

Control of Insulin Secretion during Fasting Hyperglycemia in Adult Diabetics and in Nondiabetic Subjects during Infusion of Glucose

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ABSTRACT In obese adult diabetics, the concentration of insulin in venous plasma was unrelated to the degree of hyperglycemia after an overnight fast. However, in these subjects, insulin rose and fell in proportion to the magnitude of change in plasma glucose induced by small intravenous infusions of glucose. The minimal dose of glucose to cause a significant rise in insulin above the fasting level was similar in normal subjects, obese nondiabetic subjects, and in obese, hyperglycemic adult diabetics. This dose lay between infusion of 60 and 100 mg of glucose per min for 30 min. These results suggested that the secretion of insulin was under regulation by changes in blood glucose but was not stimulated in proportion to the stable raised blood glucose concentration of the hyperglycemic diabetic. Artificial hyperglycemia was induced in fasting normal subjects by constant intravenous infusion of glucose at rates of 100–250 mg of glucose per min for periods up to 8 hr. Plasma glucose rose during the 1st hr of infusion and then remained constantly elevated for up to 8 hr. The concentration of plasma insulin paralleled that of plasma glucose. During the period of constant hyperglycemia and elevated insulin, superimposition of a brief additional glucose load resulted in a prompt rise in glucose and insulin, both returning to the previous elevated levels.

Thus in normals as well as obese diabetics, stable hyperglycemia does not produce a pancreatic response sufficient to return the blood glucose to an arbitrary normal fasting concentration, yet the beta cells remain readily responsive to a change in plasma glucose. These data suggest that the beta cells do not operate as a control system with an absolute reference point when pre-

sented with systemic hyperglycemia. The behavior of the beta cells during hyperglycemia in the fasting obese adult diabetic suggests that the regulation of the basal insulin secretion may not be determined by factors directly related to the prevailing concentration of glucose. It is postulated that the beta cells adapt to hyperglycemia perhaps through the operation of controls directed toward a normal delivery of free fatty acids or some other cellular metabolic substrate during fasting.

INTRODUCTION

It has been obvious since the advent of the radioimmunoassay for insulin that adult diabetics retain the ability to regulate insulin secretion in response to a glucose stimulus (1). A number of investigators have sought to define the special characteristics of the insulin response in adult diabetics in an attempt to explain the altered glucose homeostasis of diabetics (1–8). In most recent studies (2–6, 8), there has been general agreement that the insulin response in diabetics is delayed and quantitatively less than in weight-matched nondiabetics, and that the deficiency of response is proportional to the degree of glucose intolerance. These conclusions are based primarily upon responses after large nutrient loads. In studies of the pattern of insulin response to normal meals and then to a fasting period in adult diabetics (9), we were struck by the paradox that, although insulin was readily secreted during assimilation of a meal, it was not apparently called forth to correct fasting hyperglycemia. In the experiments to be reported, we have attempted to examine the regulatory responses of the beta cells during fasting hyperglycemia. The results show that in the obese hyperglycemic diabetic, the secretion of insulin is under regulation around the elevated blood glucose level. In fact, the mini-

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mal dose of glucose necessary for a change in fasting insulin concentration was indistinguishable from normals. A similar phenomenon could be induced in non-diabetics during intravenous infusion of glucose, suggesting that under these conditions, the beta cells are responsive to changes in glucose concentration and are not primarily operating to restore an absolute concentration.

METHODS

Subjects. Volunteers with adult-onset diabetes were recruited from the Diabetes Clinic at King County Harborview Hospital. The clinical features of the subjects are summarized in Table I. With the exception of three subjects, diabetics were 20% or more over ideal body weight according to Metropolitan Life tables. Although none of the diabetic group had ever received insulin, all but three had received oral hypoglycemic agents in the form of acetohexamide, tolbutamide, or phenformin. In all cases, oral agents were discontinued and control maintained by diet alone for at least 1 wk before inclusion in the study. None of the subjects was receiving thiazides, and no complicating illnesses were present. The estimated duration of diabetes ranged from 3 months to 16 yr. The diabetic subjects were admitted to the Clinical Research Ward for periods of 3–12 days to permit daily collection of blood samples and to monitor caloric intake. In all cases, diabetic subjects were permitted an unrestricted choice of dietary intake.

Nondiabetic normal control and nondiabetic obese subjects were volunteers selected from a group of hospital personnel, and clinical features of these two groups are also summarized in Table I. All of the obese group were more than 30% over ideal body weight by Metropolitan Life tables. All had a normal oral glucose tolerance test,¹ and all had a negative family history for diabetes. None of the subjects had any complicating illness, and none were receiving any oral medications.

Nondiabetic normal controls were less than 15% overweight and had negative family histories for diabetes. All had normal oral glucose tolerance tests or a normal blood glucose 2 hr after 100 g of glucose orally. With the exception of two subjects who were receiving thyroid replacement (0.3 mg of L-thyroxine/day), none were receiving any medication, and none had any complicating illness. In most instances, studies on normal subjects were carried out after overnight admission to the Clinical Research Ward.

Experimental protocols. The subjects were studied after an overnight fast of 15 hr. Neither smoking nor any oral intake was permitted on the morning of the study. Studies were performed with the subject at rest in bed. In those cases studied as outpatients, an interval of bed rest of at least 2 hr preceded the experimental period. Studies were carried out utilizing an indwelling plastic venous needle to obtain blood samples. After placement of the venous collection needle, an intravenous saline infusion was begun in the contralateral forearm and continued throughout the experiment. After placement of the needles, a period of 30 min was allowed for relaxation before collection of the first control sample. Control periods usually began at 8:00 a.m., and, with the exception of 8-hr infusions, protocols were completed by noon. To minimize confusion, a single operator

¹ According to the U. S. Public Health Service criteria (10).

TABLE I
Experimental Subjects

Subject	Sex	Age	Height	Weight	Ideal body wt
		<i>yr</i>	<i>in.</i>	<i>lb.</i>	<i>%</i>
Normals					
J. H.	M	29	75	206	112
J. W.	M	34	75	195	105
K. H.	M	30	70	162	106
J. T.	F	25	66	115	96
D. M.	F	29	60	110	103
J. F.	F	27	72	144	96
T. S.	M	35	72	162	95
M. C.	M	32	71	167	106
A. B.	F	27	64	137	114
B. H.	F	25	65	122	100
R. R.	F	29	64	106	88
A. K.	M	23	70	164	107
Diabetics					
M. A.	F	50	67	195	149
C. R.	M	42	69	160	110
R. T.	M	51	68	190	131
M. W.	F	42	65	220	179
M. C.	F	31	63	300	251
L. O.	F	61	65	215	175
D. S.	F	43	65	190	154
L. T.	F	53	66	185	145
J. C.	F	44	66	198	155
K. S.	F	36	64	320	267
F. A.	F	63	60	220	206
P. C.	M	56	65	143	107
S. S.	F	30	67	139	106
J. S.	F	25	66	133	104
E. B.	F	21	63	120	103
T. B.	F	21	63	117	100
S. F.	M	54	70	160	101
Obese nondiabetics					
A. D.	F	46	60	202	184
B. T.	F	53	63	160	136
R. M.	M	30	68	195	135
L. N.	F	17	63	224	187
L. G.	M	26	70	240	157
M. J.	M	25	72	233	144
B. W.	F	42	69	206	147
J. S.	M	31	72	360	212
E. W.	F	50	62	147	130
P. B.	M	50	65	210	158
H. B.	M	53	70	220	144
A. C.	F	56	62	132	117
G. P.	F	58	64	178	148
C. W.	M	50	70	172	120
P. O.	M	54	58	120	120
S. H.	F	58	60	143	134
S. Y.	F	58	62	143	126
I. W.	F	54	61	184	167

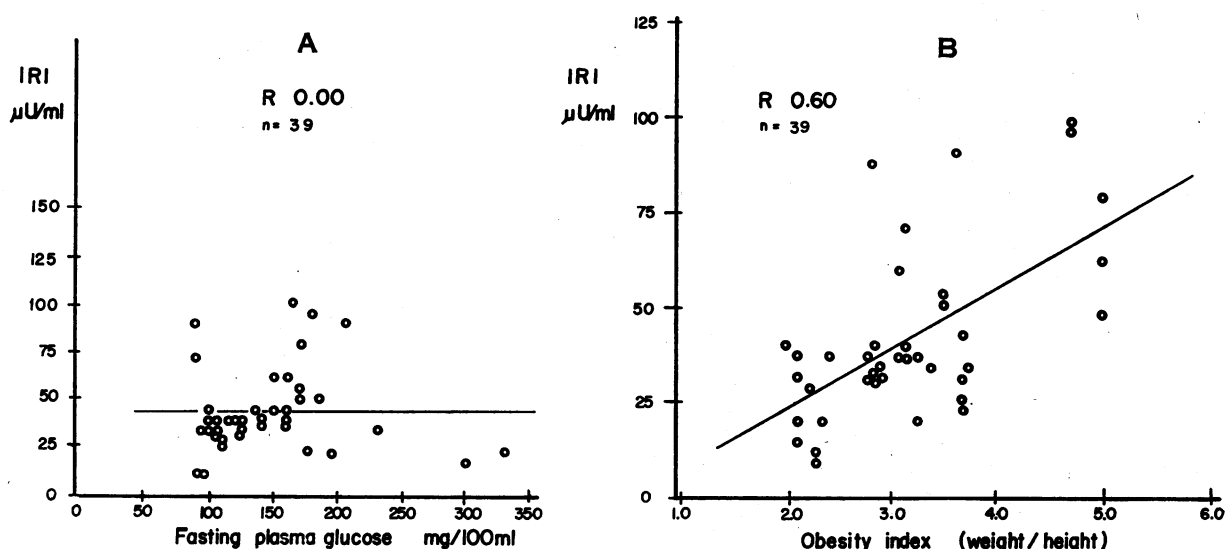


FIGURE 1(A) Absence of correlation between concentration of plasma insulin and glucose in 39 fasting adult-onset diabetics. (B) Significant positive correlation ($P < .001$) of fasting insulin concentration with the degree of obesity in the same 39 subjects.

remained with each subject during the experiment. In those instances in which pain developed about the needle site, the studies were discontinued and the results discarded. After a control period of 30 min, a glucose infusion was begun utilizing a sidearm connector in the intravenous tubing. The infusions were continued for varying intervals at a constant rate maintained by the use of a motor-driven syringe pump. In general, the subjects were not aware of the timing or content of the infusions.

Diabetic and normal subjects were studied with 30-min infusions. Seven studies were carried out in six nonobese, normal individuals prepared as described above, in which glucose was infused at 100 mg/min for a period of 120 min. In a second group of seven nonobese, normal subjects, glucose was infused at a rate of 250 mg/min for 120 min, the rate was doubled (500 mg/min) for 30 min, and then continued at 250 mg/min for 60 min. Four additional nonobese, normal subjects were studied during an 8 hr period of glucose infusion at 100 mg/min. With the exception of the 8 hr infusion studies, blood samples were collected at 15-min intervals during the control and infusion periods; after the 30 min infusions, sample collection was continued for 60 min after the infusion had been terminated. During the 8 hr infusion studies, blood samples were collected at 30-min intervals.

Analyses. Plasma and serum samples were stored at -20°C until analysis. Plasma samples were analyzed in duplicate for glucose with a Technicon AutoAnalyzer, using the ferricyanide method. Free fatty acids (FFA) were measured by the Dole and Meinertz method (11). Serum insulin determinations were performed using the double-antibody method of Morgan and Lazarow (12). All samples from each subject were assayed concurrently.

In addition, fasting plasma samples were obtained from 17 adult-onset diabetics followed in the King County Harborview Hospital Diabetes Clinic. These specimens were prepared and analyzed in the same manner as those obtained from patients participating in the infusion studies.

RESULTS

Fasting glucose insulin relationships. After an overnight fast, the concentration of plasma glucose in the nonobese controls ranged from 76 to 100 mg/100 ml, with a mean of 88 mg/100 ml ($\text{SD} \pm 6$ mg/100 ml). Concomitant insulin levels ranged from 7 to 19 $\mu\text{U/ml}$, with a mean concentration of 13 $\mu\text{U/ml}$ ($\text{SD} \pm 3.5$ $\mu\text{U/ml}$). The mean fasting plasma glucose concentration in the nondiabetic obese group was 95 mg/100 ml ($\text{SD} \pm 10$ mg/100 ml), with a range from 81 to 110 mg/100 ml. Fasting insulin values were higher in this group, ranging from 13 to 53 $\mu\text{U/ml}$, with a mean of 34 $\mu\text{U/ml}$ ($\text{SD} \pm 10$ $\mu\text{U/ml}$). These values corresponded closely with those from the diabetic group in which a mean fasting insulin level of 39 $\mu\text{U/ml}$ ($\text{SE} \pm 16$ $\mu\text{U/ml}$) was found. The fasting plasma glucose in the diabetic group ranged from 100 to 195 mg/100 ml, with a mean of 135 mg/100 ml ($\text{SE} \pm 31$ mg/100 ml). These values represent the average of the three control samples obtained before infusion studies in all the subjects. When individual fasting insulin values were plotted vs. their corresponding glucose values, no apparent relationship was present in the hyperglycemic diabetic subjects. Regression analysis of the fasting insulin and glucose determinations from 39 adult diabetics (22 subjects from Table I and 17 clinic patients) failed to show a significant correlation, as shown in Fig. 1A. These results demonstrate a lack of relationship between the fasting plasma glucose level and fasting insulin levels in diabetic subjects over a much broader range of fasting hyperglycemia than previously reported (5). In

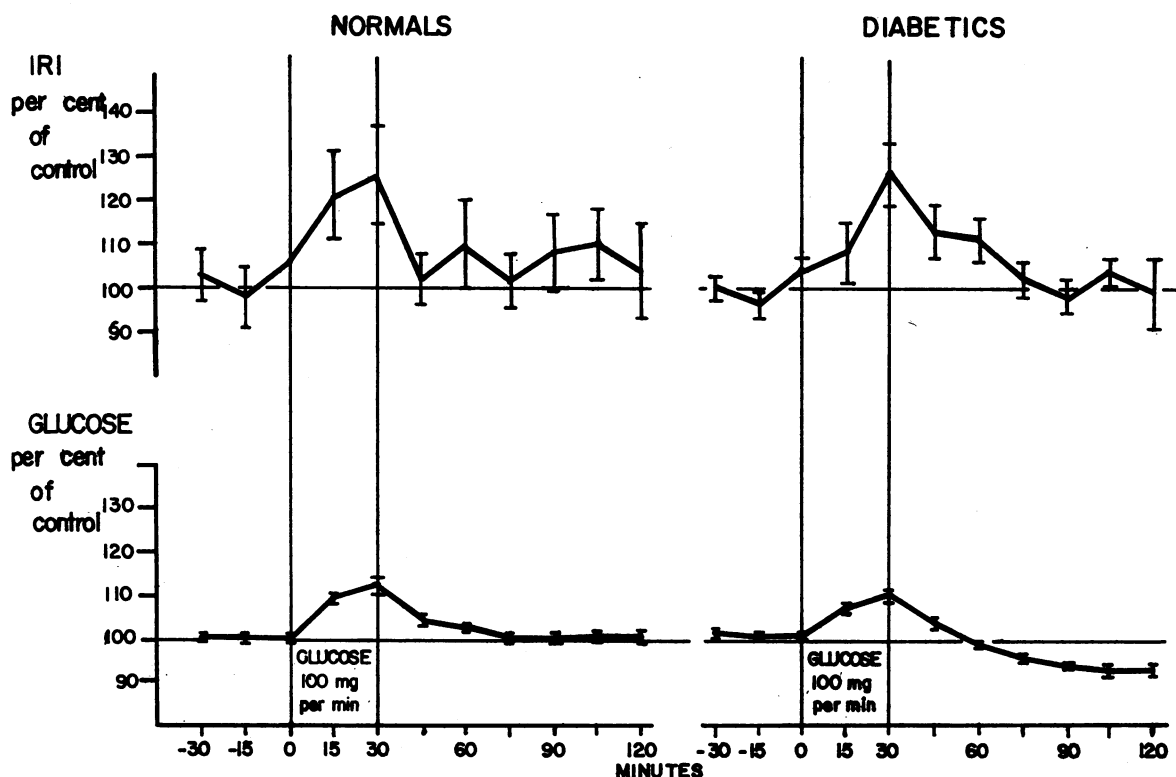


FIGURE 2 The response of plasma insulin and glucose to 30-min intravenous infusions of glucose in seven normal and seven adult diabetic subjects. The preinfusion concentrations of glucose were 93 ± 7 (sd) and 131 ± 32 (sd) mg/100 ml in the two groups respectively. The preinfusion concentrations of glucose and insulin have been set equal to 100 and the data expressed as per cent of these values. The brackets denote 2 SE of the mean.

contrast, when these fasting insulin values were plotted vs. the degree of obesity as indicated by the height-weight ratio (obesity index), a significant positive correlation was noted ($P < 0.01$), as shown in Fig. 1 B. Similar relationships between degree of obesity and fasting insulin levels have been reported by others (13, 5).

Thus the fasting diabetic appears to maintain an insulin level appropriate to body weight but in apparent disassociation from the degree of hyperglycemia. To assess whether or not the basal insulin of the hyperglycemic diabetic is under regulation by the blood glucose concentration, graded challenges with glucose were induced by intravenous infusion.

First the response to a single short-term glucose infusion (100 mg/min for 30 min) was compared in diabetic and normal subjects. In order to eliminate the effect of differences in body weight and initial plasma glucose concentration, the glucose and insulin values are expressed in terms of percentage change of the average control values, which was set as 100%. The results are displayed graphically in Fig. 2. As shown, a qualitatively

similar response was seen in both the diabetic and the normal group, in that a rise in plasma glucose was accompanied by a rise in insulin level. After termination of the stimulus, the glucose and insulin concentrations returned to or below the base line.

To evaluate the minimal dose of infused glucose necessary to cause a significant change in basal insulin secretion, a series of 30-min glucose infusions were carried out in the three groups of subjects. The responses of each group to a glucose infusion of 60 or 100 mg/min for 30 min are summarized in Table II. Results are expressed both as absolute changes during the infusion, as well as in terms of percentage change of the average of the control values, to permit comparison of the relative changes in the three groups. The relative changes are summarized graphically in Fig. 3. Each individual control value was expressed as a percentage of the average of the three preinfusion determinations for that subject, and the mean and standard deviation of the percentage variation during the control period was determined. Both the absolute and relative increases in plasma glucose were remarkably similar in all three groups during

TABLE II
Summary of Responses to Infusion of Glucose Intravenously at 60 and 100 mg/min for 30 min

Group (n)	Dose	Fasting plasma glucose	Increase with infusion	Increase with infusion	Fasting IRI	Change in IRI with infusion	Change in IRI with infusion
	mg/min	mg/100 ml	mg/100 ml	% of control	$\mu\text{U/ml}$	$\mu\text{U/ml}$	% of control
Normals							
10	60	86 \pm 1.6*	+5.6 \pm 0.5†	107 \pm 0.7	11.7 \pm 1.1	+2.2 \pm 1.3	123 \pm 13
13	100	88 \pm 2.0	+10.5 \pm 0.8	112 \pm 0.9	13.0 \pm 1.0	+6.8 \pm 1.1	169 \pm 17
Obese							
7	60	97 \pm 3.9	+5.0 \pm 1.0	105 \pm 1.3	36 \pm 5	+7.0 \pm 1.7	122 \pm 6
6	100	94 \pm 3.5	+7.5 \pm 1.4	112 \pm 2.5	26 \pm 4	+7.8 \pm 3.5	128 \pm 12
Diabetic							
11	60	131 \pm 9	+8.4 \pm 1.4	107 \pm 1.3	39 \pm 5	+6.5 \pm 2.1	120 \pm 5
15	100	135 \pm 8	+12 \pm 1.0	110 \pm 1.0	38 \pm 5	+11 \pm 1.7	131 \pm 4

The increments in plasma glucose and serum insulin (IRI) during the infusion are given as absolute and percentage change from the mean preinfusion concentration.

* Mean \pm SEM.

† The italicized differences are significant.

infusion at 60 or 100 mg/min, a finding indicating that the glucose stimuli were comparable between groups. Significant increases in insulin concentration were present during infusion of glucose at 100 mg/min in the normal group, 60 mg/min in the obese group, and both 60 and 100 mg/min in the diabetic group when the *t* test was applied to the mean differences over control (Table II). Individual responses were assessed by arbitrarily assigning significance to a rise in insulin during infusion beyond 2 SD above the control (Fig. 3). A rise in insulin of this magnitude occurred in 2 out of 10 normals, 1 out of 7 obese, and 4 out of 11 diabetic subjects during infusion at 60 mg/min. With infusion at 100 mg/min, 8 out of 13 normals, 4 out of 6 obese, and 8 out of 15 diabetics had such a rise. Significant responses to infusions of glucose at 20 mg/min for 30 min have not been observed in diabetics, obese, or normal subjects. Thus responses begin to appear between 20 and 60 mg/min and become more frequent at 100 mg/min in all three groups. In all groups when responses occurred, the magnitude of the insulin rise was proportional to the size of the stimulus. However, the relative magnitude of changes in insulin appeared to be somewhat less in the diabetic and obese groups than in the normal group for each stimulus.

To further evaluate the proportionality of insulin response to successive glucose stimuli, five diabetic subjects were studied by carrying out two glucose infusions on the same day, first at 100 mg/min for 30 min, followed by a second infusion of 200 mg/min for 30 min. The second infusion was started 30 min after completion of the first infusion. The results of these studies are shown graphically in Fig. 4 and demonstrate a rise in

insulin which is proportional to the size of the glucose stimulus.

Interpretation. The preceding studies demonstrate that in the diabetic, the fasting insulin level is unrelated to the level of the fasting blood sugar but is related to the degree of obesity. However, though the diabetic subject tolerates fasting hyperglycemia without additional secretion² of insulin, further alteration of the plasma glucose by glucose infusion does result in an insulin response. Similarly, the size of the glucose stimulus necessary to initiate a change in basal insulin secretion appears to be about the same in nonobese, obese nondiabetics, and hyperglycemia obese diabetic subjects. Although the quantitative insulin response to any given dose of glucose is less in the diabetic group than in the normals, the diabetic responds to increasing glucose stimuli in a proportional manner, so that the larger the glucose stimulus, the greater the insulin rise. In all studies, the plasma insulin returned promptly to the control levels upon termination of the stimulus. Taken together, these data indicate that insulin secretion is under regulation by small changes in plasma glucose in the hyperglycemic diabetic. The fact that the adult-onset diabetic appears to be able to initiate additional insulin secretion in response to an added glucose stimulus, but tolerates fasting hyperglycemia without evidence of increased insulin secretion, suggests that the beta cells in diabetics may develop an altered sensitivity to an ele-

²In the discussion to follow, changes in plasma concentration of insulin are equated with changes in secretion of insulin. This assumption has been made for convenience and, although not strictly proven under all circumstances, does have experimental support (14).

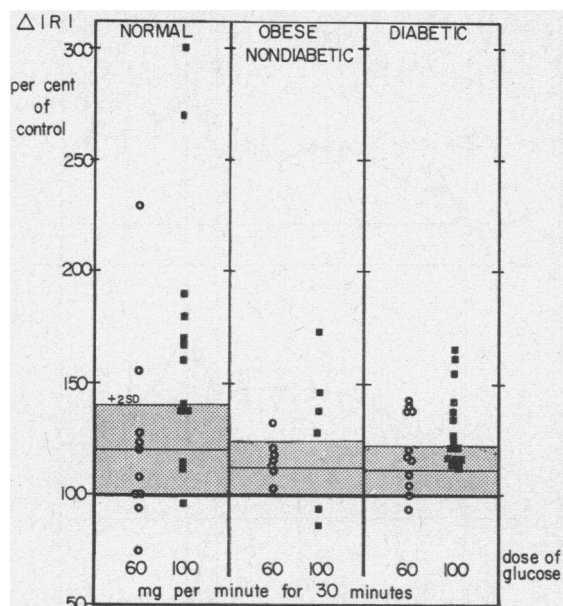


FIGURE 3 Estimation of the threshold dose of glucose for stimulation of insulin secretion. The maximal concentrations of insulin achieved during intravenous infusion of glucose at 60 or 100 mg/min for 30 min are plotted as a percentage of the mean control concentration of insulin for each subject. The mean concentration of insulin in the three samples collected during the preinfusion control period is set equal to 100%. The shaded areas denote 2 sd above the mean for variation of samples during preinfusion control periods in each group. The fasting plasma glucose averaged 135 ± 31 (sd) mg/100 ml in the 15 diabetic subjects studied with a dose of 100 mg/min.

vated but stable glucose level. To evaluate this concept further, sustained hyperglycemia was induced in non-obese normal subjects.

Glucose insulin relationships during induced hyperglycemia. Seven studies were carried out in six normal subjects in which glucose was infused at a constant rate of 100 mg/min for 2 hr. The results of these studies are graphically summarized in Fig. 5 A. As can be seen in the diagram, during the infusion period glucose levels rose 15 mg/100 ml over the first 60 min from a fasting level of 85 to 100 mg/100 ml and stabilized thereafter for the 2nd hr of infusion. Similarly, insulin levels rose and plateaued, tending to remain stable throughout the remainder of the infusion period.*

A similar pattern of response was noted in seven other normal subjects in whom glucose was infused at 250 mg/min for 2 hr (Fig. 5 B). Again, during infu-

* An examination of individual patterns of insulin response during glucose infusions in these normal subjects suggests that the insulin concentration varies as a sine-wave function. Because of asynchrony between subjects, this characteristic was obscured in graphic presentation of mean values.

sion, the plasma glucose rose and stabilized at a higher level with a parallel response in insulin concentration. When the new equilibrium was further distorted after 2 hr by doubling the rate of glucose infusion, glucose and insulin again rose in a parallel fashion but returned to the range of the previous stable state when the infusion rate was returned to 250 mg/min. In both groups of infusion studies, it is evident that the period of changing insulin secretion occurred during the period of change in plasma glucose. When the plasma glucose levels achieved a stable level, no further rise in insulin was noted. That additional insulin was available is evident from the fact that superimposition of another glucose stimulus resulted in a secondary rise in insulin levels. These observations suggest that in the normal individual, as in the obese diabetic, the secretory activity of the beta cells is closely linked to changes in plasma glucose, but does not progressively increase in the face of a stable plasma glucose level, regardless of the relative height of the plasma glucose. This pattern of behavior is remarkably similar to that of the perfused pancreas in vitro (15, 16). At least over the short term, then, it may be stated that the beta cell is not regulated to restore the concentration of glucose to an arbitrary normal value. Thus, although insulin ap-

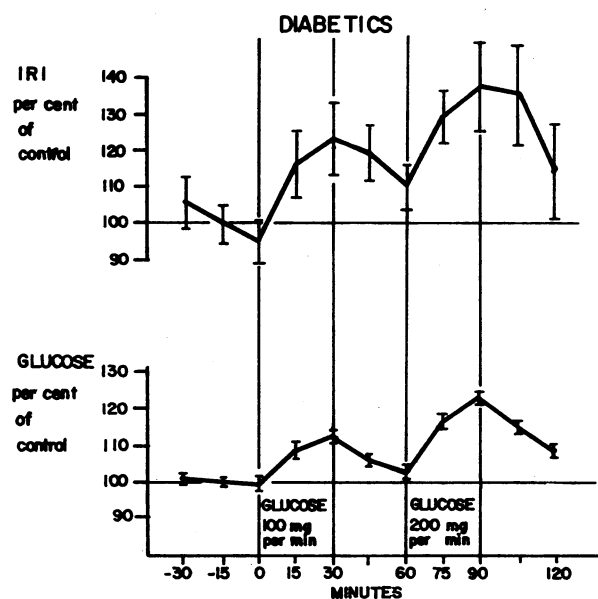


FIGURE 4 The insulin response to two successive doses of glucose in hyperglycemic diabetic subjects. Five subjects were infused with 100 and 200 mg of glucose per min for two successive 30 min periods. The mean preinfusion glucose concentration was 122 ± 24 (sd) mg/100 ml. The preinfusion concentrations of glucose and insulin have been set equal to 100 and the data expressed as per cent of these values. Brackets denote 2 se of the mean. The insulin responses were proportional to the size of the stimulus.

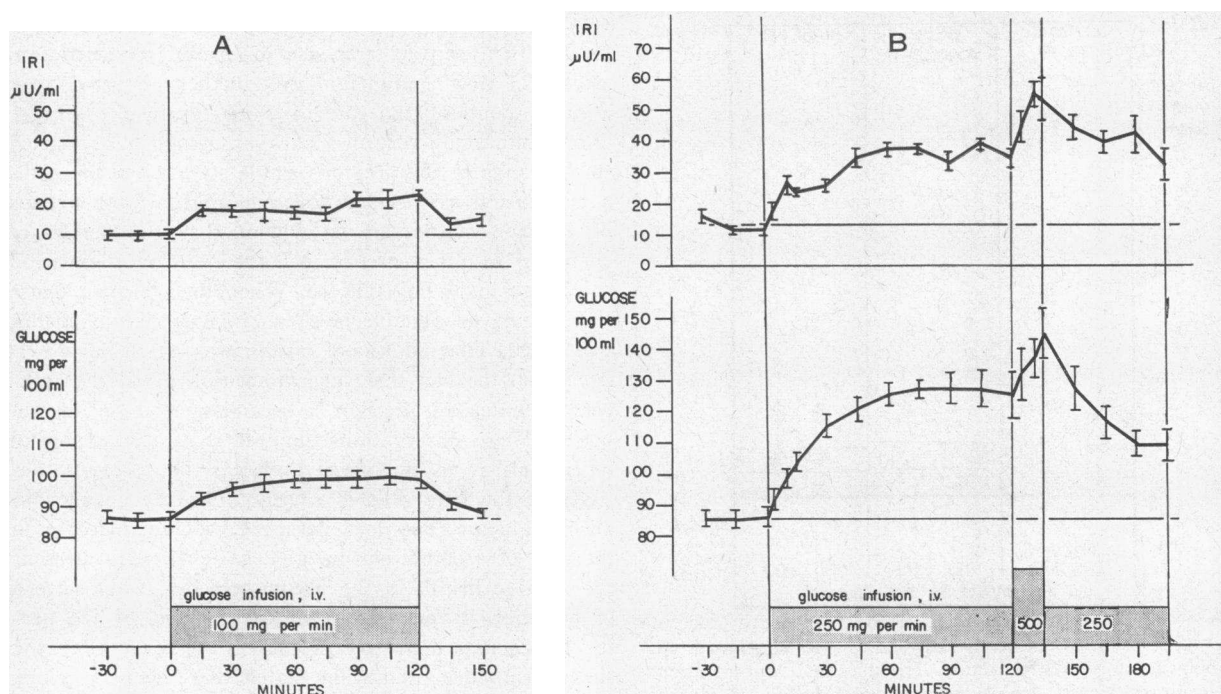


FIGURE 5(A) The changes in the concentration of plasma insulin and glucose during intravenous infusion of glucose for 2 hr at 100 mg/min in six normal subjects. The values are the mean of seven studies in six normal individuals. Brackets denote 2 se of the mean. (B) The behavior of plasma insulin and glucose during intravenous infusion of glucose at 250 mg/min in seven normal subjects. After 2 hr of infusion, the rate of infusion was doubled for 30 min and then returned to the original rate. The plotted values are the mean \pm se for seven experiments.

pears to be secreted in proportion to the prevailing concentration of glucose in the blood, the amount secreted is insufficient to overcome the hyperglycemia induced by an intravenous infusion of glucose.

When the infusion period was extended to 8 hr in four normal subjects (Fig. 6), the same relationships persisted until the infusion was stopped. In these studies, the concentration of insulin tended to return toward control levels after 3 hr infusion before the brief period of increased infusion, and again at the end of the 8 hr period. The concentration of FFA fell initially, but rose toward the fasting level during the last 3 hr of infusion. These studies indicate that the tolerance for sustained hyperglycemia noted during 2 hr infusions persists for at least 8 hr. The tendency for the insulin concentration to return toward basal levels reinforces the concept that the beta cells adapt to the higher glucose concentration. The prompt rise in insulin during a brief additional glucose challenge in mid-infusion demonstrates that the beta cells retain the ability to alter secretion in response to a changing glucose concentration.

DISCUSSION

The concentration of blood glucose after an overnight fast is ultimately the result of the same determinants in normals and diabetics. The completeness of assimilation of the last meal and the prevailing rate of hepatic glucose production are the two major positive contributors to the size of the glucose pool after an overnight fast. Both are counter-regulated by the secretion of insulin. On the other hand, if the blood glucose falls below a critical concentration, diminution of insulin secretion, the response of the sympathetic nervous system, and the response of the alpha cell of the pancreas provide a floor of support for the glucose concentration. In normal individuals, the fasting blood glucose is held within a very narrow range, and this observation has led to the view that the beta cells of the pancreas are part of a precise control system with a reference point in the range of the normal fasting glucose (17).

However, the present results indicate that the maintenance of an arbitrary absolute glucose concentration, i.e., the return to a given reference point, does not seem to be the immediate goal of the glucose-regulating system in either obese diabetics or normals. If such were

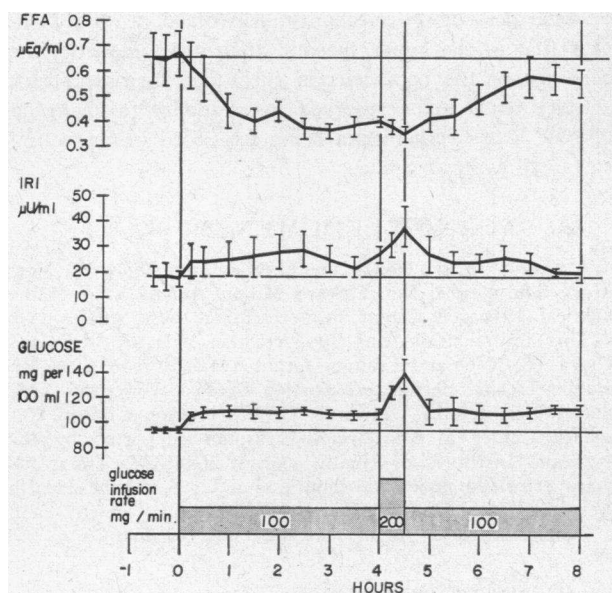


FIGURE 6 The response to 8 hr infusion of glucose in four normal subjects. Glucose was infused intravenously at 100 mg/min for 4 hr. The rate was doubled for 60 min and then returned to the original rate. The plotted values are the mean \pm SE for four experiments.

the case, one would expect the secretion of insulin to continuously rise until the raised blood glucose had begun to decline toward the normal fasting concentration. With continued infusion in normals (18, 19) or prolonged fasting in adult diabetics (20), the glucose concentration returns eventually to the normal range, suggesting that, given sufficient time, a reference point is regained.

In terms of control system theory, the response during the short-term infusions generally fits a model which exhibits proportional negative feedback control with its characteristic steady-state error (21). The eventual return of the glucose concentration to a normal range during long-term infusion in normals or with continued fasting in diabetics would be compatible with the presence of an error-correcting component with a long time constant.

It should be emphasized that the foregoing interpretation pertains to data collected during delivery of glucose intravenously. However, the importance of the route of delivery of glucose is apparent when the plasma concentration of glucose attained in normal subjects in these infusion studies is compared with the normal response during standard oral glucose tolerance testing. For example, the total dose of glucose delivered over 2 hr after infusion at 250 mg/min was only 30 g, yet the plasma glucose over the entire 2nd hr of the infusion averaged 127 mg/100 ml. In contrast, the peak

glucose concentration 1 hr after 100 g of glucose administered orally was 128 mg/100 ml in a large group of normal subjects (22). Obviously, the gut factor described by others is of great quantitative importance in glucose homeostasis (23-25, 6). In the context of our data, and the descriptive control theory developed above, we would speculate that perhaps the contribution of the gut factor to the beta cells as a control system may be to add the capability to correct steady-state error and promptly return the glucose concentration to a predetermined reference point. Thus, during intravenous infusion of glucose, the beta cells may operate as a simple negative feedback system in the absence of stimulation by the gut factor. In diabetics, initial failure of the complete system to correct the blood glucose after a meal might leave only the more limited control system operative in the morning after dissipation of the original postprandial events.

One of the basic observations in these studies, in confirmation of a previous report (5), is that during fasting hyperglycemia the basal insulin concentration relates to the degree of obesity and not to glucose concentration in the diabetic subjects. These observations can be interpreted in two general ways. If the insulin concentrations achieved in normals, infused with glucose to comparable blood glucose levels, are compared with the basal insulin concentrations in hyperglycemic diabetics, then it could be said that the diabetics exhibit inadequate insulin secretion. Since the ability to secrete insulin in response to various stimuli is impaired in diabetics (2-6, 8), the relatively lower basal levels with respect to glucose concentration might simply reflect impaired beta cell function or reduced beta cell mass. Alternatively, if the basal insulin secretion is controlled in part by factors other than glucose, then the concentrations of insulin in hyperglycemic diabetics might reflect an adaptation to the elevated glucose because of other regulatory priorities.

The first interpretation is based upon the behavior of the endocrine pancreas in vitro where the secretion of insulin per unit mass of islet tissue is proportional to the prevailing glucose concentration. Therefore, for any given glucose concentration, total insulin output in a system depends upon the number and (or) intrinsic activity of the beta cells present. Thus the relatively lower insulin secretion in the presence of fasting hyperglycemia in the diabetics might represent the maximal output of insulin for that particular concentration of glucose. Upon raising the concentration of glucose by infusion, an increased output of insulin per cell in proportion to the increased concentration of glucose would result in an insulin response as observed. The magnitude of the response would be reduced from normal in proportion to the magnitude of functional or numerical

defect in the diabetic beta cells. Because this interpretation relates our data to other studies, it is attractive, but such an interpretation is not entirely compatible with the basal glucose-insulin relationships observed in the diabetic group. For, if the basal insulin output in the diabetic group were largely determined by the prevailing glucose concentration as this formulation would predict, then one would expect a significant positive relationship between these two variables, whereas none was found (Fig. 1A). Although such a relationship may have been obscured by the operation of other variables, the severity of the diabetic defect and obesity, we tend to favor the alternative hypothesis that some form of negative adaptation to hyperglycemia by the beta cells has taken place during a constant state of hyperglycemia.

Viewing the control of insulin secretion as a system concerned primarily with the regulation of the concentration of glucose may be an oversimplification. It is possible that regulation is ultimately keyed to the mixture of fuels delivered to specific cells in the body. If this is the case, it is possible that the failure of the beta cells to attempt normalization of the blood sugar in the hyperglycemic diabetic or in the glucose-infused normal individual may reflect the operation of controls geared to other cellular fuels. For example, we have observed that over a very wide range of blood glucose concentration, the concentration of FFA in plasma of fasting adult diabetics remains within the normal, nondiabetic range (26). Accordingly, we have suggested that this dissociation between the regulation of lipolysis and the regulation of blood glucose in adult diabetics may reflect the operation of controls geared to provide an appropriate mixture of fuels to the cells in the fasting state. In the context of the present data, one might postulate that the beta cell response to sustained hyperglycemia in diabetics has been partially inhibited to permit the relatively normal delivery of FFA in the postprandial period. The return of FFA toward the fasting level in the normal subjects infused for 8 hr with glucose is compatible with operation of a similar system in normals. The mechanisms for modulating insulin secretion in response to the mixture of circulating fuels might be through the operation of central nervous system receptors⁴ (27, 28) and the sympathetic nervous system (29, 30) or at the level of the beta cell itself through direct effects of a number of circulating fuels and hormones (31). Whether such postulated events are playing a role in producing the pattern of insulin secretion during sustained hyperglycemia must remain speculative until additional work is done.

⁴ Conway, M. J., C. J. Goodner, J. H. Werrbach, and C. C. Gale. 1968. Studies of substrate regulation in fasting. II. The effect of infusion of glucose into the carotid artery upon fasting lipolysis in the baboon. *J. Clin. Invest.* 48: 1349.

Regardless of the mechanisms involved, it would appear that in the hyperglycemic adult-onset diabetic, the behavior of the beta cells is such that their secretory activity tends to be reserved for response to changing glucose levels rather than being expended in correcting sustained hyperglycemia.

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