerance test.

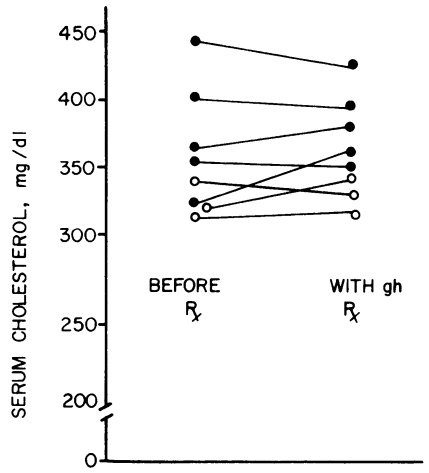

FIGURE 6 Serum concentrations of cholesterol are shown for five growth hormone-deficient subjects and three hypercholesterolemic subjects of normal stature. Human growth hormone (gh), 2.5 mg, was given twice a day for 5 d. ●, dwarfs; ○, controls.

bers of six of these families, and partial studies in a seventh family. With additional data, we believe it is now possible to define more accurately the lipid abnormalities of this state. The following conclusions would seem to be reasonable: First, it would appear that growth hormone deficiency per se does not cause an abnormality in serum lipids as initially thought (2, 14), but rather that growth hormone deficiency "unmasks" a hereditary predisposition to develop hyperlipidemia. Second, the hyperlipidemia associated with growth hormone deficiency can be identified with some confidence as familial combined hyperlipoproteinemia, although the distribution of lipoprotein phenotypes in dwarfs appears different from family members with normal stature. Third, growth hormone deficiency does not affect serum lipids indirectly via carbohydrate intolerance and insulin sensitivity.

The first point above is supported by the pedigree studies. Serum lipid concentrations were found to be elevated in multiple members of three families, with growth hormone-deficient dwarfs having quantitatively greater elevations of serum cholesterol and/or triglycerides than nongrowth hormone-deficient members. In another three families (A–C) 19 individuals, 10 of whom were growth hormone deficient, consistently exhibited normal serum lipids.

In regard to the second point, the hyperlipoproteinemia of growth hormone-deficient state fits best the category of familial combined hyperlipoproteinemia (15–18). The characteristic of this disorder is a scatter of lipoprotein phenotypes within a family, and this was clearly evident in multiple families (Table I and Results).

Although it is clear that a primary receptor defect does not occur in familial combined hyperlipoproteinemia, the exact cause of this condition is unknown. It is therefore only possible to speculate about mechanisms by which growth hormone deficiency makes manifest this trait. An effect of growth hormone on insulin and carbohydrate metabolism does not appear likely. An effect on pathways of VLDL degradation might be possible.

Findings from different techniques of studying human lipoprotein metabolism are in agreement that VLDL is synthesized and secreted by the cells of the liver and to a lesser extent by the small intestine (19). It appears that there are at least three pathways and not merely one of progressive delipidation leading from VLDL to LDL (20). Thus, the phenotypic manifestations of hypercholesterolemia (LDL increased) hypertriglyceridemia (VLDL increased) or their combined elevation can be viewed as resulting from alteration within a pedigree or individual of the relative activities of these pathways. Growth hormone or growth hormone deficiency may be one of several forces capable of affecting this balance. That growth hormone deficiency does have some effect, at least in susceptible individuals, is suggested by the difference in distribution of the phenotypes for growth hormone-deficient and nongrowth hormone-deficient subjects as shown in Table III.

These studies make it possible to understand several hitherto confusing findings relative to lipids in the growth hormone-deficient state. If growth hormone deficiency enhances the manifestation of familial combined hyperlipoproteinemia, then discrepancies in the incidence reported in growth hormone-deficient patients becomes understandable (20, 21). Familial combined

TABLE III
Types of Lipid Abnormalities in Hyperlipidemic Families

	Growth hormone-deficient					Normal stature				
Family	No.	IIA	IIB	IV	Normal	No.	IIA	IIB	IV	Normal
D	2	0	2	0	0	4	2	0	1	1
E	2	1	1	0	0	4	1	0	0	3*
F	3	0	3	0	0	3	1	0	1	1
Total	7	1	6	0	0	7	4	0	2	5

* Includes one subject age 12.

hyperlipoproteinemia is rarely manifested in the first 2–3 decades of life, and a low incidence could be expected in studies of children with growth hormone deficiency (18, 22, 23). Furthermore, growth hormone treatment over a more prolonged period could be predicted to decrease but not totally abolish the hyperlipidemic state. Acute studies with growth hormone for 5 d were negative. We were not able to treat any of the hyperlipidemic dwarfs with growth hormone for a prolonged period of time.

The data raise another question for which we have no certain answer. If hyperlipidemia in growth hormone-deficient dwarfs is due to the chance occurrence of the gene for familial combined hyperlipidemia, then one would expect that only one out of 200 growth hormone-deficient dwarfs should be hyperlipidemic, since the frequency of familial combined hyperlipidemia in the general population is no more than one in 200 persons. Our findings would imply that a substantial percentage of the general population have some genetic susceptibility to hyperlipidemia that can be unmasked by growth hormone deficiency. Alternatively, one must consider some form of association between growth hormone deficiency and familial combined hyperlipoproteinemia.

In summary, the hyperlipidemia of the chronic growth hormone-deficient state appears to be the result of an enhanced manifestation and severity of familial combined hyperlipoproteinemia. Growth hormone deficiency does not cause hyperlipidemia in nonsusceptible individuals.

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