Levels of Plasma Insulin During Cortisone Glucose Tolerance Tests in "Nondiabetic" Relatives of Diabetic Patients

Implications of Diminished Insulin Secretory Reserve in Subclinical Diabetes

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SUMMARY

Plasma levels of insulin were determined during standard oral glucose tolerance tests and during cortisone glucose tolerance tests performed upon "nondiabetic" subjects (normal standard GTT) who were first degree relatives of diabetic patients. The standard test was also performed upon mildly diabetic patients and healthy control subjects. The results of the standard glucose tolerance test (levels of plasma insulin and blood glucose) did not differentiate the relatives with positive cortisone glucose tolerance tests (subclinical diabetes) from those with negative cortisone glucose tolerance tests although in both groups levels of plasma insulin were lower than in healthy subjects. However, the results of the *cortisone glucose tolerance test* did distinguish the group with subclinical diabetes from the relatives with negative tests since the secretion of insulin was delayed and insufficient in the subjects with positive tests. During the *standard test* patients with mild "maturity-onset" diabetes showed delayed and insufficient secretion of insulin as compared to the healthy subjects.

It is concluded that during the cortisone glucose tolerance test, "nondiabetic" relatives of diabetic patients who have positive tests (subclinical diabetes) exhibit a defect in the secretion of insulin which distinguishes them from subjects with negative tests. This defect is similar in pattern to that observed in mildly diabetic patients during the standard test. This deficiency in the secretion of insulin represents an important part of the mechanism which induces a positive cortisone glucose tolerance test.

This demonstration that, in some relatives of diabetics, a grossly normal standard glucose tolerance can exist at a time when decreased reserve insulin secretory capacity can be measured, justifies a careful evaluation of whether some form of therapy is indicated at this stage of the disease (subclinical diabetes) and, if so, what form it should be. The meaning of the statistically significant subnormal response of plasma insulin to a standard glucose load in relatives with negative cortisone glucose tests is not yet apparent. Since in them the reserve insulin secretory capacity, as measured by the CGTT, remains intact, it is premature, pending additional data, to raise the question of possible treatment of this group. DIABETES *19*:1-10, 1970.

In previous studies we have reported that a subclinical defect in carbohydrate metabolism can be uncovered in some apparently healthy relatives of diabetic patients by the use of a standardized dose of cortisone.[3-6] The results obtained with the cortisone glucose tolerance test permitted the separation of nondiabetic first degree relatives (children, siblings or parents) of diabetic patients into two groups. Those with a "positive response" to the test responded as did the majority of mildly diabetic patients, while those exhibiting a "negative response" reacted as did the majority of control subjects who had been selected because they had no family history of diabetes. Long-term follow-up studies of both groups have shown that 26 per cent of individuals with positive responses have progressed in subsequent years to clinical diabetes, while, over the same period of time, this course occurred in only 3.6 per cent of subjects with negative responses.[4-6]

We have suggested that a positive response might be the result of a diminished *reserve* capacity of the in-

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TABLE 1

Characterization of groups tested

Group tested	Number of individuals	Per cent desirable body weight*†	Age in years*	Number of individuals tested with Glucose tolerance test males	females	Cortisone GTT males	females
Patients with diabetes (I)	29	97.2 (87.0-109.5)	27.3 (12.5-45)	20	9		
"Nondiabetic" relatives of diabetic patients with positive cortisone GTT (II)	26	95.8 (76.0-115.4)	29.7 (15-46)	1	25	1	25
"Nondiabetic" relatives of diabetic patients with negative cortisone GTT (III)	41	100.3 (84.2-115.7)	26.0 (12-46)	20	20	20	21
Healthy subjects (IV)	31	104.3 (89.5-112.3)	22.3 (19-35)	31	0		

*Mean and range.
†Metropolitan Life Insurance tables.

sulinogenic mechanism when suddenly challenged by an excess of glucocorticoid activity.[3-5] The present study was designed to determine (a) whether, during glucose and cortisone glucose tolerance tests, a difference exists in the insulin secretory response between "nondiabetic" relatives with and without positive cortisone glucose tolerance tests, and (b) to compare the patterns of insulin secretion of both of these groups with those obtained during standard glucose tolerance tests in healthy control subjects and in patients with latent or chemical diabetes.

The results indicate that *during the standard test* the levels of blood glucose and plasma insulin in the "nondiabetic"* relatives with positive cortisone glucose tolerance tests (subclinical diabetes)† were not significantly different from those of the relatives with negative tests.

*"Nondiabetic" = normal standard GTT.
†Normal standard GTT but positive cortisone GTT.

TABLE 2 *(Continued on page 3)*

Standard glucose tolerance tests in "nondiabetic" relatives of diabetic patients with positive (Group II) and negative (Group III) cortisone glucose tolerance tests and in healthy subjects (Group IV)

Group tested		Plasma insulin at time in minutes (μU./ml.) 0	30	60	90	120	150	180	Blood glucose at time in minutes (mg./100 ml.) 0	30	60
Nondiabetic relatives of diabetic patients with positive cortisone GTT (II)	Mean (n=26)	10.7	66.2	83.0	69.7	62.6	59.0	51.3	78.9	121.2	112.2
	± S.E.M.	0.8	6.9	11.3	8.7	6.7	6.1	7.0	1.5	5.2	5.3
	p*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
	p†	NS	<.005	<.02	<.02	<.05	<.025	NS	NS	<.1	<.1
	p‡	NS	<.001	<.01	NS	NS	NS	NS	<.005	<.001	<.001
Nondiabetic relatives of diabetic patients with negative cortisone GTT (III)	Mean (n=40)	10.5	76.2	86.8	62.8	52.3	46.8	44.1	80.5	122.1	105.7
	± S.E.M.	0.7	6.4	8.6	6.6	4.2	5.2	4.7	1.0	3.3	5.0
	p†	NS	<.02	<.01	<.001	<.001	<.001	<.05	NS	<.05	<.02
	p‡	NS	<.001	<.005	NS	NS	NS	NS	<.001	<.001	<.001
Healthy subjects (IV)	Mean (n=31)	10.9	105.0	130.0	116.4	93.1	87.8	61.9	81.5	132.3	123.9
	± S.E.M.	0.9	9.6	13.9	15.2	11.8	8.5	7.2	1.1	3.5	4.5

*Comparison with Group III.
†Comparison with Group IV.
‡Comparison with Group I.

In contrast, however, during the cortisone glucose tolerance test, relatives with positive tests had increases in plasma insulin which were delayed and insufficient as compared to those of relatives with negative tests. This pattern of response is similar to that of the mildly diabetic patients during the standard test. Thus, a deficiency in the secretion of insulin is demonstrated during the cortisone glucose tolerance tests in subjects who have what we[5] have termed subclinical diabetes.* It seems likely that this defect in the release of insulin is an important factor in the mechanism by which a positive cortisone glucose tolerance test is produced. That one can demonstrate a sharply diminished insulinogenic reserve capacity in some subjects who still maintain the ability to exhibit normal blood sugar values during the standard glucose tolerance test indicates the need to reappraise our definitions, concepts, and therapeutic objectives as we become able to detect "diabetes" at an earlier time than heretofore.

MATERIAL AND METHODS

Standard oral glucose tolerance tests (GTT) were performed on twenty-nine subjects with the mild maturity-onset type of diabetes (Group I); on twenty-six "nondiabetic" subjects with family histories† of diabetes and positive cortisone glucose tolerance tests (Group II); on forty-one "nondiabetic" subjects with family histories of diabetes and a negative cortisone glucose tolerance test (Group III); and on thirty-one healthy subjects without a family history of diabetes or large babies (Group IV—table 1). Eight of the twenty-five women of Group II and two of the twenty-one women of Group III were taking oral contraceptive agents. Cortisone glucose tolerance tests (CGTT) were performed on the subjects in Groups II and III. The results of standard glucose tolerance tests and cortisone glucose tolerance tests were assessed according to our previously published criteria.[3-6] In most of the subjects in whom the CGTT was positive, it was strongly positive (mean two-hour blood glucose 211.1 mg./100 ml., range 140 to 309 mg./100 ml.). Patients and subjects were of normal body weight. Four of the patients with diabetes had definite fasting hyperglycemia (146, 147, 171 and 178 mg./100 ml.). Two others had fasting blood sugar levels of 105 and 103 mg./100 ml. Nineteen of the patients with diabetes had been treated with diet alone, and ten patients with diet and tolbutamide* for periods of twenty-three to 116 months prior to testing. The medication had been discontinued for two or three days before study except in the case of four patients whose last dose was taken the night before the glucose tolerance test. One patient had been treated with insulin in the past. The "nondiabetic" relatives (Groups II and III) and the diabetic patients (Group I) ingested diets containing 250 to 300 gm. of carbohydrate per

*Normal standard GTT but positive cortisone GTT.
†Diabetes in at least one parent, sibling, or child.

*1-Butyl-3 (p-tolylsulfonyl) urea.

TABLE 2 *(Continued from page 2)*

Standard glucose tolerance tests in "nondiabetic" relatives of diabetic patients with positive (Group II) and negative (Group III) cortisone glucose tolerance tests and in healthy subjects (Group IV)

Group tested		Blood glucose at time in minutes (mg./100 ml.)				Sum of increments plasma insulin (μU./ml.)		Sum of increments blood glucose (mg./100 ml.)		plasma insulin / blood glucose	
		90	120	150	180	first hour	three hours	first hour	three hours	first hour	three hours
Nondiabetic relatives	Mean (n=26)	96.7	90.3	88.3	84.2	125.6	333.3	77.4	139.3	3.42	4.87
of diabetic patients	± S.E.M.	5.1	3.4	3.1	3.1	14.8	40.7	8.9	18.5	1.13	1.32
with positive	p*	NS	NS	NS	NS	NS	NS	NS	<.1	NS	NS
cortisone GTT (II)	p†	NS	NS	NS	NS	<.005	<.05	NS	NS	NS	NS
	p‡	<.001	<.001	<.001	<.001	<.001	<.1	<.001	<.001	<.01	<.005
Nondiabetic relatives	Mean (n=40)	89.9	84.2	83.0	83.3	139.2	310.1	71.7	107.3	2.90	4.70
of diabetic patients	± S.E.M.	3.3	2.6	2.7	2.7	11.5	22.8	6.5	10.8	0.43	0.74
with negative	p†	<.005	<.05	NS	NS	<.005	<.005	<.02	<.005	NS	NS
cortisone GTT (III)	p‡	<.001	<.001	<.001	<.001	<.001	<.1	<.001	<.001	<.001	<.001
Healthy subjects (IV)	Mean (n=31)	104.7	92.5	90.0	85.5	213.7	537.5	93.6	155.7	2.89	4.81
	± S.E.M.	3.0	2.9	4.5	3.6	20.3	57.6	5.7	12.8	0.58	1.26

*Comparison with Group III.
†Comparison with Group IV.
‡Comparison with Group I.

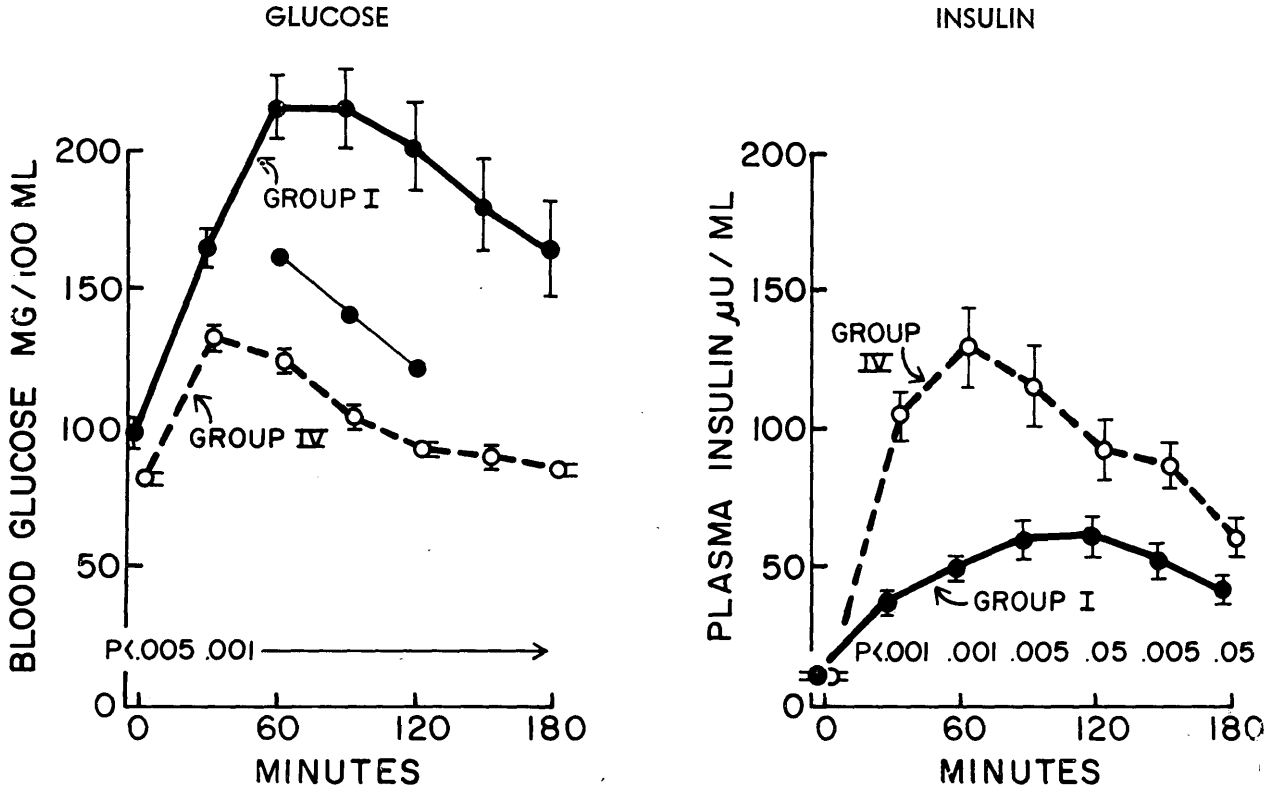

FIG. 1. Levels of blood glucose and plasma insulin (mean ± S.E.M.) during standard GTT in twenty-nine patients with mild diabetes (Group I) and in thirty-one healthy subjects (Group IV).

day for at least three days prior to testing. The healthy subjects (Group IV) ingested diets containing 300 gm. of carbohydrate per day for three days prior to testing. Glucose (1.75 gm./kg. ideal body weight) was administered orally for both GTT and CGTT. Blood was sampled before and at intervals of one-half hour for three hours after the administration of glucose.

Concentrations of blood glucose were determined with the Technicon AutoAnalyzer, and were frequently verified by the Somogyi-Nelson technic.[7] In this laboratory the AutoAnalyzer technic has been adjusted to give results comparable to those of the Somogyi-Nelson technic. Levels of plasma insulin were determined by the immunoassay technic of Yalow and Berson,[8] and by the Morgan and Lazarow[9] modification of the Yalow and Berson assay. In this laboratory the two methods have given comparable results.[10] Increases in plasma insulin and blood glucose are expressed as the sum of increments over control levels for the half-hour intervals of the first hour, as well as for all six intervals of the three-hour glucose tolerance tests. Levels of plasma insulin and blood glucose are also expressed as insulin/glucose ratios, which relate the intensity of the insulin secretory response to that of the glycemic stimulus. These ratios, both for the first hour and for the three hours of the GTTs, are derived from the sums of the increments of plasma insulin and blood glucose as described above.

RESULTS

1. *Standard glucose tolerance test*

Plasma insulin. Mean levels of plasma insulin for subjects with positive cortisone GTT (Group II) and for subjects with negative cortisone GTT (Group III) were similar to one another at each interval of the standard test (table 2). However, both groups exhibited significantly lower levels (Group II at thirty through 150 minutes and in Group III at thirty through 180 minutes) than normal subjects (Group IV, table 2), and significantly higher levels at thirty and sixty minutes than diabetic patients (Group I, table 2). In the patients with diabetes (Group I) the level of plasma insulin was significantly lower than that of Group IV at thirty through 180 minutes (figure 1).

The sum of increments in plasma insulin for Group II was similar to that of Group III for both one and

three hours (table 2). For Groups I and IV the respective sums of increments for one hour were 66.0 and 213.7 μU./ml., and for three hours 238.6 and 537.5 μU./ml. The differences were significant for both time intervals. The sums of increments for both one and three hours were also significantly less in Groups II and III than in Group IV (table 2). The sum of increments for the first hour was significantly greater in Groups II and III than in Group I.

Blood glucose. Mean levels of blood glucose for Groups II and III were similar at each interval (table 2). Levels of Group II were similar to those of Group IV while those of Group III were modestly but significantly lower than those of Group IV at thirty through 120 minutes (table 2). For Group I, fasting levels as well as all levels after ingestion of glucose were significantly higher than for Groups II, III (table 2) and IV (figure 1).

The sums of increments in blood glucose for both one and three hours were greater for Group II than for Group III but differences between the groups were not statistically significant (table 2). For Groups I and IV the respective sums of increments for one hour were 184.7 and 93.6 mg./100 ml. and for three hours 555.9 and 155.7 mg./100 ml. The increments were significantly greater for Group I than for Group IV and also significantly greater for Group I than for Groups II and III (table 2). They were significantly greater in Group IV than Group III (table 2).

Plasma insulin/blood glucose. The ratios, plasma insulin/blood glucose, for each time interval are shown in figure 2 as mean values for each group. The ratios for Groups II and III (figure 2A) are similar to one another. The ratios are significantly higher for Group IV, the healthy subjects, at thirty through 180 minutes than for the diabetic patients (Group I) whose ratios show a slow rise with a peak at two-and-one-half hours (figure 2B). The ratios for Group IV are consistently higher than those of Groups II and III. They are significantly higher than those of Group II at thirty through 150 minutes and significantly higher than those of Group III at ninety through 180 minutes.

The ratios, sum of increments in plasma insulin/sum of increments in blood glucose, for Groups I and IV for one hour were, respectively, 0.41 and 2.89 and for three hours 0.61 and 4.81 ($p < .001$ and $p < .005$, respectively). Ratios were not significantly different for Groups II, III and IV, while they were significantly greater for Groups II and III (table 2), and Group IV than for the diabetic patients.

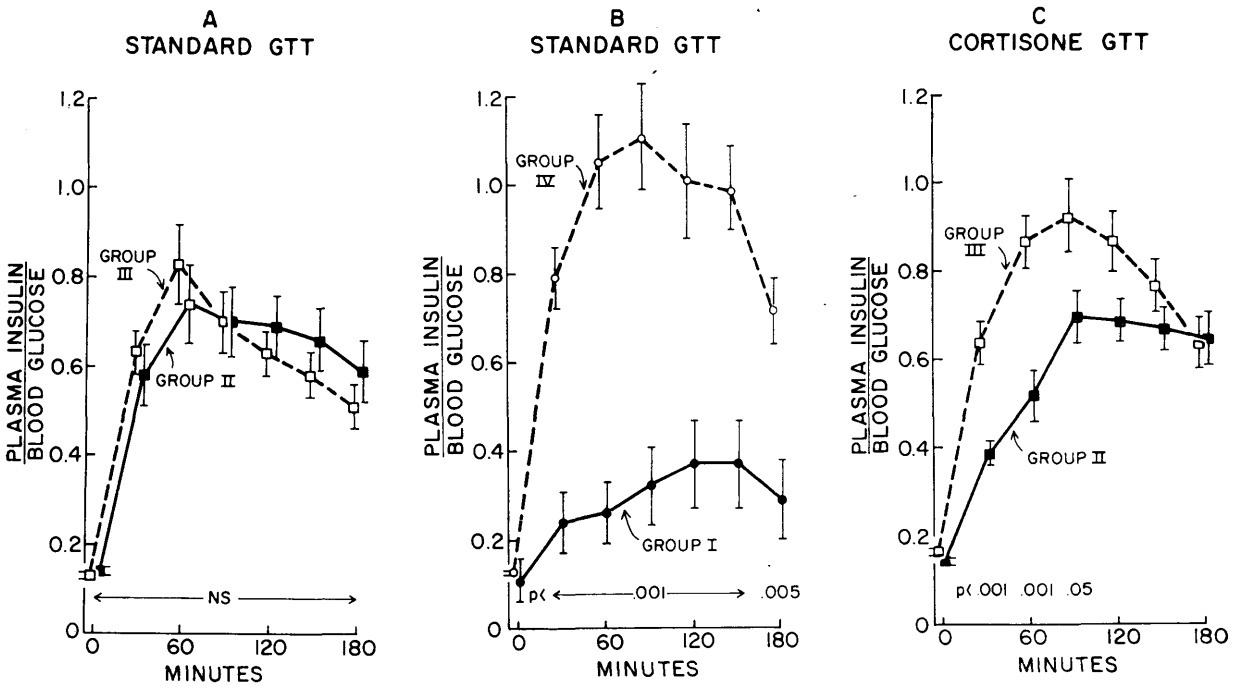

FIG. 2. Ratio, plasma insulin/blood glucose (mean ± S.E.M.) during (A) standard GTT and (C) cortisone GTT in "nondiabetic" relatives of diabetic patients with positive (Group II, twenty-six subjects) and negative (Group III, forty-one subjects) cortisone GTT and during (B) standard GTT in twenty-nine patients with mild diabetes (Group I) and in thirty-one healthy subjects (Group IV).

2. *Cortisone glucose tolerance test*

Plasma insulin. Mean fasting levels of plasma insulin in Groups II and III were similar to each other (figure 3, table 3) and in both groups were higher than their fasting levels before cortisone (see standard glucose tolerance tests, table 2). At thirty minutes after the ingestion of glucose the level of Group II (73.2 μU./ml.; 79.5 ± 9.2 μU./ml. for the eight subjects taking oral contraceptive agents and 70.4 ± 7.3 μU./ml. for the other eighteen subjects) was significantly less than that of Group III (97.7 μU./ml.). In Group II the level reached at thirty minutes during the cortisone GTT was 7 μU./ml. higher than during the standard GTT, while in Group III the increment was 22 μU./ml. Maximal levels of plasma insulin were reached at sixty minutes in Group III and at ninety minutes in Group II. At ninety minutes and onward levels were significantly higher in Group II than in Group III. The sum of increments in plasma insulin was less for one hour and significantly greater for three hours in Group II than in Group III (table 3). The sums of increments in plasma insulin in Group II were 167.6 ± 29.9 and 150.9 ± 18.9 for one hour, and 657.6 ± 95.9 and 600.1 ± 58.8 for three hours in the eight subjects taking oral contraceptive agents and in the other eighteen subjects, respectively.

Blood glucose. After cortisone, the mean fasting level of blood glucose and the levels at all intervals following the ingestion of glucose were significantly higher in Group II than in Group III (figure 3, table 3). Similarly, the sums of increments in blood glucose for one and three hours were significantly greater in Group II than in Group III (table 3).

Plasma insulin/blood glucose. The mean ratio, plasma insulin/blood glucose, is less in Group II than Group III at thirty through 150 minutes (figure 2C). The difference in levels is significant at thirty, sixty and ninety minutes. In addition, the ratios, sum of increments in plasma insulin/sum of increments in blood glucose, for one hour and three hours were both significantly less in Group II than in Group III (table 3).

DISCUSSION

The results of the standard glucose tolerance test

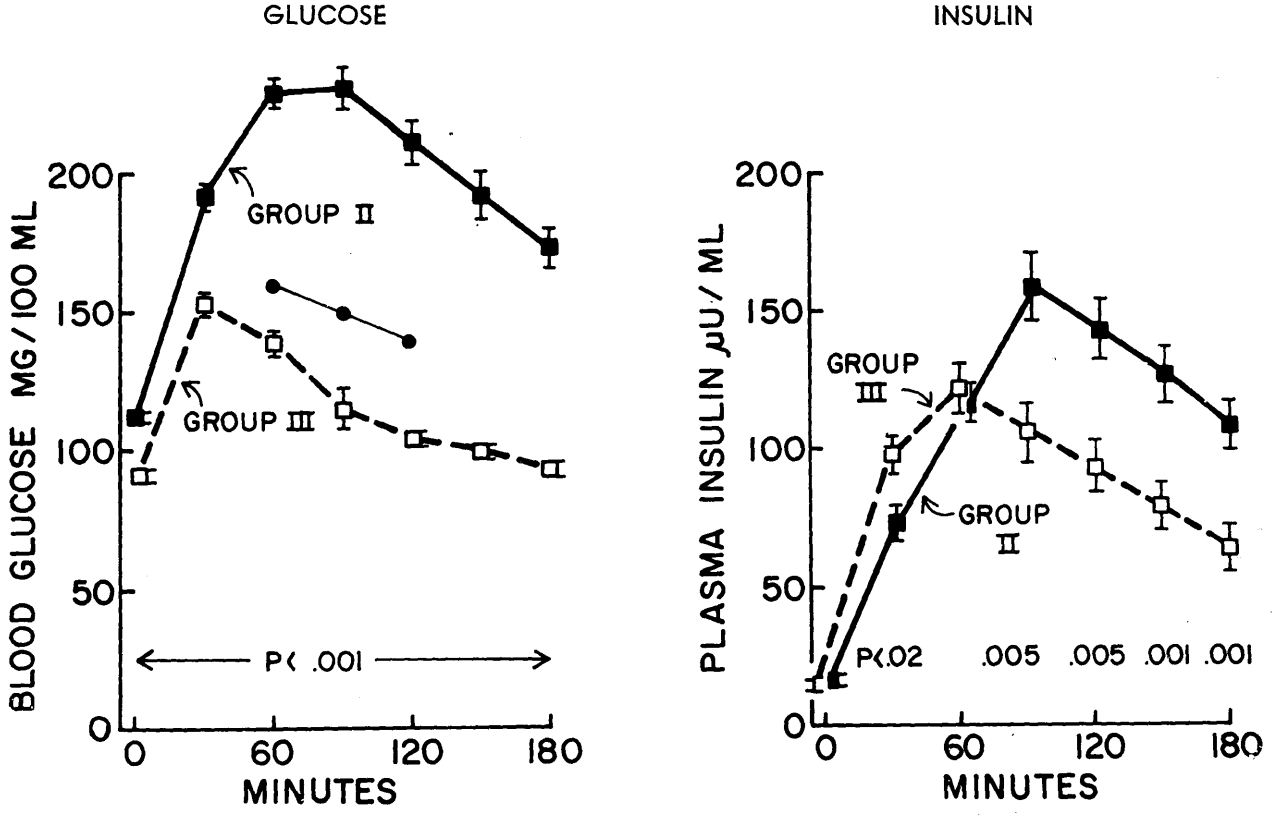

FIG. 3. Levels of blood glucose and plasma insulin (mean ± S.E.M.) during cortisone GTT in "nondiabetic" relatives of diabetic patients with positive (Group II, twenty-six subjects) and negative (Group III, forty-one subjects) cortisone GTT.

TABLE 3 *(Continued below)*

Cortisone glucose tolerance tests in "nondiabetic" relatives of diabetic patients

Group tested		Plasma insulin at time in minutes (μU./ml.)							Blood glucose at time in minutes (mg./100 ml.)		
		0	30	60	90	120	150	180	0	30	60
Subjects with positive cortisone GTT (II)	Mean (n=26)	16.4	73.2	116.3	158.2	142.8	126.5	108.4	112.0	191.6	229.2
	± S.E.M.	1.2	5.8	12.3	12.9	11.2	10.4	8.7	2.7	4.3	5.6
	p*	NS	<.02	NS	<.005	<.005	<.001	<.001	<.001	<.001	<.001
Subjects with negative cortisone GTT (III)	Mean (n=41)	15.5	97.7	122.0	105.6	93.3	79.6	63.8	91.4	152.8	139.0
	± S.E.M.	1.0	6.8	9.4	10.7	9.3	8.1	8.6	1.5	3.8	4.7

*Comparison of Group II with Group III.

show that increases in plasma insulin following the ingestion of glucose were delayed and subnormal in the patients with diabetes. Levels of plasma insulin at thirty through 180 minutes (figure 1), the insulin/glucose ratios at thirty through 180 minutes (figure 2B), the sum of increases in plasma insulin during the first hour, and the insulin/glucose ratios derived from each subject's one and three-hour increments were significantly less in the diabetic patients than in the healthy subjects. Similar findings in similar patients (nonobese patients with maturity-onset type of diabetes) have been demonstrated by others after oral,[8,11-15] as well as after intravenous glucose loading.[12,14,16]

The results of the standard test failed, however, to distinguish the "nondiabetic" relatives who had positive cortisone glucose tolerance tests from those whose tests were negative. There were no significant differences between Groups II and III in plasma insulin or blood glucose whether the results were expressed as absolute levels, as increments for one and three hours, or as ratios. It is noteworthy, however, that for both groups, levels of plasma insulin were lower than in healthy subjects and that ratios of plasma insulin to blood glucose were also less than those of the healthy subjects. However, the ratios for one and three-hour increments were not significantly different from those of the healthy subjects (table 2). Thus, "nondiabetic" relatives, both Groups II and III, secreted less insulin than the control group during the standard glucose tolerance test although, when the ratios are considered, the evidence of impaired secretion of insulin is not as clear as in the case of the diabetic patients. In addition, since the relatives of diabetic patients maintained normal glucose tolerance in the presence of decreased levels of plasma insulin they do not exhibit evidence of greater than normal resistance to the action of endogenous insulin. If anything, they may have increased sensitivity to it. Alternatively, they could be maintaining normal tolerance in the presence of decreased levels of plasma immunoreactive insulin because they are producing, in

TABLE 3 *(Continued)*

Cortisone glucose tolerance tests in "nondiabetic" relatives of diabetic patients

Group tested		Blood glucose at time in minutes (mg./100 ml.)				Sum of increments plasma insulin (μU./ml.)		Sum of increments blood glucose (mg./100 ml.)		plasma insulin / blood glucose	
		90	120	150	180	first hour	three hours	first hour	three hours	first hour	three hours
Subjects with positive cortisone GTT (II)	Mean (n=26)	230.6	211.1	192.4	173.4	156.3	620.1	196.7	557.9	0.88	1.95
	± S.E.M.	7.4	8.1	8.6	7.3	15.7	49.7	8.4	31.1	0.09	0.14
	p*	<.001	<.001	<.001	<.001	NS	<.05	<.001	<.001	<.001	<.001
Subjects with negative cortisone GTT (III)	Mean (n=41)	115.4	104.0	99.7	93.4	189.0	471.2	109.5	177.1	1.88	3.01
	± S.E.M.	7.9	3.2	2.8	3.2	13.5	41.9	5.9	13.2	0.14	0.22

*Comparison of Group II with Group III.

addition to immunodetectable insulin, a moiety, with insulin activity which is not measured by current immunoassays for insulin.

In contrast to the results of the standard test, those of the cortisone GTT distinguished Group II from Group III. During the cortisone GTT the rise in plasma insulin in Group II was delayed so that at thirty minutes the level of plasma insulin was significantly lower than in Group III even though the concomitant blood glucose value was significantly higher in Group II (figure 3, table 3). Beyond the sixty-minute interval plasma levels of insulin were higher in Group II. This was probably due to the great hyperglycemia that characterizes this group during the cortisone glucose tolerance test, as opposed to the levels of blood sugar exhibited by the negative responders (Group III). The deficiency in insulin secretion of Group II during the cortisone glucose tolerance test becomes more apparent when ratios of plasma insulin to blood glucose for both Groups II and III are compared (figure 2C). The ratios are significantly lower in Group II at thirty, sixty and ninety minutes. This deficiency is also demonstrated by lower ratios of increments in plasma insulin to blood glucose, calculated for one and three hours of the cortisone glucose tolerance test (table 3).

Beck and Wells[17] have reported that subclinical diabetic women given oral contraceptives either increase or do not change their plasma insulin responses to an oral glucose load. However, a suppressive effect[18] of oral contraceptive agents on plasma levels of insulin *during* the steroid glucose tolerance test has been reported in subclinical diabetic women. In the present study, there were no significant differences in plasma levels of insulin during the cortisone glucose tolerance test between the subjects taking oral contraceptive agents and those who were not.

When the ratios of plasma insulin to blood glucose are plotted against time, the difference in the patterns of Groups II and III during the cortisone GTT (figure 2C) is shown to resemble the difference shown between Groups I and IV during the standard glucose tolerance test (figure 2B). Thus, it appears that subjects with subclinical diabetes (Group II) exhibit a defect in the secretion of insulin during the cortisone glucose tolerance test, which is similar in pattern to that seen in mildly diabetic patients during the standard glucose tolerance test. It also seems likely that this defect shown by the subjects with subclinical diabetes is an important factor in the mechanism by which the positive cortisone glucose tolerance test is produced.

Impairment in the ability to raise levels of plasma insulin rapidly during the prednisolone GTT has also recently been demonstrated by Kalkhoff et al.[19] who studied nonpregnant women who previously had given birth to a heavy infant. The subjects with positive steroid glucose tolerance tests were unable at the thirty-minute interval of that test to raise plasma insulin to a level higher than that induced at the same period during their standard test. The subjects with negative steroid glucose tolerance tests, however, were able to raise plasma insulin at thirty minutes to a level significantly greater than that observed during their standard test.

Berger et al.[20] have postulated that the peripheral tissues of subjects with positive cortisone GTT are abnormally sensitive to the effects of cortisone which act to inhibit the disposal of glucose in peripheral tissues. This postulated exaggeration of cortisone-induced resistance to the peripheral disposal of glucose they considered to be the mechanism of production of the positive cortisone glucose tolerance test. Nevertheless, the results of their study show that at the thirty-minute point of the cortisone GTT there was a lesser increase from fasting levels of plasma insulin in their subjects with positive tests (76.8μU./ml.) than there was in the subjects with negative tests (94.5 μU./ml.), a difference which becomes even more significant in the light of the respective increases in blood glucose at the same point in time (75.8 and 64.3 mg./100 ml.). The insulin/glucose ratios derived from these values at thirty minutes are lower for the subjects with positive tests (1.01) than for those with normal tests (1.47) and this disparity becomes greater at each succeeding interval of the test. Their findings are, therefore, similar to ours in that subjects with positive tests exhibit a defect in the secretion of insulin as compared with the response given by negative responders.

It is of great interest that, during the standard glucose tolerance test, both groups of "nondiabetic" relatives of diabetic patients (Group II with and Group III without positive CGTT) secrete significantly less insulin than do healthy subjects, but significantly more insulin than do mildly diabetic subjects. The meaning of this observation is not clear since the insulin/glucose ratios (sum of increments for one hour) of both groups suggest a normal insulin secretory response. However, the CGTT does categorize these relatives into two groups: one with a relatively severe defect in the *reserve* capacity to secrete insulin and the other with this capacity essentially intact. In the past, we[5] have

given the name "subclinical diabetes" to the former group on the basis of their blood sugar responses during the cortisone glucose tolerance test. The present insulin data strongly support that interpretation.

Temporarily, at least, that designation seems appropriate for such patients and is in conformity with our original concept that the cortisone glucose tolerance test can detect decreased insulinogenic reserve even when the standard glucose tolerance test remains normal. We have already reported[5,6] from a long-term follow-up study that, among "nondiabetic" relatives, those with positive cortisone glucose tolerance tests develop clinically evident diabetes eight times more frequently than do those whose tests were initially negative. It thus seems reasonable to assume that those "nondiabetic" relatives with positive tests have progressed further toward failure of normal insulinogenesis than have those with negative tests. That they are distinguishable at this point in the evolution of the diabetic state from the other relatives (negative CGTT) represents an important advance in early detection. Some relatives with negative CGTT will progress to positive tests while others will not.[6] Why relatives of diabetics with negative CGTT exhibit, as a group, a subnormal plasma insulin response to glucose requires further study. It must be emphasized that our negative CGTT group is heterogeneous (not all "prediabetic") while the group which responds positively to this test represents homogeneity in the sense that it is selected from the group as a whole.

Finally, the demonstration that cortisone priming can uncover in some relatives of diabetics a significantly deficient insulin-secretory mechanism, the character of which is similar to that exhibited by mildly diabetic patients given glucose alone; and that such "subclinical diabetics," while maintaining normal standard glucose tolerance curves, have a demonstrably diminished insulinogenic reserve, provides substantial evidence that in the evolution of the diabetic state a deficient insulin-secretory mechanism precedes loss of tolerance for carbohydrate.

It is not unexpected that decreased insulin activity precedes the development of diminished carbohydrate tolerance. But, in one's efforts to study the evolution of the diabetic state, he finds himself attempting to distinguish between decreased insulin sensitivity and decreased insulin secretion, particularly when obesity is a complicating factor. The present data focus attention on early insulin insufficiency and upon the fact that it can exist in the presence of what is currently regarded as a normal standard glucose tolerance test.

These results lead us to raise several questions, the answers to which must await future research:

1. Can relatively severe hypoinsulinemia occurring intermittently in the subclinical diabetic during periods of stress, over a number of years, be harmful to various tissues of the body?

2. Could the cells of the microvascular system be particularly vulnerable to such bouts of insulin insufficiency?

3. If one can detect the hypoinsulinemic response to "stress" at a stage when the standard glucose tolerance test remains normal, should some form of treatment be instituted then or should such efforts be postponed until a diagnostic hyperglycemic standard glucose tolerance test develops?

4. If treatment for subclinical diabetes appears to be reasonable and if the objective is to insure normal postprandial levels of plasma insulin, how will this objective be accomplished?

5. In an effort to prevent vascular lesions, or halt their progress, should a prime objective of therapy of diabetes, at all stages of the disease, be correction of the hypoinsulinemia of the immediate postprandial period, a phenomenon which begins early in the disease and increases in intensity with its progression? For example, could we expect insulin-dependent diabetics, given rapidly acting insulin before each meal, to avoid or forestall the appearance of such complications, an expectation which has not been satisfied during a thirty-year period with use of the more convenient, longer acting preparations of insulin?

The idea that hypoinsulinemia should be corrected, if possible, regardless of the stage of the disease in which it is encountered, does not seem too radical. It would simply sharpen presently accepted therapeutic aims. Whether such an objective is attainable practically and whether its accomplishment would prevent vascular lesions are problems for future research.

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