Obesity: Evidence of Decreased Secretion of Glucagon

Abstract. *The increase in concentration of glucagon in plasma caused by infusion of alanine was reduced in obese subjects as compared to that in nonobese control subjects. This was true when the subjects were in the postabsorptive state as well as after an 84-hour fast, at which time the basal glucagon concentration had risen in the nonobese subjects, but remained unaltered in the obese group.*

Obesity is characterized by a variety of abnormalities in carbohydrate metabolism. Hyperinsulinemia (*1*), diminished responsiveness to insulin (*2*), and an increased incidence of diabetes mellitus (*3*) have been documented as occurring in overweight subjects. Little information is available, however, regarding glucagon secretion in obese subjects. The influence of obesity on pancreatic alpha cell function is of interest in view of recent evidence implicating abnormalities of glucagon secretion in the pathogenesis of diabetes mellitus (*4*). In this study we have evaluated glucagon secretion in obese subjects by examining the response to starvation and to infusion of alanine, the major gluconeogenic percursor (*5*) and potent stimulator of alpha cell secretion (*6*).

Two groups were studied: one composed of eight obese subjects (32 to 42 years old) whose body weight was 53 to 170 percent above ideal weight (*7*), and a second group composed of six nonobese subjects (28 to 35 years old) whose body weight was within 12 percent of ideal weight (*7*). All of the subjects were in apparent good health, and had no evidence of diabetes as indicated by an absolute glucose disappearance rate (K) of 1.0 or greater on intravenous glucose tolerance testing (*8*).

The subjects were hospitalized at the Clinical Research Center of the Yale–New Haven Hospital. They were fed a weight-maintaining diet containing 40 percent carbohydrate for 3 to 7 days, after which they fasted for 84 hours. During the fast, intake was limited to water. L-Alanine was administered to all subjects after a 12- to 14-hour overnight fast (postabsorptive state), and after 84 hours of starvation. The alanine was infused intravenously during 2 to 4 minutes as a sterile, pyrogen-free 10 percent solution, in doses of 0.15 g per kilogram of body weight. Blood samples were drawn when the subjects were in the basal condition, prior to the infusion of alanine (both when the subjects were in the postabsorptive state, and after 84 hours of fasting) and at 10- to 30-minute intervals for 2 hours after completion of the alanine infusion.

The concentration of glucose in plasma was measured by the glucose oxidase procedure (*9*). The amount of pancreatic glucagon in the plasma was determined by radioimmunoassay with an antibody (Unger, lot 30K) that cross reacts minimally with gut glucagon (*10*). The concentration of insulin in the plasma was measured by immunoassay, with talc separating bound from free insulin (*11*).

In Table 1 basal concentrations and peak increments after alanine infusion are shown for glucagon, glucose, and insulin in the obese and nonobese subjects in the postabsorptive state, and after an 84-hour fast. The changes in glucagon concentrations from basal amounts during the 2-hour period after completion of the alanine infusion were compared for the two groups (Fig. 1). Although basal concentrations of glucagon were equivalent in the obese and nonobese subjects while they were in the postabsorptive state, the maximum glucagon response to alanine infusion was reduced by 50 percent in the obese group. Following starvation, a significant elevation in basal concentration of glucagon was observed in the nonobese subjects ($P < .05$). In contrast, in the obese group, basal concentrations of glucagon after 84 hours of fasting were unchanged from those observed when the subjects were in the postabsorptive state, and were significantly lower than those in fasted nonobese control subjects. The diminished glucagon response to alanine infusion in obese subjects was also apparent after they were starved, the peak increment in the obese group remaining less than 50 percent of that observed in the controls. Accompanying the decreased glucagon response, a smaller increment in the concentration of glucose in plasma was observed after alanine infusion in the obese subjects. Basal concentrations of insulin were higher in the obese group (*1*), while the concentration of glucose in the plasma declined less markedly in these subjects during the course of the fast (*12*).

Our data provide evidence of decreased alpha cell function in obese, nondiabetic subjects. Although glucagon concentrations were comparable in obese and nonobese subjects while they were in the basal, postabsorptive state, the glucagon response to infusion of alanine, and to starvation, was decreased in the obese group. In a previous study, Unger *et al.* demonstrated that there was no relation between body weight and the glucagon response to infusion of arginine in maturity-onset diabetics (*4*); however, obese subjects with normal glucose tolerance were not evaluated. Marliss *et al.* reported a transient increase in the concentration of glucagon in the plasma of obese subjects who fasted for prolonged periods, but no comparison was made in that study with individuals whose weight was normal (*13*). More recently, Floyd *et al.* observed no consistent increase in the concentration of glucagon in the plasma of obese subjects who fasted for 84 hours (*14*).

With regard to the mechanism of decreased glucagon secretion in over-

Table 1. Concentrations of glucagon, glucose, and insulin in the plasma of obese and nonobese subjects while they were in the postabsorptive condition, and after an 84-hour fast. Max. inc., maximum increase above basal amount after infusion of alanine; NS, not significant. P is the significance of difference between the mean concentrations in obese and nonobese subjects. Results are expressed as means ± standard error.

Subject	Glucagon (pg/ml)		Glucose (mg/100 ml)		Insulin (μunit/ml)	
	Basal	Max. inc.	Basal	Max. inc.	Basal	Max. inc.
			Postabsorptive			
Obese	83.6 ± 22.5	57.9 ± 9.4	75.3 ± 2.1	3.8 ± 0.7	25.6 ± 3.6	44.0 ± 7.6
Nonobese	92.0 ± 18.3	121.0 ± 14.0	80.1 ± 3.5	7.6 ± 1.2	7.4 ± 0.9	7.6 ± 1.2
P	NS	< .005	NS	< .01	< .001	< .001
			84-Hour fast			
Obese	78.1 ± 10.5	123.1 ± 13.3	60.0 ± 4.4	14.2 ± 1.2	18.2 ± 1.7	25.8 ± 5.6
Nonobese	150.0 ± 17.6	270.0 ± 35.2	49.8 ± 1.9	25.0 ± 1.1	3.4 ± 1.2	9.6 ± 2.7
P	< .005	< .005	< .05	< .001	< .001	< .02

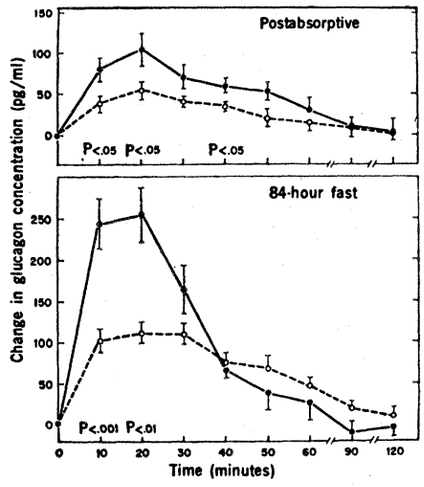

Fig. 1. Changes in glucagon concentration in plasma from basal amounts in nonobese and obese subjects infused with alanine when they were in the postabsorptive state, and after an 84-hour fast. Results shown represent the means ± standard error. *P* values indicate significance of differences between nonobese and obese subjects. Solid line, nonobese subjects; dotted line, obese subjects.

weight subjects, the relative importance of such factors as obesity per se, prolonged alterations in dietary intake, and hyperinsulinemia cannot be determined from the present data. However, the higher concentrations of glucose in the blood of the obese group while they were starved may contribute to the diminished alpha cell response observed at that time.

The demonstration that obese individuals are capable of maintaining glucose homeostasis during starvation in the absence of an elevation in concentration of glucagon in the plasma suggests than an increase in secretion of this hormone is not essential for glycogenolytic and gluconeogenic processes induced by starvation. The question may be raised as to whether the high incidence of reactive hypoglycemia reported in obese subjects (*15*) may be related to altered alpha cell function.

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Synthesis of Cysteine from Methionine in Normal Adult Subjects: Effect of Route of Alimentation

Abstract. *Parenteral alimentation solutions free of cysteine, probably an essential amino acid for premature infants, were administered continuously to eight healthy men through catheters in the superior vena cava and through nasogastric tubes. When the preparation was administered parenterally, the plasma cystine concentration dropped markedly. When feeding was switched to the oral route, the concentration rose immediately, but returned to baseline only when a cystine-containing diet was fed. These studies indicate that the synthesis of cysteine from methionine is limited, even in the adult subject, when cystine-free diets are administered parenterally.*

The administration of high-calorie solutions by central venous catheter to infants and adults who are unable to take an adequate diet orally has gained wide acceptance. Such intravenous preparations supply an adequate amount of calories in the form of dextrose and sufficient quantities of a protein hydrolyzate to achieve positive nitrogen balance and net protein synthesis.

These solutions given by the central venous route bypass the liver and the gut, two important sites in the control of plasma amino acid concentrations. When solutions are administered orally, the liver has direct access to dietary amino acids through the portal circulation. These ingested amino acids and peptides, together with liver and plasma proteins, comprise an important part of the labile protein reserve. The liver can alter the concentration of amino acids in portal blood before entry into peripheral circulation and can supply or utilize amino acids rapidly in a manner complementary to the needs of other tissues, properties important to the homeostatic control process (*1*). One example of such complementary interaction has been noted for the amino acid alanine during starvation and exercise (*2*). The gut also is important in amino acid metabolism, affecting such factors as stereospecificity of amino acid absorption, rapid absorption of peptides and their conversion to component amino acids before release into the portal circulation, interconversions of certain amino acids, degradation and synthesis of amino acids by the intestinal flora, the length of time a meal is available for absorption, and interactions due to the metabolic activity of the tract itself (*3*).

The nitrogen sources of solutions designed for total parenteral alimentation in this country are usually protein hydrolyzates of casein or beef fibrin, and contain approximately equal quantities of free amino acids and peptides. Stegink and Baker (*4*) showed that the amino acid composition of these hydrolyzates directly affects amino acid concentrations in plasma, and noted that these concentration changes could be logically explained when the amino acid composition of each nitrogen source was considered. In particular, the absence of cystine in such preparations was reflected by low plasma cystine and taurine concentrations in infants maintained by parenteral feeding. They suggested that the composition of amino acid solutions infused