Relationship Between Body Composition and Insulin and Growth Hormone Responses in Obese Adolescents

Robert B. Schultz, M.D., and Adalberto Parra, M.D., Baltimore

with the dietary assistance of Angelita Lim

SUMMARY

The clinical characteristics and predicted body composition of ten obese nondiabetic and six normal adolescents were compared in regard to plasma insulin, growth hormone, glucose, free fatty acids and alpha-amino nitrogen in response to different stimuli. Analysis of the data suggested the presence of two groups of patients. In obese Group A there was no family history of obesity, the youngsters first became obese between seven to twelve years of age, had a normal height for age, moderate increase in body weight and estimated total body fat, and normal or less than normal fasting levels of insulin. In obese Group B there was a strongly positive family history of obesity, the subjects became obese in infancy or early childhood, they were tall for their age, had marked increase in total body weight and total body fat as well as significantly higher than normal fasting insulin levels. Hyperinsulinemia was present in Group A during the oral glucose tolerance test and protein glucose meal. Normal insulin responses were observed during the protein meal and the arginine tolerance test. On the other hand, Group B manifested hyperinsulinemia in response to all stimuli. Both obese groups had undetectable plasma growth hormone levels during both the protein and the protein-glucose meal, but normal growth hormone responses during the oral glucose and the arginine tolerance tests. The differences in plasma levels of glucose and free fatty acids were minimal. Significant differences in plasma alpha-amino nitrogen values were observed during the protein-glucose meal. Differences in the hormonal responses of obese adolescents and adults are discussed. Possible explanations for heterogeneous responses of obese adolescents are presented. DIABETES *19*:492-501, July, 1970.

In recent years various investigators have shown that hyperinsulinemia and diminished plasma growth hormone responses to various provocative stimuli are characteristic of the adult obese state.[1-7] The similarity of findings in these studies may suggest to some that obesity represents a homogeneous disorder and that the previously mentioned metabolic abnormalities simply represent adaptive mechanisms for the normal individual who has become overweight by overeating. In many of the previous studies obesity was defined as a body weight 20 per cent or more above the ideal weight for height. This approach only crudely estimates the precise "fatness" of an individual, however, since the same body weight in different subjects may represent different proportions of fat and lean body mass.[8]

The work of Forbes,[8] has shown that in children, there are at least two types of obesity, characterized by differences in body composition. This would suggest that the metabolic responses of obese youngsters may be heterogeneous. In the present study we have attempted to examine the metabolic profiles of obese adolescents in response to different stimuli in an effort to determine whether responses of the obese adolescent are similar to those described in obese adults and to observe the relationship, if any, between their body composition and plasma insulin and growth hormone levels.

MATERIAL AND METHODS

Ten obese, otherwise healthy, youngsters (seven males and three females), age ten and one-twelfth to sixteen and nine-twelfth years, were selected as voluntary subjects for this study. Their body weights ranged from 67.9 to 179.0 kg. None had lost weight in the previous two years, except one patient (P.F.) who was treated elsewhere with a three-week starvation period, five months prior to this study. Six healthy youngsters (four males and two females) age eight and eleven-twelfths to sixteen and six-twelfth years with normal body weights, served as a normal control group. There was no family or personal history of diabetes mellitus in any of the subjects under investigation. Prior to

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From the Department of Pediatrics, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Maryland 21205. Address requests for reprints to Dr. Robert B. Schultz, Department of Pediatrics, Sinai Hospital of Baltimore, Baltimore, Maryland 21215.

TABLE 1

Body composition and fasting plasma immunoreactive insulin levels in obese and normal children (Mean ± S.E.M.)

Patient	Sex	Chronological age (yrs.)	Height (cm.)	Weight (kg.)	Predicted total body water (liters)	Predicted total body fat (kg.)	Fasting insulin (μU./ml.) II
Obese Group A							
J.K.	F	10 1/12	152.4	67.9	24.6	33.78	4.7
J.H.	F	15 9/12	174.6	86.6	32.0	42.09	16.6
D.R.	M	12 10/12	151.1	81.0	25.8	45.20	6.4
V.S.	M	15 5/12	160.0	91.0	31.2	47.62	13.0
D.P.	M	16 0/12	168.3	98.8	36.3	48.35	9.1
Mean		14 2/12	161.2	85.0	30.0*	43.40†	9.97‡
± S.E.M.		—	—	—	2.14	2.18	2.2
Obese Group B							
C.B.	F	12 10/12	168.3	100.09	29.9	59.34	71.6
H.D.	M	13 2/12	163.8	100.04	33.6	53.76	60.5
Ch.R.	M	15 5/12	173.9	119.70	39.8	64.46	29.8
M.W.	M	16 1/12	174.6	153.50	40.2	98.70	64.8
P.F.	M	16 9/12	185.4	179.00	46.8	114.00	33.6
Mean		14 10/12	173.20	130.90	38.0*	78.00†	52.0‡
± S.E.M.		—	—	—	2.92	8.52	4.0
Normal group							
L.R.	F	10 8/12	156.2	41.0	24.6	6.80	13.0
J.R.	F	12 4/12	168.1	48.6	28.7	8.79	22.4
P.R.	M	8 11/12	148.7	37.7	23.6	4.92	23.6
D.H.	M	14 2/12	181.6	73.0	42.5	13.98	22.6
M.J.	M	14 9/12	180.9	68.6	43.6	8.00	21.9
R.A.	M	16 6/12	171.4	60.4	38.1	9.60	28.0
Mean		12 10/12	167.20	54.8	33.5*	6.39‡	21.9‡
± S.E.M.		—	—	—	3.67	0.82	2.7

*No significant difference.
†$p = 0.02$.
‡$p = 0.001$.
II = Mean value of eight fasting plasma values per patient.

admission each patient had been on an ad libitum diet providing at least 250 gm. of carbohydrate daily. All subjects were admitted to the Pediatric Clinical Research Unit of The Johns Hopkins Hospital for a period of five days, during which time the following tests were performed after an overnight fast:

A) Oral glucose tolerance test: 1.75 gm. of glucose per kg. actual body weight to a maximum of 100 gm. Glucose was given as a 50 per cent solution in water.

B) Protein meal: 1.0 gm. of beef protein per kg. actual body weight in the form of steak or hamburger.

C) Protein-glucose meal: A combination of the oral glucose tolerance test and the protein meal.

D) Arginine tolerance test: 0.5 gm. of L-arginine monohydrochloride* per kg. actual body weight to a maximum of 40 gm. The arginine was administered intravenously as a 10 per cent solution in water during a period of thirty minutes.

All blood specimens were collected from indwelling needles placed in an antecubital or dorsal hand vein. Samples were collected in heparinized test tubes, immediately centrifuged and the plasma separated and kept frozen at —4° C. for later analysis. Blood specimens were obtained at —15, 0, 30, 60, 90, 120, 180, 240 and 300 min. during the oral glucose tolerance test and at —15, 0^1, 0^2, 30, 60, 90, 120, 240, and 300 min. during the protein and the protein-glucose meal.

*Kindly supplied by Cutter Laboratories.

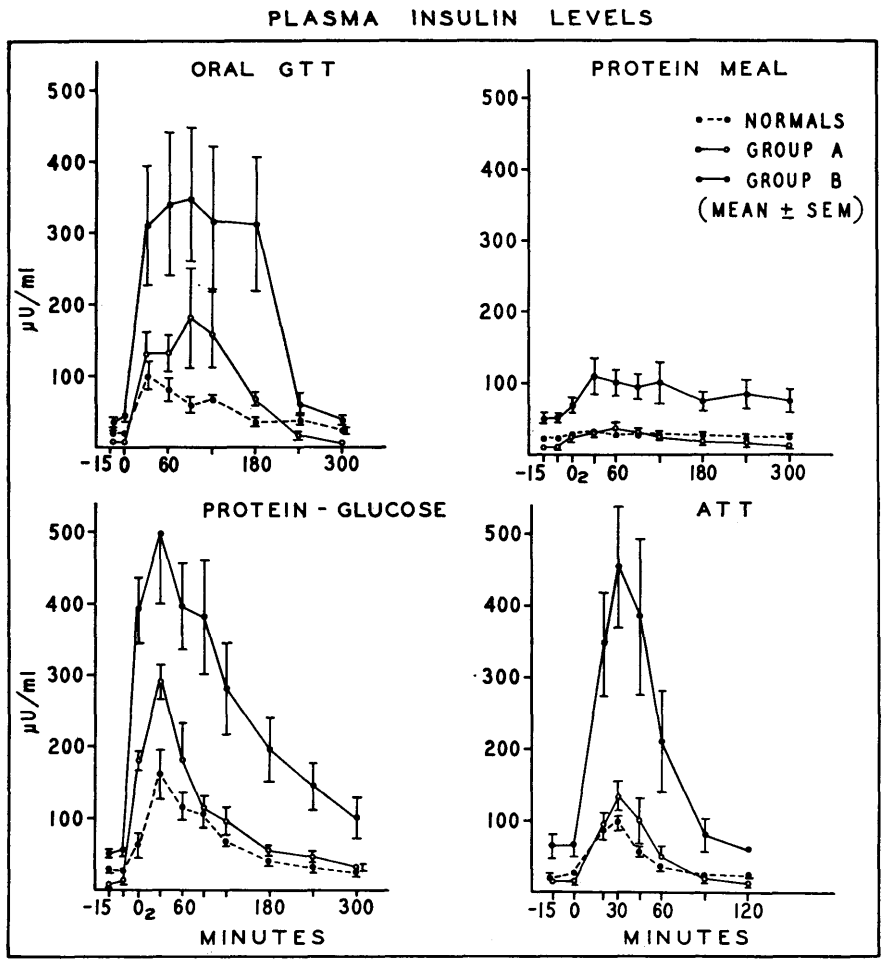

FIG. 1.

Plasma IRI responses of normal and obese A and B groups. Significant differences of the values at different times are described in the text.

Time o^1 indicates the time at which the meal was begun and time o^2 when the meal was completed. The time required for the subjects to ingest the test meal varied between fifteen and twenty minutes. All subsequent times for sampling represent the time elapsed since completion of the meal. During the arginine tolerance test blood was drawn at —15, 0, 20, 30, 45, 60, 90 and 120 min. after the start of the infusion.

Plasma glucose was determined by a glucose oxidase method,[9] plasma alpha-amino-nitrogen by a modified ninhydrin method[10] and plasma free fatty acids (FFA) by the Dole method[11] as modified by Trout, Estes and Friedberg.[12] Plasma immunoreactive insulin (IRI) and plasma immunoreactive growth hormone (HGH) were assayed by the radioimmunoassay methods of Yalow and Berson[14] respectively, with a slight modification.[15] All plasma specimens for insulin determinations were analyzed in one single immunoassay. The fasting insulin values referred to in the subsequent text represent the mean of eight separate fasting values per patient. All values are presented as mean ± S.E.M.

Estimates of body composition were made from calculations of total body water (TBW) based on the formulas derived by Cheek.[16]

All statistical analyses were performed by means of the Student *t* test.

RESULTS

Body composition and fasting immunoreactive insulin (IRI)

The obese subjects were divided in two groups based on body composition and clinical characteristics. A summary of the data is shown in table 1.

Group A consisted of the obese adolescents who developed their obesity between seven to twelve years of age, and Group B consisted of those who manifested clinical obesity in infancy or early childhood. Although both groups had comparable chronological ages at the time of study, subjects in Group B were taller than those in Group A, and there were marked differences

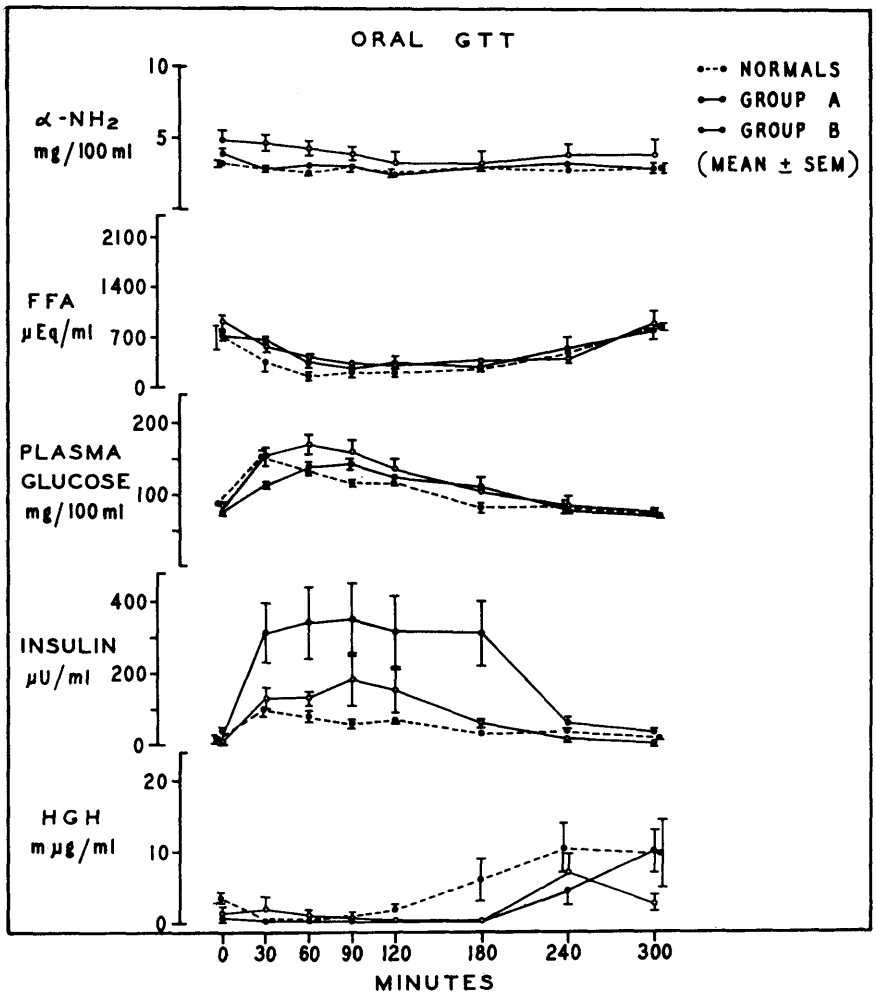

FIG. 2.

Plasma values of normal and obese subjects during the oral glucose tolerance test. Statistically significant differences are described in the text.

in body weights. The values for predicted total body water were similar between the normal and both obese groups. The differences in TBF were significant between the normal and each obese group ($p < .001$) and between both obese groups ($p < .02$). The fasting IRI level in the normal group was 21.9 ± 2.7 μU./ml. (mean ± S.E.M.), and 9.97 ± 2.2 μU./ml. and 52.0 ± 4.0 μU./ml. in obese Groups A and B respectively. The differences between the normal and each obese group and between both obese groups were highly significant. A significant correlation between fasting plasma IRI values and TBF was not found, however.

Plasma IRI levels

The results are presented in figure 1. During the oral glucose tolerance test the plasma IRI levels in Group A were higher than those of the normals at 60, 180 and 300 min. ($p < .01$, $< .02$, $< .05$ respectively). Group B had elevated plasma IRI levels when compared with the normal group at 60, 90, 120 and 180 min. ($p < .05$ and $< .02$) and with Group A at 180, 240 and 300 min. ($p < .05$, $< .05$ and $< .005$ respectively).

In response to the protein meal, Group A had normal plasma IRI levels. Group B had plasma IRI levels higher than those of both the normal group (p range from $< .02$ to $< .005$) and Group A (p range from $< .05$ to $< .02$) throughout the entire test.

The degree of hyperinsulinemia achieved by normals and both obese groups during the protein-glucose meal was greater than during any of the other tests employed. Group A achieved higher plasma IRI response than normals only at thirty minutes ($p < .05$). The plasma IRI levels in Group B were higher than normals at 0², 30 and 300 min. ($p < .005$, $< .005$, $< .02$ respectively) and than Group A at 30, 60 and 300 min. ($p < .005$, $< .01$, $< .005$ respectively).

During the arginine tolerance test, Group A again

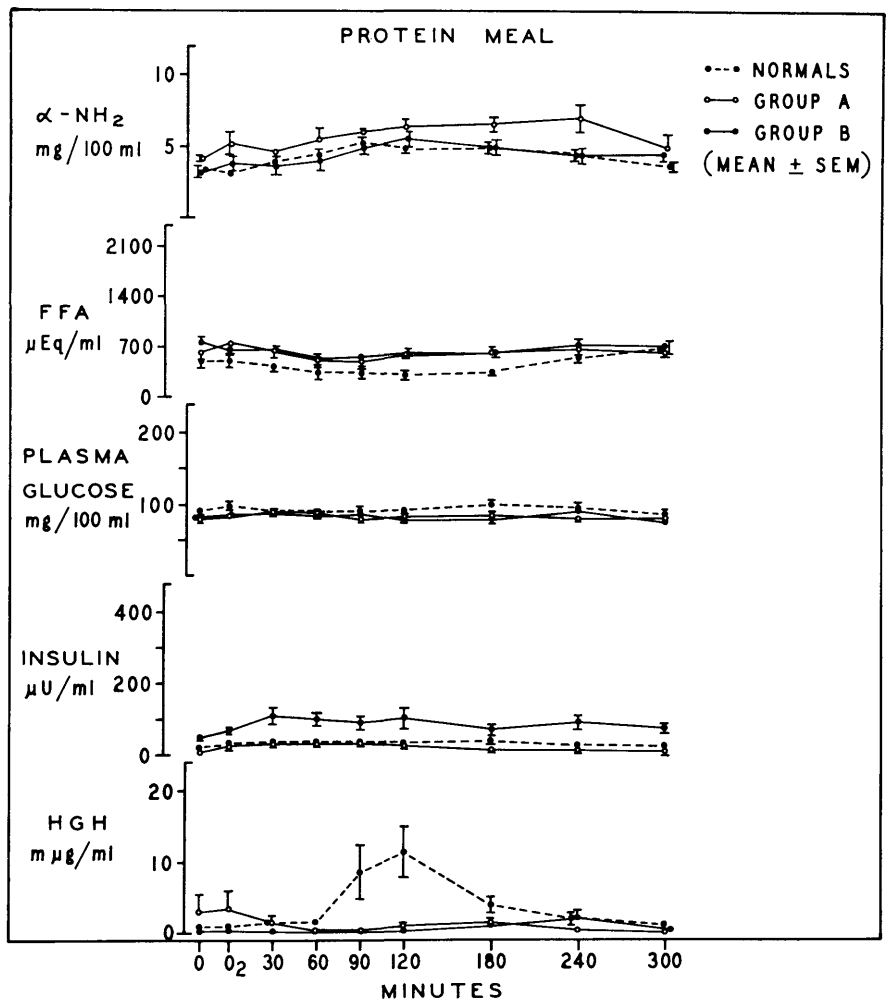

FIG. 3.

Plasma values of normal and obese subjects during the protein meal. Statistically significant differences are described in the text.

had an insulin response comparable to the normal group. Group B had plasma IRI levels significantly higher than either the normals or Group A at thirty and 120 minutes ($p < .01$).

Plasma HGH levels

The fasting plasma HGH levels ranged from < 1.0 to 6.2 ng./ml. in normals and from < 1.0 to 2.9 ng./ml. in Group A. Subjects in Group B had fasting levels consistently < 1.0 ng./ml. The differences among the three groups were not significant.

The peak plasma HGH responses of normals and Group A subjects during the oral glucose tolerance test occurred at 240 minutes (10.4 and 7.0 ng./ml. respectively). The peak HGH response for Group B (9.8 ng./ml.) was observed at 300 minutes (figure 2). The peak values were not different among the groups.

During the protein meal, the normal group had a peak plasma HGH value of 11.2 ng./ml. at 120 minutes (figure 3), while in neither of the obese groups was there a significant rise. In response to the protein glucose meal the normal group had a peak HGH response of 10.5 ng./ml. at ninety minutes. Again, neither of the obese groups had a significant rise in plasma HGH (figure 4).

During the arginine tolerance test, the normal group had a peak HGH response of 8.1 ng./ml. at thirty and forty-five minutes. The peak value in Group A was 13.6 ng./ml. at forty-five minutes. In Group B the peak HGH response of 10.0 ng./ml. occurred at 120 minutes, however (figure 5).

Plasma glucose

The mean fasting value for normals was 81.4 mg./100 μl., for Group A, 79.4 mg./100 μl. and for Group B 77.9 mg./100 μl. The values were not different from each other. Throughout the entire four tests, all these groups studied had very similar plasma glucose values (figures 2-5) except during the protein-glucose meal at time 0^2 when Group A had higher glucose levels

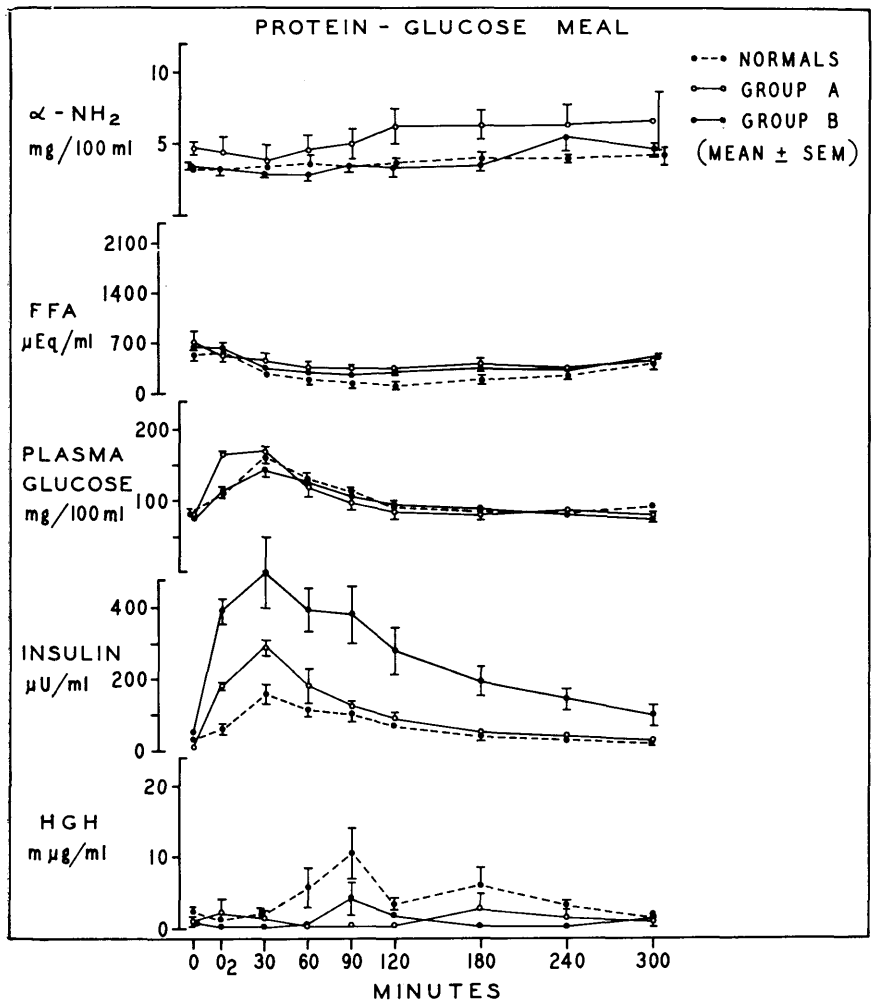

FIG. 4.

Plasma values of normal and obese subjects during the protein-glucose meal. Statistically significant differences are described in the text.

than either normals or Group B ($p < .001$).

Plasma free fatty acids

There were no significant differences among the fasting plasma levels of the three groups studied (figure 6). In all three groups there was a progressive fall in the plasma FFA level during each of the tests with a slow return to the basal level toward the end of the tests. No significant differences in the absolute values were observed among any of the groups.

Plasma alpha-amino nitrogen

There were no significant differences in the fasting levels in the different groups. During all the tests there was a general tendency for Group A to maintain higher plasma levels than either the normals or Group B. The only signficant differences between Group A and normals occurred during the protein meal at 0^2, 180 and 300 minutes ($p < .05, < .05, < .02$) and during the protein-glucose meal at 180 minutes ($p < 0.025$). On the other hand, the plasma levels in Group A were significantly higher than in Group B during the oral glucose tolerance test at thirty minutes ($p < .025$), during the protein meal at 240 minutes ($p < .05$) and during the protein-glucose meal at 180 minutes ($p < .025$). When the plasma values during the protein-glucose meal were expressed as mean delta ($\triangle$) increments or decrements from the basal level, both A and normal groups had very similar increment above the fasting level; however, Group B had consistent decrements from the basal level from 0^2 to 180 minutes. These differences were significant between normals and Group B at thirty minutes ($p < .05$) and between Groups A and B at 120 and 180 minutes ($p < .02$ and $< .005$).

DISCUSSION

It is clear that the plasma insulin and growth hor-

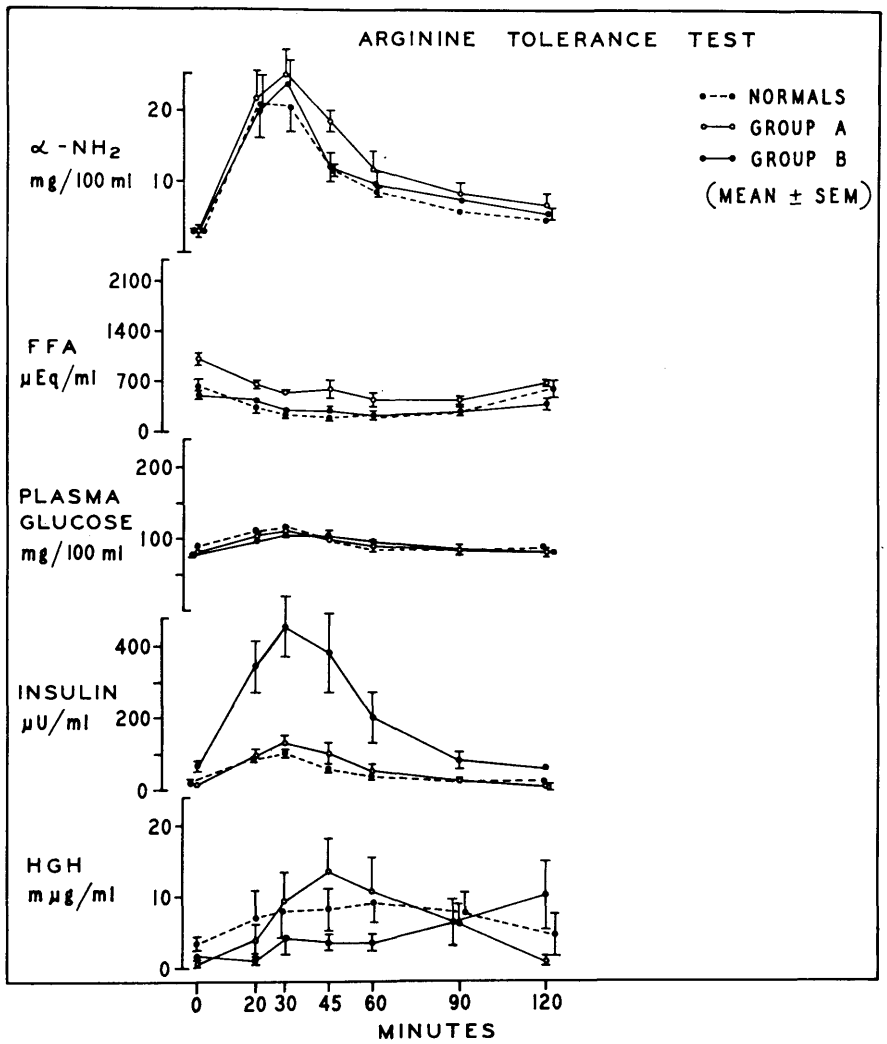

FIG. 5.

Plasma values of normal and obese subjects during the arginine tolerance test. Statistically significant differences are described in the text.

mone response of the obese adolescent in this study differ in certain respect from those reported in obese adults.[1,2] The degree of hyperinsulinemia achieved varied with the stimulus employed. Indeed, glucose alone or protein plus glucose resulted in insulin responses significantly greater than those of the normals. Arginine or a protein meal did not cause differences in insulin responses between Group A subjects and the normals, however. This suggests that in Group A glucose served as a dominant stimulus for insulin secretion, whereas in Group B glucose, protein and arginine were each capable of inducing hyperinsulinemic responses. The present study does not provide an explanation for these differences. Furthermore, in response to either oral glucose or an arginine infusion obese subjects had peak plasma HGH responses not significantly different from those of normals, although the times at which these peak responses occurred did differ from normals. This observation is in contrast to the results observed in obese adults.[3]

There have been many attempts to classify overweight children into different groups based on a variety of factors.[8,17-20] In the present study, the obese subjects were divided into two groups based on differences in body composition estimates and clinical characteristics. The differences between Groups A and B with respect to the amount of TBF, as well as the fasting insulin levels, were directly related to the age of onset of obesity. Thus, we could designate Group A as the "late" onset and Group B as the "early" onset obese groups. These observations are in agreement with those of previous studies showing a direct correlation between percentage overweight and fasting plasma insulin.[21] Others[22] found no correlation, however, between TBF

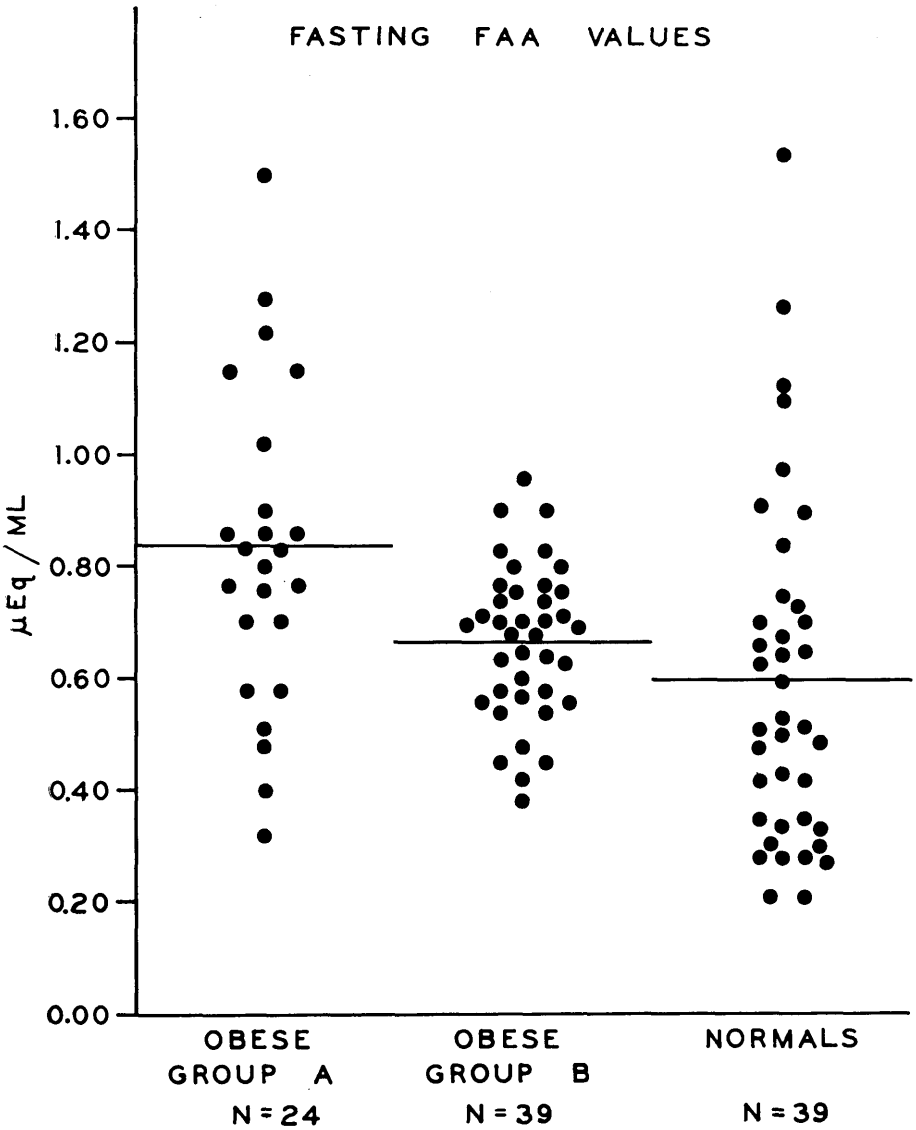

FIG. 6.

This figure indicates the accumulated individual basal FFA values obtained during four days. Each dot represents a single FFA value for one patient. The mean value for each group is represented by the horizontal bar.

and fasting insulin levels in eight obese children.

In the present study the correlation between TBF and fasting plasma insulin levels was not significant. The lack of correlation in this study was anticipated since Group A subjects were observed to have significantly lower fasting plasma insulin levels than normals. This latter observation is unexplainable at present but suggests that the absolute plasma insulin values as conventionally expressed in μU./ml. may not precisely reflect the total circulating insulin at any given moment in some obese subjects. The lack of correlation may simply be due to the small number of patients studied, however.

On the basis of differences in plasma IRI observed one would assume that the obese subject maintained normal plasma levels of glucose, free fatty acids and alpha-amino nitrogen at the expense of greater insulin production. This concept applies directly to subjects in Group B and could be explained simply on the basis of insulin resistance, which one would presume to be greater in the more obese patient. The observation that Group B subjects maintained generally lower plasma levels of alpha-amino nitrogen during the protein-glucose meal (as expressed in mean decrement from fasting levels), however, suggests the biological effectiveness of IRI in these subjects in translocating amino acids into tissues. Thus, it is conceivable that the phenomenon of insulin resistance in Group B subjects

can be applied to glucose and lipids but not plasma amino acids. If this observation does in fact represent effective transport of amino acids, then this may subsequently initiate a greater rate of protein synthesis and perhaps overgrowth, which in turn could account for the clinical observations of greater musculature and stature in Group B subjects.

Lessof et al.[6] have previously found an inverse correlation between plasma growth hormone levels and the degree of obesity in adults. Obese subjects in Groups A and B achieved normal growth hormone elevations in response to oral glucose or intravenous arginine. It is possible that this normal growth hormone response will eventually decline as the obese adolescents pass into adulthood; since the obese children and adolescents in this study are still in a phase of rapid somatic and statural growth they presumably require the presence of growth hormone in order to accomplish a useful rate of protein synthesis[23] and to influence the ultimate number of cells in different tissues.[24] Thus, whatever the mechanism is in obese adults which blunts growth hormone response, it does not appear to be fully operative in obese youngsters.

The data presented are consistent with the view that the obese adolescent population is homogeneous when only TBF and plasma IRI values are examined. The differences observed between Groups A and B, such as onset and duration of obesity, different IRI responses to protein or arginine stimulation, and the plasma alpha-amino nitrogen changes during the protein-glucose meal remain valid and may be explained in part by experiments performed in animals. In vitro studies with rat pancreas[25] have clearly shown a greater insulin response to glucose in a genetically obese strain of rats as compared with rats having acquired obesity. In the present subjects none in Group A and four of the five subjects in Group B had a positive family history of obesity. Genetic factor(s) alone need not necessarily be invoked to explain some of the differences observed. Environmental differences were obviously operative in Group B patients since they characteristically had the onset of obesity in either infancy or early childhood. It is clear from previous animal data[26-28] that overnutrition at such a critical age may profoundly influence the ultimate body composition of an animal and presumably similar influences may be exerted in the infant or young child.

ACKNOWLEDGMENT

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REFERENCES

1 Benedetti, A., Simpson, R. G., Grodsky, G. M., and Forsham, P. H.: Exaggerated insulin response to glucagon in simple obesity. Diabetes *16*:666-69, 1967.

2 Perley, M., and Kipnis, D. M.: Plasma insulin responses to glucose and tolbutamide of normal weight and obese diabetic and nondiabetic subjects. Diabetes *15*:867-74, 1966.

3 Rabinowitz, D., Merimee, T. J., Nelson, J. K., Schultz, R. B., and Riggs, L.: The hormonal profile in obesity. Trans. Ass. Amer. Physicians. *80*:190-97, 1967.

4 Kreisberg, R. G., Boshell, B. R., DiPlacido, J., and Roddam, R. F.: Insulin secretion in obesity. New Eng. J. Med. *276*:314-19, 1967.

5 Beck, P., Koumans, J. H. T., Winterling, D. C., Stein, M. F., and Daughaday, W. H.: Studies on insulin and growth hormone secretion in human obesity. J. Lab. Clin. Med. *64*:654-67, 1964.

6 Lessof, M. H., and Greenwood, F. C.: Growth hormone secretion in obese subjects. Guy Hosp. Rep. *115*:65-71, 1966.

7 Rabinowitz, D., and Zierler, K. L.: Forearm metabolism in obesity and its response to intra-arterial insulin. Characterization of insulin resistance and evidence for adaptative hyperinsulinism. J. Clin. Invest. *41*:2173-81, 1962.

8 Forbes, G. B.: Lean body mass and fat in obese children. Pediatrics *34*:308-14, 1964.

9 McCann, W. P., and Jude, J. R.: The synthesis of glucose by the kidney. Bull. Johns Hopkins Hosp. *103*:77-93, 1958.

10 Yemm, E. W., and Cocking, E. C.: The determination of amino acids with ninhydrin. Analyst *80*:209-13, 1955.

11 Dole, V. P., and Meinertz, H.: Microdetermination of long-chain fatty acids in plasma and tissues. J. Biol. Chem. *235*:2595-99, 1960.

12 Trout, D. L., Estes, E. H., Jr., and Friedberg, S. J.: Titration of free fatty acids of plasma: A study of current methods and a new modification. J. Lipid Res. *1*:199-202, 1960.

13 Yalow, R. S., and Berson, S. A.: Immunoassay of endogenous plasma insulin in man. J. Clin. Invest. *39*:1157-75, 1960.

14 Roth, J., Glick, S. M., Yalow, R. S., and Berson, S. A.: Secretion of growth hormone: Physiologic and experimental modification. Metabolism *12*:577-79, 1963.

15 Herbert, V., Lau, K. S., Gottlieb, C. W., and Bleicher, S. J.: Coated charcoal immunoassay of insulin. J. Clin. Endocr. *25*:1375-84, 1965.

16 Cheek, D. B.: Human Growth: Body Composition, Cell Growth, Energy and Intelligence, 1st Ed. Philadelphia, Lea

and Febiger, 1968, p. 140.

[17] Börjeson, M.: Overweight children. Acta Paediat. Scand. *51*: Suppl. 132, 1962.

[18] Mossberg, H. O.: Obesity in children. Acta Paediat. Scand. *35*: Suppl. 66, 1948.

[19] Paulsen, E., Richenderfer, L., and Ginsberg-Fellner, F.: Plasma glucose, free fatty acids and immunoreactive insulin in sixty-six obese children. Diabetes *17*:261-69, 1968.

[20] Paulsen, E. P., and Lawrence, A. M.: Glucagon hypersecretion in obese children. Lancet *2*:110, 1968.

[21] Bagdade, J. D., Bierman, E. L., and Porte, D., Jr.: The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. J. Clin. Invest. *46*:1549-57, 1967.

[22] El-Khodary, A. Z., Ball, M. F., and Ball, J. J.: Plasma insulin levels and body composition in obesity. Clin. Res. *16*:341, 1968.

[23] Snipes, C. A.: Effects of growth hormone and insulin on amino acid and protein metabolism. Quart. Rev. Biol. *43*:127-47, 1968.

[24] Cheek, D. B., and Graystone, J. E.: The action of insulin, growth hormone and epinephrine on cell growth in liver, muscle and brain of the hypophysectomized rat. Pediat. Res. *3*:77-88, 1969.

[25] Malaisse, W. J., Malaisse-Lagae, F., and Coleman, D. L.: Insulin secretion in experimental obesity. Metabolism *17*:802-07, 1968.

[26] Knittle, J., and Hirsch, J.: Infantile nutrition as a determinant of adult adipose tissue metabolism and cellularity. Clin. Res. *15*:323, 1967.

[27] Winick, M., and Noble, A.: Cellular response with increased feeding in neonatal rats. J. Nutr. *91*:179-82, 1967.

[28] Cheek, D. B.: Cellular growth, hormones, nutrition and time. Pediatrics *41*:30, 1968.

Artificial Sweeteners—Possible Photosensitizers

(*Continued from page* 479)

period of two weeks. At the end of that time, she consumed 360 mg. per day of saccharin for four days. (This was equivalent to the amount of saccharin in twelve bottles of artificially sweetened soft drink.) Exposure of her skin to ultraviolet light produced no erythema. After another two weeks of abstinence, the patient took 3,600 mg. per day of calcium cyclamate for four days. This time, exposure to ultraviolet light produced the usual eczematous dermatitis. During these studies, the patient showed no signs of abnormality other than the dermatitis.

In a letter to the Editor, E. Boros (*J. Am. Med. Assn. 194*:571, 1965) said that ingestion of six packets of the combination of saccharin and calcium cyclamates per day produced a bad taste in his mouth and a marked diuretic action shortly after consuming the sweetening agents. When he got out of bed during the night, he found himself unsteady and swaying to such an extent that on one or two occasions he would have fallen if the wall had not been nearby. He also noticed a systemic pruritis, accompanied by small patches of rash, which was especially prominent on the elbow.

Elimination of the sweetening agent from his diet for three to four days produced an almost complete subsidence of his symptoms. Reduction to one half of the usual dose produced a mild rash and some itching. Even with this lower intake, he noticed "a fluttering" within his left ear canal. This was an intermittent sensation but did not impair his hearing. Again, elimination of the sweetening agent cleared his ear difficulty within forty-eight hours. . . .

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