Plasma Insulin in Reactive Hypoglycemia

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SUMMARY

Among 663 standard four-hour oral glucose tolerance tests (OGTT) performed in a Department of Internal Medicine, forty-seven curves demonstrated reactive hypoglycemia of 45 mg. per 100 ml. or less at one or more occasions. Subsequent analysis of the records of the corresponding patients allows their partition into the following groups: IA. Obesity (11), IB. Obesity with chemical diabetes (9), II. Postgastrectomy syndrome (3), III. Chemical diabetes without obesity (1), IV. Renal glycosuria (7), V. Isolated reactive hypoglycemia (16).

In order to determine the role of plasma insulin in the pathogenesis of the syndrome, the insulin response of each group of subjects presenting reactive hypoglycemia was compared to that of a control group of similar age, sex and weight with similar pathological findings but without reactive hypoglycemia. The results indicate that plasma insulin values can not account for the reactive hypoglycemia in the groups IA, IB, III and IV, and thus other factors may be responsible for the occurrence of hypoglycemia in most cases of this syndrome.

In contrast, an exaggerated insulin response exists in group II, and in seven out of the sixteen cases of isolated reactive hypoglycemia.

No correlation was found between the presence of clinical symptoms evoking reactive hypoglycemia during the usual life and the severity of the hypoglycemia recorded during the OGTT. DIABETES *20*:435-42, June, 1971.

Hypoglycemia following a meal is a relatively frequent condition first described by Harris.[1] Its pathogenesis remains far from being elucidated.[2,3] It is usually associated with abnormalities such as obesity, chemical diabetes, gastrectomy or accelerated gastric emptying.[4-7] The present study has been undertaken in order to investigate the role of insulin in the pathogenesis of the syndrome. In contrast to other similar studies, the major criterion used was the existence of a true biological hypoglycemia with or without clinical signs of neuroglucopenia. Furthermore, the plasma insulin response to an oral glucose tolerance test was compared between patients with reactive hypoglycemia and patients with similar abnormalities *but* without reactive hypoglycemia. This methodology was adopted to determine if a *specific* factor might be responsible for the occurrence of the hypoglycemia.

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METHODS

Of 663 subjects undergoing a standard four-hour oral glucose tolerance test (OGTT) in a Department of Internal Medicine between January 1, 1966 and September 1, 1969, forty-seven patients of both sexes were selected on the basis of a reactive hypoglycemia of 45 mg./100 ml. or less at one or more occasions. Analyses of the records of these patients led to their separation into five groups as indicated in table 1. Additional characteristics of patients from group V (isolated reactive hypoglycemia) are given in table 2.

In order to identify a possible specific factor in the pathogenesis of the reactive hypoglycemia, control groups were constituted so that they present the same mean initial blood glucose curve as every group of patients presenting reactive hypoglycemia. Moreover, the groups to be used for comparisons were constituted of individuals with similar characteristics: age, sex, weight and eventually, presence of renal glycosuria. The main features of each group are summarized in table 3.

Prior to testing the subjects were maintained on a diet providing a minimum of 250 gm. of carbohydrate per day for at least three days. All subjects were fasted overnight before performance of the test. In the standard

TABLE 1

Reactive hypoglycemia associated with

		Number of cases
I. Obesity and	A. Normal glucose tolerance	11
	B. Decreased glucose tolerance	9
II. Postgastrectomy syndrome		3
III. Chemical diabetes without obesity		1
IV. Renal glycosuria		7
V. Isolated		16
Total		47

OGTT, 100 gm. of glucose were administered in 400 ml. of water flavored with lemon juice.

Blood samples were taken at rest before the ingestion of the glucose and every thirty minutes thereafter during a four-hour period. Blood glucose was determined according to the method of Hoffman[8] adapted to the Technicon AutoAnalyzer. Comparison with an enzymatic determination for glucose[9] performed both for normal and low blood sugar values, indicates that the AutoAnalyzer method gives results similar to those of the enzymatic method for normal blood glucose values, and slightly higher figures for low blood sugar levels. The limit of 45 mg./100 ml. with the AutoAnalyzer corresponds to 41 mg./100 ml. with the enzymatic method using hexokinase. Subjects were classified as having a normal or a chemical diabetes-type curve according to the criteria of Wilkerson et al.[10] Plasma insulin levels were determined by a modification[11] of the method of Hales and Randle[12] with use of human insulin as standard.

RESULTS

Obesity was present (weight excess > 25 per cent of ideal body weight*) in twenty out of forty-seven subjects with reactive hypoglycemia during the OGTT. Eleven of the twenty subjects had a normal rise in blood sugar, and nine had decreased glucose tolerance. As shown in figure 1, the plasma insulin response was similarly excessive (normal OGTT) or excessive and delayed (decreased glucose tolerance) in both groups, as was found in the control groups. No statistically significant difference was found between insulin levels of the hypoglycemic groups and those of their respective control groups.

*Tables of the Metropolitan Life Insurance Co., 1959.

TABLE 2

Group V: Isolated reactive hypoglycemia

Subject	Age	Sex	Weight excess (per cent over ideal weight)	Insulin response	Symptoms
1.	54	M	0	Normal	+
2.	29	M	1	Normal	+
3.	24	F	9	Normal	+
4.	25	M	—9	Normal	+
5.	49	F	—3	Normal	+
6.	24	M	0	Normal	0
7.	52	M	19	Normal	+
8.	49	F	0	Normal	+
9.	34	F	17	Normal	+
10.	48	F	8	Excessive	+
11.	28	M	14	Excessive	+
12.	56	M	17	Excessive	0
13.	55	F	0	Excessive	+
14.	55	M	9	Excessive	+
15.	34	F	18	Excessive	+
16.	20	F	10	Excessive	+

Only three of the forty-seven cases of reactive hypoglycemia had undergone subtotal gastrectomy. In all three subjects, the peak levels of plasma insulin were excessive (above 95 per cent confidence limit of the mean of the normal peak) and occurred at the same time as the peak of the mean level for normals (thirty minutes).

A single patient with chemical diabetes and without

TABLE 3

Patients studied

Group	Reactive hypoglycemia: Number of cases (males, females)	Age m ± SEM (range)	Weight excess (per cent ideal weight) (range)	No reactive hypoglycemia: Number of cases (males, females)	Age m ± SEM (range)	Weight excess (per cent ideal weight) (range)
I. A.	11 (1M, 10F)	29 ± 4 (13; 52)	48 ± 5 (+27; +86)	10 (4M, 6F)	29 ± 5 (12; 63)	67 ± 13 (+27; +157)
I. B.	9 (3M, 6F)	43 ± 6 (19; 66)	57 ± 10 (+28; +120)	11 (3M, 8F)	44 ± 4 (24; 61)	54 ± 6 (+25; +87)
II.	M, M, F	30, 42, 51	—13, —15, —1	—	—	—
III.	F	55	—17	13 (6M, 7F)	46 ± 4 (20; 67)	—1 ± 3 (—26; +15)
IV.	7 (5M, 2F)	34 ± 4 (17; 48)	6 ± 2 (—2; +16)	6 (5M, 1F)	27 ± 4 (13; 39)	6 ± 3 (0; +13)
V.	16 (8M, 8F)	40 ± 4 (20; 56)	8 ± 2 (—9; +19)	23 (11M, 12F)	31 ± 2 (21; 48)	1 ± 2 (—14; +15)

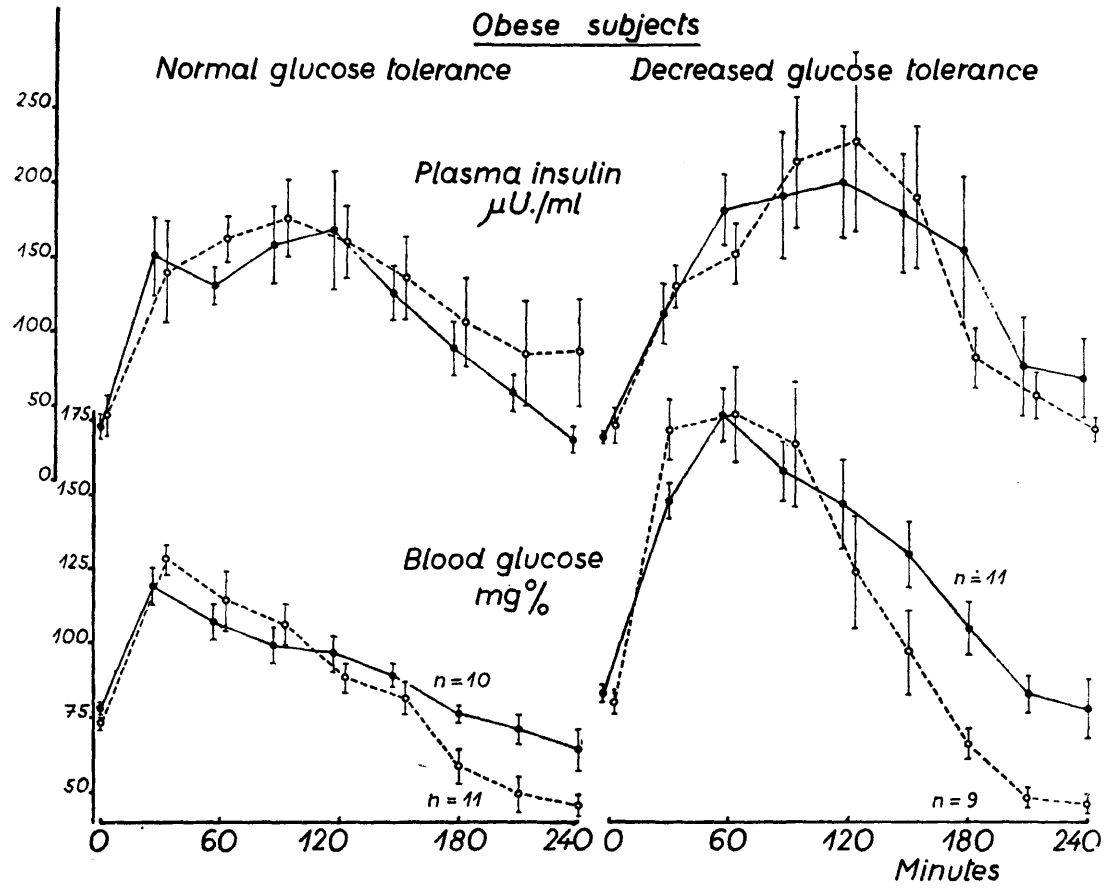

FIG. 1. Blood glucose and plasma IRI values (mean ± SEM) during OGTT performed in obese subjects with normal or decreased glucose tolerance and with (O————O) or without (●————●) reactive hypoglycemia.

obesity exhibited reactive hypoglycemia (43 mg./100 ml.) at the fourth hour. When compared to a group of thirteen subjects with chemical diabetes and normal weight, the plasma insulin response (apparently slightly increased) lay within the 95 per cent confidence limits of the control group (figure 2), however.

In seven patients, reactive hypoglycemia was associated with renal glycosuria. We classify patients as having renal glycosuria who are free from renal disease and have fasting or postprandial glucosuria in the absence of any abnormality of their glucose tolerance. All the patients of this group were of normal weight. They were compared to a group of six subjects of approximately the same age and weight with renal glycosuria but no reactive hypoglycemia (figure 3). The glucose tolerance values were approximately the same in both groups. Slightly higher but not statistically different values were obtained during the initial phase of the test in the group of patients lacking reactive hypoglycemia. In the latter group, the plasma insulin response was also slightly higher, but not statistically different, than in the group of patients presenting reactive hypoglycemia.

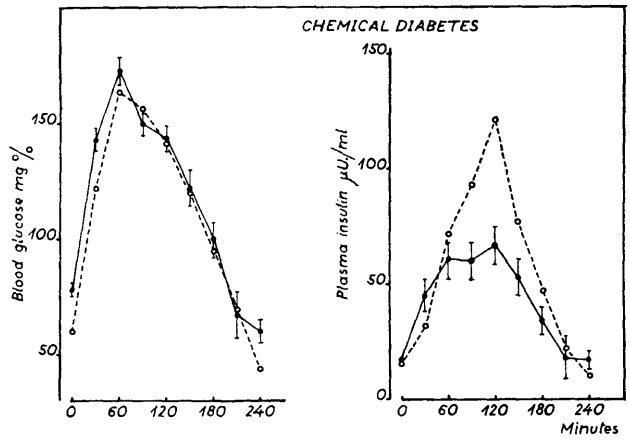

FIG. 2. Blood glucose and plasma IRI values (mean ± SEM) during OGTT performed in thirteen normal weight patients presenting chemical diabetes (●————●) and in the single individual associating chemical diabetes and reactive hypoglycemia (O————O).

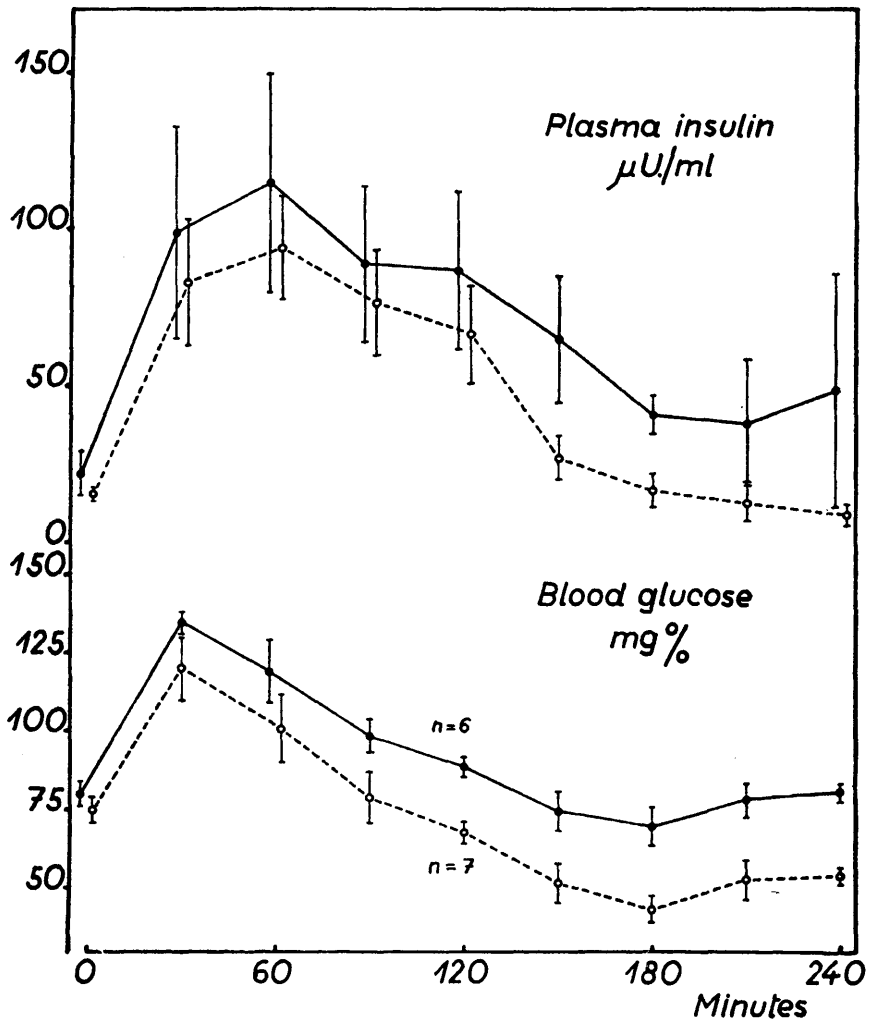

FIG. 3.

Blood glucose and plasma IRI values (mean ± SEM) during OGTT performed in patients with renal glycosuria with (O————O) or without (●————●) reactive hypoglycemia.

Finally, in sixteen patients, reactive hypoglycemia was apparently isolated, i.e. these patients had a normal weight, a normal glucose tolerance, and no glycosuria. The insulin response during OGTT in these patients was compared (figure 4) to the response in a group of twenty-three control subjects of comparable weight* and age and in which the sex ratio was comparable (see table 2). Despite the large scattering of plasma insulin response in the hypoglycemic group, the plasma insulin values were significantly higher at the sixtieth and ninetieth minute when compared to the ones of the control group. In fact, this group of isolated reactive hypoglycemia was not homogenous according to insulin responses, as nine of the sixteen patients had an insulin response comparable to the normal subjects, whereas seven presented an excessive insulin response which exceeded the 99 per cent confidence limits of the controls at one or more plasma insulin values during the test. On this basis, the data from these patients were calculated separately and compared to the control group (figure 5).

In order to compare the relationship of the plasma IRI and blood glucose between these groups of patients, the correlation coefficients and the linear regression of mean plasma IRI (y) on mean blood glucose (x) were calculated for each group as proposed by Soeldner et al.[13] In all groups, blood glucose and plasma IRI were significantly correlated ($p < 0.05$ or < 0.01) (figure 6). Comparison of the slopes of the regression equations between the different groups lacking reactive hypoglycemia revealed a less steep slope in chemical diabetes (III*) and, on the contrary, a steeper slope in the

*Statistical analysis indicates that the mean weight excess (per cent of ideal weight) of the patients presenting reactive hypoglycemia is slightly, but significantly, greater than the one of the control group, as indicated in table 3.

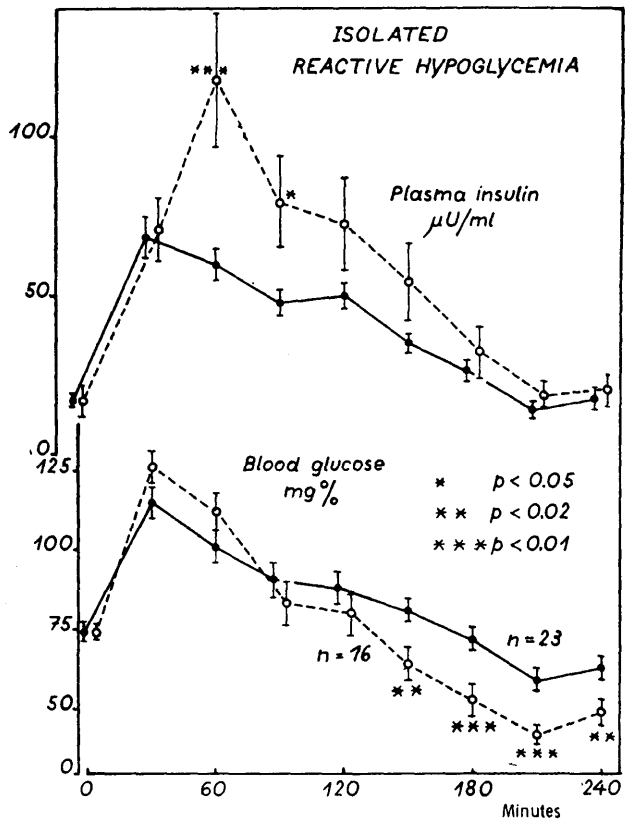

FIG. 4. Blood glucose and plasma IRI values (mean ± SEM) during OGTT performed in patients with isolated reactive hypoglycemia (O———O) and normal control subjects (●———●).

group of nondiabetic, obese subjects (IA•). Furthermore, the existence of decreased glucose tolerance in the obese subjects (IB•) was associated with a reduction of the slope which lay between those of obese, nondiabetic (IA•) and control subjects (V•). With this method of calculation it has not been possible to demonstrate a statistically significant difference between the groups with reactive hypoglycemia and the corresponding control group (IA° versus IA•; IB° versus IB•; III° versus III•; IV° versus IV•). Out of the three gastrectomized patients, a single individual (II° no. 3) exhibited a significantly steeper slope when compared to the controls.

For group V° (isolated reactive hypoglycemia), the slope of linear regression equation does not differ from the one of the control group (V•). However, the elevation of the regression line for the group of isolated hypoglycemia (V°) is statistically different from the one of the controls ($p < 0.05$).

DISCUSSION

Among several hundred OGTT performed for numerous reasons in a Department of Internal Medicine, a series of tests were selected on the basis of one or more frankly hypoglycemic values in the late phase of the glucose tolerance curve. Similar to the criterion of Sussman et al.,[2] the value of 45 mg./100 ml. for whole venous blood was chosen as the upper limit of hypoglycemia. A less severe criterion has been used by some other investigators.[4-6,14]

The relationship between the symptoms of neuroglycopenia and the presence of biochemical hypoglycemia during the performance of the OGTT is still a matter of controversy.[15] Evaluation of this relationship in the present study reveals that thirty out of forty-seven patients who had biochemical reactive hypoglycemia had claimed signs of neuroglycopenia occurring two to four hours after a meal in the usual life. Such signs and symptoms were weakness, faintness, nervousness, anxiety, irritability, palpitations, inward trembling, hunger, headache, vertigo and syncope. These signs of neuroglycopenia were present in all three cases of gastrectomy, in fourteen out of sixteen patients with the isolated syndrome, but only in about half of the patients in the other groups.

It is common to find reactive hypoglycemia with neuroglycopenic symptoms in patients with a partial gastrectomy.[4,5,15-17] The number of patients of this group in the present study is small due to the fact that the syndrome is so common and well known that oral glucose tolerance tests are not always conducted to confirm the diagnosis. On the contrary, obesity and renal glycosuria have been more systematically studied by the OGTT in our Institute for the past three years. In these two groups, a number of cases of reactive hypoglycemia have been detected, and it appears that about half the patients with biochemical hypoglycemia do in fact have symptoms of neuroglycopenia. In the last group (those with isolated reactive hypoglycemia), it appears that fourteen of the sixteen patients had clinical signs of neuroglycopenia. For all the groups, no obvious correlation appeared between the presence or the absence of clinical signs and the degree or severity of hypoglycemia. This implicates the concept of an individual sensitivity to hypoglycemia which could correspond to individual variations in the cerebral threshold for utilization of glucose,[18] or to individual variations in the counterregulatory mechanisms evoked by hypoglycemia.

The pathogenesis of reactive hypoglycemia is far from being elucidated. For a number of years a defect in the secretion of insulin has been postulated and often the term "functional hyperinsulinism" (proposed by

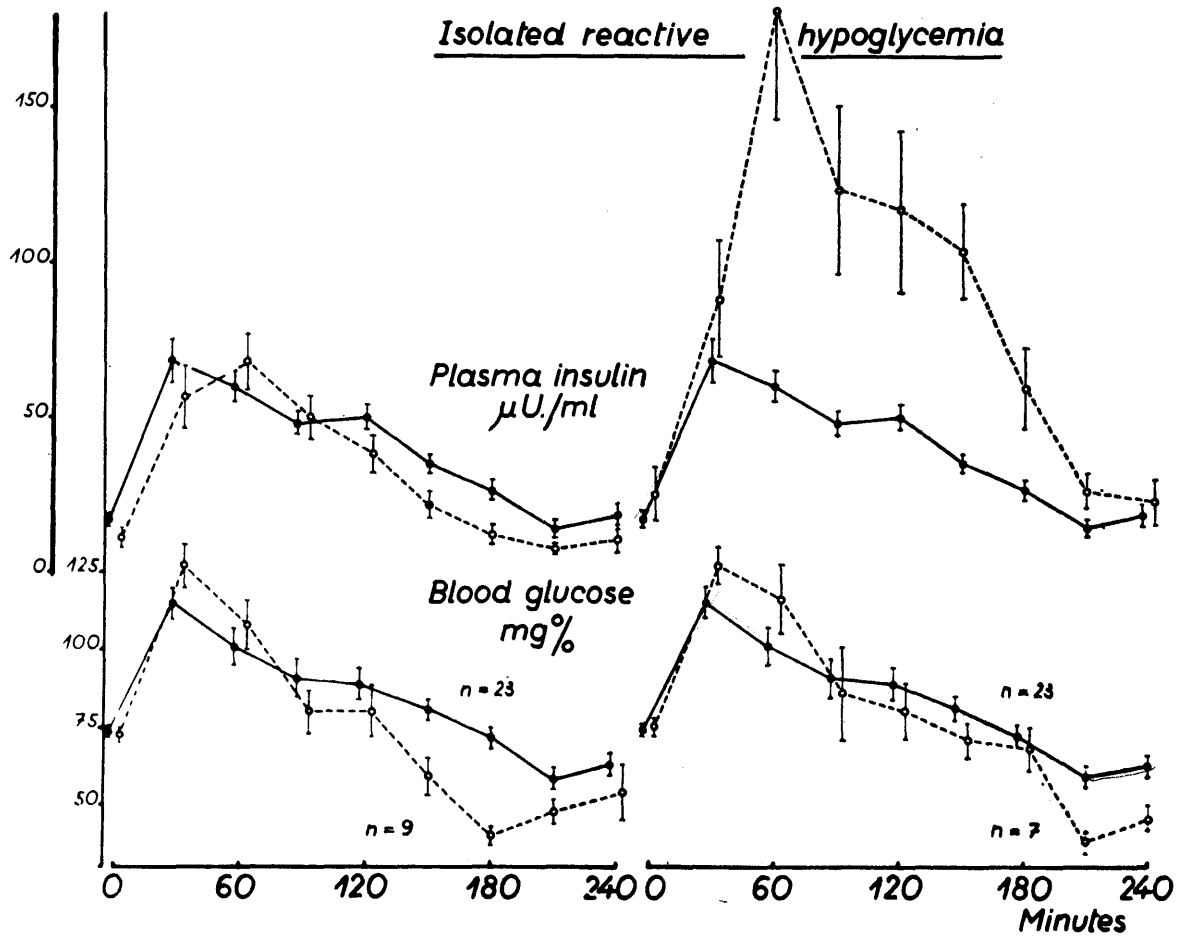

FIG. 5. Blood glucose and plasma IRI values (mean ± SEM) during OGTT performed in: twenty-three healthy controls (●————●); nine cases of isolated reactive hypoglycemia and normal IRI response (left part O————O); seven cases of isolated hypoglycemia and excessive IRI response (right part O————O).

Conn[19]) has been utilized for describing the syndrome. With the extensive utilization of methods for the assay of plasma insulin, studies have been undertaken to confirm this hypothesis. As indicated earlier, variations in plasma insulin do not explain all the cases of reactive hypoglycemia (blood glucose < 45 mg./100 ml.). In the present study in which patients having reactive hypoglycemia were compared with patients of similar age and sex having the same morbid associations, but no reactive hypoglycemia, the following points have to be stressed. Reactive hypoglycemia is frequently associated with obesity (42 per cent of patients with reactive hypoglycemia were obese in this series) whether or not the initial part of the glucose tolerance curve is normal or of the diabetic type. It was therefore tempting to correlate the reactive hypoglycemia with the hyperinsulinism usually encountered in these patients.[4,20,21] This association was particularly suggestive when the release of insulin is sluggish and the insulin peak delayed with respect to the peak value for blood glucose, as recently discussed by Freinkel.[17] This consideration cannot account for a pathological reactive hypoglycemia, since neither in the initial phase nor at the end of the test do plasma insulin values of subjects presenting exaggerated reactive hypoglycemia exceed those of control subjects with comparable obesity. This was true for either normal or decreased glucose tolerance. This suggests that in obesity, associated or not with early diabetes mellitus, abnormalities in circulating plasma insulin do not explain excessive reactive hypoglycemia, and leads to the speculation of the existence of an inadequate counterregulation in these subjects or of a possibility of a relatively exaggerated sensitivity to insulin.

As demonstrated by others[4,5] and confirmed here, the hypoglycemia which occurs after a glucose load in gas-

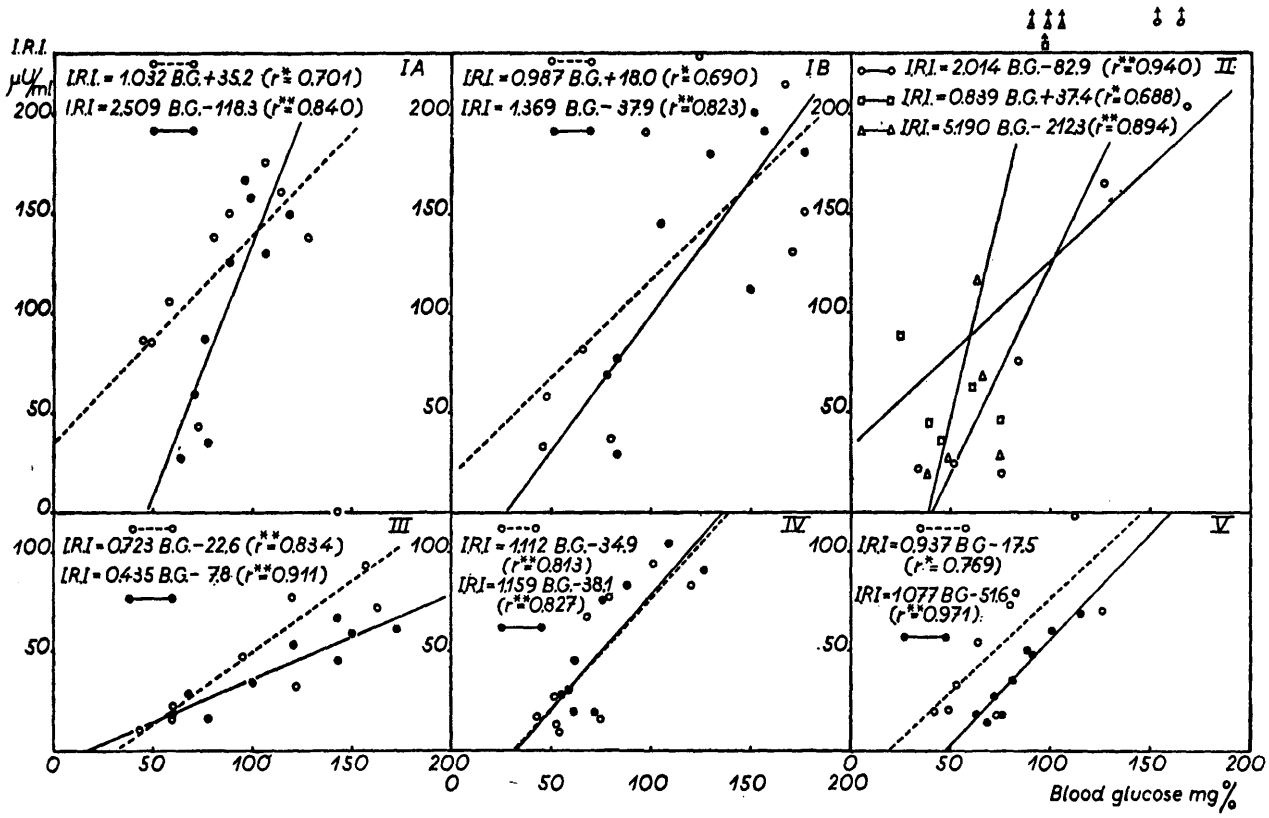

FIG. 6. Regression line of serum IRI (y) on blood glucose (x) during OGTT in various groups studied. (*Solid circles* = *without* reactive hypoglycemia; open circles = with reactive hypoglycemia). Circles indicate mean serum IRI-mean blood glucose at each of the nine time intervals (* $p < 0.05$; ** $p < 0.01$). In square II (upper right-hand corner), a regression line has been calculated for each gastrectomized patient (see text).

trectomized patients is apparently related to an excessive insulin response.

Reactive hypoglycemia is frequently associated with renal glycosuria—seven cases out of thirteen patients with renal glycosuria have recently been observed.[22] Although an excessive insulin response during the OGTT has been described in certain cases of renal glycosuria,[23-25] the hyperinsulinism is apparently not involved in the pathogenesis of reactive hypoglycemia. In fact, in the series of patients presented here, the mean plasma insulin response was slightly smaller but not statistically different from nonhypoglycemic glycosuric controls. The excessive loss of glucose in urine could be a mechanism to explain reactive hypoglycemia in renal glycosuria if one postulates that the insulin response is related to the amount of the glucose load and that an important amount of this load is lost in the urine. Further investigations are needed to establish a correlation between the presence or the absence of reactive hypoglycemia and the amount of glucose eliminated in the urine.

Individual analysis of the sixteen cases with idiopathic reactive hypoglycemia reveals that a frankly excessive insulin response was present in seven cases only. This finding is similar to the observations of Sussman et al.[2] who demonstrated elevated plasma insulin values associated with normal initial blood glucose levels in six out of nine patients with reactive hypoglycemia. Comparison has been made between nonhypoglycemic control insulin hyperresponders (in fact the eight subjects with the highest insulin response out of the group of the twenty-three controls) and excessive insulin hyperresponders with essential reactive hypoglycemia. The statistically significant hyperinsulinism is still present when this calculation is performed. Hyperinsulinism as a causal factor for the occurrence of idiopathic reactive hypoglycemia in these patients may be reasonably suspected. In five other patients of the series of Sussman et al.,[2] the reactive hypoglycemia has been attributed to the exaggerated or delayed insulin response observed in patients with mild diabetes mellitus. The values of plasma insulin reached in these patients suggest the existence of a certain degree of obesity but unfortu-

nately these authors did not indicate the weight of their patients.

Finally, we have identified a group of nine patients with idiopathic reactive hypoglycemia and absolutely normal plasma insulin response. Other factors must be evoked to explain the reactive hypoglycemia in these patients and are, actually, under study: increased insulin sensitivity and/or abnormal counterregulatory mechanisms.

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