Fasting Hyperinsulinemia Is a Predictor of Increased Body Weight Gain and Obesity in Pima Indian Children

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Hyperinsulinemia is commonly associated with obesity, but it has not been determined which defect comes first. Some have proposed that hyperinsulinemia may precede obesity in populations prone to NIDDM, such as Pima Indians or Pacific Islanders. In contrast, longitudinal studies in adults show that insulin sensitivity and low fasting insulin concentrations are associated with increased weight gain, whereas insulin resistance seems to protect against weight gain. The present study examined whether fasting plasma hyperinsulinemia is a risk factor for weight gain in prepubertal children in the Pima Indian population—a population that is prone to obesity. Fasting plasma insulin concentration was measured in 328 5- to 9-year-old Pima Indian children (147 boys and 181 girls) with normal glucose tolerance. Follow-up weight was obtained an average of 9.3 ± 1.9 years (means ± SD) later at age 15–19 years. Fasting plasma insulin concentration correlated with the rate of weight gain per year in both boys ($r = 0.42$; $P < 0.0001$) and girls ($r = 0.20$; $P < 0.01$) and was associated with the rate of weight gain, independent of known determinants of weight change, i.e., initial relative weight, change in height, age, and sex. Similar relationships were found between fasting plasma insulin concentration and the change in relative weight and in triceps skinfold thickness—two indicators of obesity. In conclusion, fasting hyperinsulinemia may be a risk factor for the development of obesity in young children. ***Diabetes*** **46:1341–1345, 1997**

Obesity, insulin resistance, and hyperinsulinemia are common features of NIDDM (1) and predict the development of NIDDM in Pima Indians (2). Despite the fact that overfeeding and weight gain cause hyperinsulinemia in humans, it remains to be determined whether the converse is true, i.e., that hyperinsulinemia leads to obesity (3,4).

In 1962, Neel (5) postulated that individuals predisposed to diabetes differ metabolically from those who are not and that hyperinsulinemia may precede obesity (6). Fundamental to his "thrifty genotype" hypothesis is the concept that hyperinsulinemia increases efficiency of fat storage and thus plays a crucial role in the development of obesity and diabetes. Contrary to the thrifty genotype hypothesis, observations in adult Pima Indians show a lower body weight gain in insulin-resistant subjects compared with insulin-sensitive subjects (7,8). Similar associations have also been observed in Hispanic and Caucasian subjects (9–11). These findings suggest that insulin resistance and its associated hyperinsulinemia are secondary rather than primary to obesity and that insulin resistance represents a physiological adaptation to obesity that limits further weight gain (12). However, many of these studies were carried out in adult members of populations with a high prevalence of obesity and NIDDM. Such individuals may have long-standing insulin resistance and many may have developed compensatory mechanisms to overcome the initial defects, thus making it difficult to identify causal abnormalities. One approach to understanding the sequence of defects preceding obesity and NIDDM is to study children genetically predisposed to obesity. Pima Indian children are hyperinsulinemic (13) with a strong genetic predisposition to obesity (14,15). The present study examined whether fasting hyperinsulinemia is a risk factor for excess body weight gain in 5- to 9-year-old Pima Indians followed for ~10 years. In both boys and girls, higher baseline fasting insulin concentration was associated with higher rates of weight gain and most likely excess fat disposition, as assessed by the changes in relative weight for height and in triceps skinfold thickness.

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Received for publication 29 October 1996 and accepted in revised form 9 April 1997.

RESEARCH DESIGN AND METHODS

Subjects and protocol. Data from children participating in a longitudinal study of the etiology of obesity and diabetes in the Gila River Indian Community of central Arizona (16) were examined. Analyses were restricted to all children examined initially at age 5–9 years and with a follow-up examination at age 16–19 years. The initial and follow-up ages were selected to minimize the confounding effects of puberty on insulin resistance, compensatory hyperinsulinemia, and growth (17–19). Children diagnosed with NIDDM or impaired glucose tolerance at baseline examination were excluded from the analyses, leaving 328 Pima Indian children, 147 boys and 181 girls. Informed parental consent was obtained, and all procedures were explained to both parents and children. The studies were approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Indian Health Service, and the Tribal Council of the Gila River Indian Community.

For each examination, subjects were instructed to eat their habitual diet the day before the test and to refrain from eating and drinking after 9:00 P.M. They reported to the clinic at 8:00 A.M., where height and weight were measured with the subject wearing light clothing and no shoes. Relative weight for sex, age, and height was determined using a reference population described by Jelliffe (20). While the children were seated, the triceps skinfold thickness was measured at the midpoint of the right arm (between the acromion and the olecranon processes), using a Lange Skinfold Caliper (Cambridge Scientific Industries, Cambridge, MD). Values were recorded to the nearest millimeter. Subjects then had a 75-g oral glucose tolerance test, and glucose tolerance was assessed according to World Health Organization criteria (21).

Biochemical analysis. Plasma glucose concentrations were measured by the ferricyanide method (22) using a Technicon Auto Analyzer (Technicon Instruments, Tarrytown, NY) and with the hexokinase method (23) since 1991. Serum insulin concentrations were determined by the Herbert modification (24) of the radioimmunoassay method of Yalow and Berson (25) and, since 1987, using a radioimmunoassay analyzer (Concept 4, ICN, Horsham, PA). The mean interassay coefficients of variation for plasma insulin concentrations were 7 and 12% for the manual and automated methods, respectively. Insulin concentrations measured using automated methods were made comparable to the manual method by an algorithm established on the basis of 542 samples measured by both methods.

Statistical analysis. Plasma insulin concentrations had a skewed distribution and were therefore $\log_{10}$ transformed to approach a normal distribution. Weight change was calculated as the difference between the last visit at age 16–20 years and the first visit at age 5–9 years. The changes in relative weight and in triceps skinfold thickness were used as indicators of fat deposition. Because of the variability in the duration of follow-up, changes were expressed as annual rates. We examined the relationship between fasting plasma insulin concentrations and changes in weight or obesity indicators by two different approaches: *1*) correlation analyses to determine the relationships between weight/obesity changes and variables, such as initial fasting or 2-h plasma insulin concentration, age, change in height, initial relative weight, and parental BMI (weight/height^2); and *2*) multiple linear regression models to examine the relationship between weight/obesity changes and fasting or 2-h plasma insulin independent of confounding factors, such as age, change in height, initial relative weight, parental BMI, and sex. Because our group of Pima Indian children was, on average, overweight at baseline, we repeated the entire analysis in the 239 children (109 boys and 130 girls) whose relative weight was <130%. All statistical analyses were performed using the procedures of the SAS Institute (Cary, NC). *P* values <0.05 were considered statistically significant.

RESULTS

Physical and metabolic characteristics of subjects. The physical and metabolic characteristics of the subjects at initial and follow-up examinations are shown in Table 1. At the initial examination, boys and girls were similar in age, height, weight, relative weight, triceps skinfold thickness, and fasting and 2-h postload plasma glucose. However, girls had higher mean fasting and mean 2-h plasma insulin concentrations than boys. Subjects had a wide range of relative weight for height (79–215%) but were on average overweight (relative weight = 119 ± 24%). Subjects also had a wide range of triceps skinfold thickness values from 3 to 38 mm. After a mean follow-up of 9.3 ± 1.9 years (5.3–14.6), subjects gained 5.3 kg/year (1.2–14.4 kg/year) or 2.4 ± 2.8%/year (–6 to 12%) of relative weight and 1.6 ± 1.3 mm/year of triceps skinfold. The increase in weight was larger than expected from the standards (20) on the basis of changes in height and age and resulted in a mean relative weight of 142 ± 35% (85–286%) at follow-up. Although the absolute weight gain was similar in males and females, the relative weight change per year and the yearly change in triceps skinfold thickness were significantly greater in females than in males ($P < 0.05$ and $P < 0.0001$, respectively), indicating a higher incidence of obesity in girls compared with boys. At baseline, the relative weight of the "normal-weight" group (relative weight <130%) was 106 ± 10% in boys and 107 ± 12% in girls. On average, in this subgroup, boys gained 5.2 ± 1.5 kg/year and girls gained 4.7 ± 1.4 kg/year.

Correlation analyses between changes in weight/obesity indicators and baseline metabolic characteristics. The relationships between weight/triceps change and the physical and metabolic parameters were analyzed for the entire group and separately in both sexes. In the entire group, yearly weight gain correlated positively with the logarithm of fasting plasma insulin concentration ($r = 0.27$, $P < 0.0001$) and 2-h plasma insulin concentration ($r = 0.13$, $P = 0.02$), the initial relative weight ($r = 0.45$, $P < 0.0001$), the change in height ($r = 0.23$, $P < 0.0001$), the maximum BMI of the mother ($n = 280$, $r = 0.17$, $P < 0.01$), and weight at birth ($n = 280$, $r = 0.12$, $P < 0.05$). There was no correlation between weight gain and the maximum BMI of the father ($r = 0.06$, NS). As shown in Fig. 1, the correlation between yearly rate of weight gain and fasting plasma insulin concentration tended to be stronger in boys ($r = 0.42$, $P < 0.0001$) than in girls ($r = 0.20$, $P < 0.01$). In contrast, the correlation between the changes in triceps skinfold thickness and fasting insulin concentration was significant in girls ($r = 0.22$, $P < 0.01$) but not in boys ($r = 0.09$, NS). In the subgroup of 239 children with a relative weight <130% at baseline, yearly weight gain correlated positively with the logarithm of fasting plasma insulin ($r = 0.17$, $P < 0.01$), especially in boys ($r = 0.33$, $P < 0.001$) but not in girls ($r = 0.11$, $P = 0.22$).

Multiple linear regression analysis of body weight gain and fasting plasma insulin concentration. Since annual weight gain correlated not only with fasting plasma insulin concentration but also with initial age, relative weight, and

TABLE 1
Physical and metabolic characteristics at baseline and follow-up in 328 nondiabetic Pima Indians (147 boys and 181 girls)

	Initial examination			Final examination (9.3 ± 1.9 years later)		
	All	Males	Females	All	Males	Females
Age (years)	8.3 ± 1.2	8.4 ± 1.2	8.2 ± 1.2	17.0 ± 1.4	16.8 ± 1.4	17.2 ± 1.4
Height (cm)	129.7 ± 9.3	129.9 ± 8.8	129.5 ± 9.7	165.6 ± 8.1	171.8 ± 6.2	160.6 ± 5.6
Weight (kg)	32.6 ± 10.5	32.8 ± 10.6	32.5 ± 10.4	80.8 ± 21.8	82.1 ± 24.1	79.7 ± 19.7
Relative weight (%)	119 ± 24	120 ± 27	119 ± 22	142 ± 35	134 ± 34	148 ± 34
Triceps skinfold thickness (mm)	17 ± 6	14 ± 7	16 ± 6	28 ± 14	23 ± 12	36 ± 13†
Fasting glucose (mg/dl)	86 ± 6	87 ± 6	86 ± 6	92 ± 8	93 ± 8	92 ± 7
2-h glucose (mg/dl)	94 ± 16	92 ± 16	95 ± 17	106 ± 25	100 ± 26	111 ± 24
Fasting insulin (μU/ml)	17 ± 13	15 ± 10	19 ± 15*	—	—	—
2-h insulin (μU/ml)	85 ± 76	69 ± 58	98 ± 85*	—	—	—
Changes						
Weight gain (kg)	—	—	—	48.1 ± 17.6	49.3 ± 19.1	47.2 ± 16.2
Weight gain (kg/year)	—	—	—	5.3 ± 1.8	5.6 ± 2.0	5.0 ± 1.6*
Relative weight change (%/year)	—	—	—	2.4 ± 2.8	1.5 ± 2.7	3.1 ± 2.6†
Triceps thickness change (mm/year)	—	—	—	1.6 ± 1.3	0.9 ± 1.2	2.1 ± 1.2†

Data are means ± SD. Male/female comparison: *$P < 0.01$, †$P < 0.0001$.

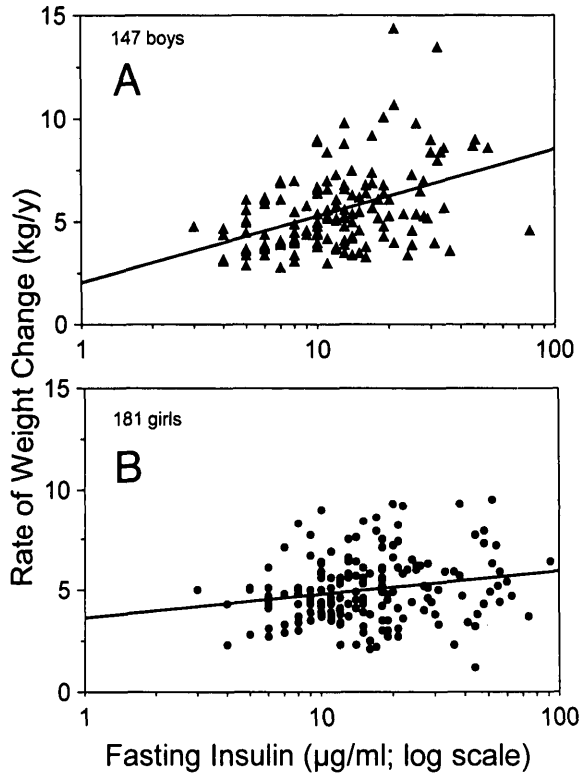

FIG. 1. Relationship between the yearly rate of weight gain and fasting plasma insulin concentration in 328 5- to 9-year-old Pima Indian children. *A*: relationship in boys (r = 0.42, P < 0.0001). *B*: relationship in girls (r = 0.20, P = 0.007).

change in height, multiple regression analyses were performed to delineate the independent contribution of fasting plasma insulin to the changes in weight change and triceps skinfold thickness. The yearly rates of weight gain (kg/year), the change in relative weight (%/year), and the change in triceps skinfold thickness (mm/year) were all significantly associated with fasting plasma insulin concentrations independent of age, sex, initial relative weight, and change in height (Table 2). When maternal BMI was added to the models, fasting insulin was still clearly associated with weight gain (P = 0.01) but less so with relative weight change (P = 0.05) or change in triceps skinfold thickness (P = 0.15). However, for the latter analyses, the sample size was reduced to 280. In the subgroup of 239 children with a relative weight <130% at baseline, the yearly rate of weight gain (P = 0.007), the yearly change in relative weight (P = 0.02), and the yearly rate of change in triceps skinfold thickness (P = 0.008) were all positively related to the log of fasting insulin independently from the factors listed in the three models shown in Table 2.

DISCUSSION

The Pima Indian children in this study gained a mean of 48 kg over an average 9.3-year follow-up period and increased their mean relative weight from 119 to 142%. It is interesting to note that even though the weight gain was similar in boys and girls, girls tended to become more obese as judged by the yearly rate of increases in relative weight and triceps skinfold thickness. The rate of yearly weight gain expressed in absolute weight or in relative weight for height as well as the rate of fat deposition as assessed by triceps skinfold thickness was positively associated with fasting plasma insulin concentrations at prepubertal age. This relationship was independent of factors known to have an effect on fasting insulin concentrations, such as sex, age, relative weight, and change in height. Unfortunately, no index of body fat distribution was measured in these children, but Pima Indians are known to have centrally distributed body fat.

These results are consistent with those in animal studies in which hyperinsulinemia precedes an increase in body weight. In rats, lesions of the ventromedial hypothalamus result in hyperinsulinemia before excess weight accumulation (26). In genetically obese animals, such as the Zucker rat and *ob/ob* mouse, increased insulin secretion precedes insulin resistance (27) and appears as a major pathogenic factor for obesity. However, our results are in contradiction to those obtained in adult Pima Indians in whom insulin resistance and high insulin secretion were associated with a lower weight gain (7,8). Reasons for the discrepant results among studies in children and adults remain to be clarified. Obviously, the degree and duration of obesity seem to be important factors in explaining the observed differences. Our study population consists of 5- to 9-year-old children, moderately obese on average, while earlier studies were conducted mostly in obese and insulin resistant adult Pima Indians. An alternative explanation is that a common factor could promote both hyperinsulinemia and obesity and that the established hyperinsulinemia/insulin resistance can then protect against further weight gain. Interestingly, a longitudinal study in 12 adult rhesus monkeys did not show any relationship between weight gain and insulin sensitivity (28).

The mechanism whereby hyperinsulinemia precipitates weight gain and obesity in children is not clear. Hyperinsulinemia is proposed to play a major role in the pathogenesis of obesity through its lipogenic actions (29). In response to

TABLE 2
Multiple linear regression analyses of yearly rate of weight gain or yearly percent relative weight change by characteristic of interest

	Regression coefficient	SE	P value
Weight gain (kg/year) (R^2 = 0.30)			
Fasting insulin (log_{10})	0.958	0.388	0.014
Initial relative weight (%)	0.031	0.004	<0.0001
Change in height (cm/year)	0.545	0.109	<0.0001
Age (years)	−0.096	0.079	NS
Sex (male)	−0.172	0.242	NS
Relative weight change (%/year) (R^2 = 0.42)			
Fasting insulin (log)	1.394	0.674	0.039
Initial relative weight (%)	−0.0076	0.007	NS
Change in height (cm/year)	−0.327	0.188	NS
Age (years)	−0.397	0.137	0.004
Sex (male)	−0.872	0.418	0.038
Change in triceps skinfold thickness (mm/year) (R^2 = 0.25)			
Fasting insulin (log)	0.641	0.299	0.032
Initial relative weight (%)	0.0039	0.003	NS
Change in height (cm/year)	−0.076	0.084	NS
Age (years)	−0.122	0.061	0.04
Sex (male)	−1.030	0.185	<0.0001

See RESULTS for the data on these three models in the 239 children with a baseline relative weight of < 130%.

mixed meals, insulin promotes fat storage and causes preferential oxidation of carbohydrate over fat. Insulin increases lipoprotein lipase activity in the adipose tissue but decreases its activity in skeletal muscle, thus decreasing fat oxidation in the muscle and increasing its storage in the adipose tissue (30). Persistent hyperinsulinemia would, therefore, promote continued fat accumulation, especially in the presence of high dietary fat intake (31). In contrast, a catabolic action of insulin opposing weight gain is based on evidence that insulin gains access to the brain via a specialized vascular transport system (32), where it suppresses signals for food intake (33) and possibly increases energy expenditure (34). The relative contribution of the opposing nature of the peripheral versus central actions of insulin in childhood and adulthood is not clear. Our findings suggest that in Pima Indian children, the peripheral actions of insulin exert a stronger effect. This effect may be strongest while the subject is relatively leaner and weakens progressively until the obese individual becomes relatively resistant to further fat accumulation, even in the face of continued insulin resistance.

Pima Indian children, compared with Caucasian children, are hyperinsulinemic (13) and probably resistant to the action of insulin, similar to adult Pimas. Even if insulin resistance is clearly associated with hyperinsulinemia (35), controversy remains as to whether increased insulin secretion and the resultant hyperinsulinemia precede insulin resistance. Clearly, in all children, puberty is associated with decreased sensitivity to insulin, which is compensated for by increased insulin secretion (36,37). Obese children have increased rates of insulin secretion compared with lean insulin-sensitive control subjects (38), suggesting that insulin resistance and hyperinsulinemia coexist in preadolescent children with moderate to severe obesity (39). Also, animal models of obesity, such as the genetically preobese Zucker rats, show that insulin resistance and hyperinsulinemia coexist (40,41). Therefore, prepubertal hyperinsulinemia may coexist with insulin resistance in Pima Indian children and this condition may be a heritable trait (42,43).

In general, our results are consistent with the thrifty genotype hypothesis that fasting hyperinsulinemia promotes rapid deposition of fat and adiposity, as indicated by its relation with changes in relative weight and changes in triceps skinfold thickness. It can be argued that this group of Pima Indians was, on average, overweight to begin with. Indeed, it would be ideal to study an even younger population to see whether hyperinsulinemia is predictive of body weight gain in normal weight children. However, the observed relationships between hyperinsulinemia and weight gain or increased obesity were also true in the subgroup of 239 children with a relative weight <130% at baseline. To our knowledge, this study represents the first attempt to look at the relationship between hyperinsulinemia/insulin resistance and body weight gain in children.

In conclusion, insulin is a predictor of weight gain in 5- to 9-year-old Pima Indian children and may play an important primary role in the pathogenesis of obesity in the Pima Indians. Hyperinsulinemia may be an early trait or expression of the thrifty genotype, initiating the development of obesity and a cycle of increasing insulin resistance and compensatory hyperinsulinemia common in adult obesity. Mechanisms whereby hyperinsulinemia affects the physiological systems that control eating behavior, energy expenditure, and the molecular mechanisms that control body weight remain to be fully elucidated.

REFERENCES

1. Bogardus C, Lillioja S, Howard BV, Reaven G, Mott D: Relationship between insulin secretion, insulin action, and fasting plasma glucose in non-diabetic and non-insulin-dependent diabetic mellitus in Pima Indians. *J Clin Invest* 74:1238–1246, 1985
2. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley J, Ravussin E, Bennett PH, Bogardus C: Insulin resistance and secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. *N Engl J Med* 329:1988–1992, 1993
3. Ravussin E, Swinburn BA: Insulin resistance is a result, not a cause of obesity: Socratic debate: the pro side. In *Progress in Obesity Research: 7*. Angel A, Anderson H, Bouchard C, Lau D, Leiter L, Mendelson R, Eds. London, John Libbey & Company, 7th International Congress on Obesity, 1996, p. 173–178
4. Sims EAH: Insulin resistance is a result, not a cause of obesity: Socratic debate: the con side. In *Progress in Obesity Research: 7*. Angel A, Anderson H, Bouchard C, Lau D, Leiter L, Mendelson R, Eds. London, John Libbey & Company, 7th International Congress on Obesity, 1996, p. 587–592
5. Neel JV: Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress." *Am J Hum Genet* 14:353–362, 1962
6. Neel JV: The thrifty genotype revisited. 1982. The genetics of diabetes mellitus. In *The Genetics of Diabetes Mellitus*. Kobberling J, Tattersall J, Tattersall R, Eds. London, Academic Press, 1982, p. 283–293
7. Swinburn BA, Nyomba BL, Saad MF, Zurlo F, Raz I, Knowler WC, Lillioja S, Bogardus C, Ravussin E: Insulin resistance associated with lower rates of weight gain in Pima Indians. *J Clin Invest* 88:168–173, 1991
8. Schwartz MC, Boyko EJ, Kahn SE, Ravussin E, Bogardus C: Reduced insulin secretion: an independent predictor of body weight gain. *J Clin Endocrinol Metab* 80:1571–1576, 1995
9. Valdez R, Mitchell BD, Haffner SM, Hazuda HP, Morales PA, Monterrosa A, Stern MP: Predictors of weight change in a bi-ethnic population: the San Antonio Heart Study. *Int J Obes* 18:85–91, 1994
10. Hoag S, Marshall JA, Jones RH, Hamman RF: High fasting insulin levels associated with lower rates of weight gain in persons with normal glucose tolerance: the San Luis Valley diabetes study. *Int J Obes* 19:175–180, 1995
11. Yost TJ, Jensen DR, Eckel RH: Weight regain following sustained weight reduction is predicted by relative insulin sensitivity. *Obes Res* 3:583–587, 1995
12. Eckel RA: Insulin resistance: an adaptation for weight maintenance. *Lancet* 340:1452–1453, 1992
13. Pettitt DJ, Moll PP, Knowler WC, Mott DM, Nelson RG, Saad MF, Bennett PH, Kottice BA: Insulinemia in children at low and high risk for NIDDM. *Diabetes Care* 16:608–615, 1993
14. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH: Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. *Am J Epidemiol* 113:144–156, 1981
15. Knowler WC, Pettitt DJ, Nelson RG, Howard BV, Bogardus C, Bennett PH: Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr* 53:S1543–S1541, 1991
16. Bennett PH, Burch TA, Miller M: Diabetes mellitus in American (Pima) Indians. *Lancet* ii:125–128, 1971
17. Marshall WA, Tanner JM: Variation in the pattern of pubertal changes in boys. *Arch Dis Child* 45:13–23, 1970
18. Marshall WA, Tanner JM: Variation in pattern of pubertal changes in girls. *Arch Dis Child* 44:291–303, 1969
19. Bloch CA, Clemens P, Sperling MA: Puberty decreases insulin sensitivity. *J Pediatr* 110:481–487, 1987
20. Jelliffe DB: *The Assessment of the Nutritional Status of the Community; With Special Reference to Field Surveys in Developing Regions of the World.* Geneva, World Health Org., 1966 (Monograph series no. 53)
21. World Health Organization: *Diabetes Mellitus. Report of a WHO Study Group*. Geneva, World Health Org., 1985, p. 9–17 (Tech. Rep. Ser., no. 727)
22. Technicon Autoanalyzer N-26: Technicon Instruments Corporation, Tarrytown, NY, 1965
23. Stein MW: D-glucose determination with hexokinase and glucose-6-phosphate dehydrogenase. In *Methods of Enzymatic Analysis*. Bergmeyer HU, Ed. New York, Academic Press, p. 117, 1953
24. Herbert V, Lau K, Gottlieb CS, Bleicher SJ: Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab* 25:1375–1384, 1965
25. Yalow RS, Berson SA: Immunoassay of endogenous plasma insulin in man. *J Clin Invest* 39:1157–1167, 1960
26. Pinecaud L, Rohner-Jeanrenaud F, Jeanrenaud B: In vivo metabolic changes as studied longitudinally after ventromedial hypothalamic lesion. *Am J Physiol* 250:E662–E668, 1986

27. Rohner-Jeanrenaud F, Jeanrenaud B: A role for the vagus nerve in the etiology and maintenance of the hyperinsulinemia of genetically obese fa/fa rats. *Int J Obes* 9:71–75, 1985
28. Bodkin NL, Ortmeyer HK, Hansen BC: Insulin sensitivity as a predictor of weight gain in the rhesus monkey. *Obes Res* 3:369S, 1995
29. Assimacopoloulos-Jeannet F, Jeanrenaud B: The hormonal and metabolic basis of experimental obesity. *Clin Endocrinol Metab* 2:337–359, 1976
30. Eckel RH, Yost TJ, Jensen DR: Alteration in lipoprotein lipase in insulin resistance. *Int J Obes Relat Metab Disord* 19:S16–S23, 1995
31. Flatt JP: Importance of nutrient balance in body weight regulation. *Diabetes Metab Rev* 4:571–581, 1988
32. Schwartz MW, Bergman RN, Kahn SE, Taborsky GJ, Fisher LD, Sipols AJ, Woods SC, Steil GM, Porte D Jr: Evidence for uptake of plasma insulin into cerebrospinal fluid through an intermediate compartment in dogs: quantitative aspects and implication for transport. *J Clin Invest* 88:1272–1281, 1991
33. Foster LA, Ames NK, Emery RS: Food intake and serum insulin responses to intraventricular infusions of insulin and IGF-1. *Physiol Behav* 50:743–749, 1991
34. Berne C, Fagius J, Pollare Y, Hemjadhl P: The sympathetic response to euglycemic hyperinsulinemia. *Diabetologia* 35:873–879, 1992
35. Reaven GM, Chen YDI, Hollenbeck CB, Sheu WHH, Ostraga D, Polonsky KS: Plasma insulin, C-peptide, and proinsulin concentrations in obese and nonobese individuals with varying degrees of glucose tolerance. *J Clin Endocrinol Metab* 476:44–48, 1993
36. Bloch AB, Clemens P, Sperling MA: Puberty decreases insulin sensitivity. *J Pediatr* 110:481–487, 1987
37. Polonsky KS, Given BD, Hirsch L, Shapiro ET, Tillil H, Beebe C, Galloway JA, Frank BH, Karrison T, Van Cauter E: Quantitative study of insulin secretion and clearance in normal and obese subjects. *J Clin Invest* 81:435–441, 1988
38. Le Stunff C, Bougneres P: Early changes in postprandial insulin secretion, not in insulin sensitivity characterize juvenile obesity. *Diabetes* 43:696–702, 1994
39. Caprio S, Bronson M, Tamborlane W: Co-existence of severe insulin resistance and hyperinsulinemia in preadolescent obese children. *Int J Obes* 20 (Suppl.):81, 1996
40. Zarjevski N, Doyle P, Jeanrenaud B: Muscle insulin resistance may not be a primary etiological factor in the genetically obese fa/fa rat. *Endocrinology* 130:1546–1570, 1992
41. Terretaz J, Jeanrenaud B: In vivo hepatic and peripheral insulin resistance in genetically obese (fa/fa) rats. *Endocrinology* 112:1346–1351, 1983
42. Lillioja S, Mott DM, Zawadzki JK, Young AA, Abbott WGH, Knowler WC, Bennett PH, Moll M, Bogardus C: In vivo insulin action is familiar characteristics in Pima Indians. *Diabetes* 36:1329–1335, 1987
43. Bogardus C, Lillioja S, Nyomba BL, Zurlo F, Swinburn B, Esposito-del Puentes A, Knowler WC, Ravussin E, Mott DM, Bennett PH: Distribution of in vivo insulin action in Pima Indians as mixture of three normal distribution. *Diabetes* 38:1423–1432, 1987