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Use of the tolbutamide tolerance test in the detection of latent diabetes mellitus

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USE OF THE TOLBUTAMIDE TOLERANCE TEST IN THE DETECTION OF LATENT DIABETES MELLITUS

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INTRODUCTION

The diagnosis of diabetes was probably easier to discuss twenty years ago when less was known about this metabolic disorder and those in clinical research were less flexible concerning the diagnostic criteria. While it is readily apparent that the overt syndrome is probably due to a lack of effective insulin, it is becoming more obvious that hyperglycemia and mild abnormalities in the glucose tolerance curve are relatively late developments in the clinical course. Thus the concept has evolved that diabetes is a "molecular disease" which involves the intermediary metabolism of protein and fat, as well as carbohydrate.[42] The absence or impairment of certain critical cellular elements is responsible for the long-term degenerative changes which ultimately result in the classical manifestations of diabetes.

Since present knowledge is still woefully lacking concerning the pathogenesis of diabetes, rational therapy cannot treat the "essential" causes and must therefore empirically seek to alleviate the symptoms of this disease and hopefully retard the inevitable progression of dreaded degenerative processes.[7] From the stand-point of preventive

medicine, only after one successfully detects the subclinical or latent diabetic can he apply those therapeutic or prophylactic measures designed to forestall the aspect of "decreased insulin activity" in diabetes---the one facet about which we know most. Since one attempts to diagnose and treat diabetes in its earliest possible stage in order to prevent, reverse or attenuate the clinical manifestations, it would be helpful at this point to review the natural progression of this carbohydrate disturbance.

SPECTRUM OF DIABETES

Fajans[10] and Conn[6] recognize four different stages in diabetes (see figure 1). The prediabetic period extends from conception to the earliest recognizable abnormality in the glucose metabolism. The subjects most likely to be found in this category are the identical twin of a diabetic, individuals with diabetes among close relatives, women with abnormal obstetrical history, obese individuals and subjects with vascular disease.[42] Until definite criteria are discovered which accurately identifies the potential diabetic, the term prediabetic can be applied only in retrospect.[10]

The next phase is that of subclinical diabetes. Under usual circumstances, there is no fasting hyperglycemia

	Prediabetes	Subclinical Diabetes	Latent Diabetes	Overt Diabetes
FBS	Normal	Normal	Normal or ↑	↑
GTT	Normal	Normal (Abnormal during pregnancy & stress)	Abnormal	Not Necessary
Cortisone GTT	Normal	Abnormal	Not Necessary	---
ILA Synalbumin Antagonist	↑	↑	↑	↑
Vascular Changes	±	+	++	++++

Figure 1. Four stages of diabetes (from Fajans[10])

Note: progression(or regression) from earliest stage may-
(a) never occur
(b) proceed slowly
(c) be rapid or explosive.

and the oral glucose tolerance test (OGTT) is normal. Diabetes may be suspected because of evidence of insufficient functional reserve of the pancreatic islet cells, as shown by an abnormal OGTT during pregnancy or stress, an abnormal cortisone-GTT or an abnormal cortisone-intravenous tolbutamide tolerance test (IVTT). These patients are asymptomatic. Consequently, they unknowingly proceed down the path of vascular degeneration until the abnormality in carbohydrate disturbance becomes manifest. This is the individual for whom diabetes-detection programs should search most diligently.

In the latent or chemical, but clinically detectable diabetes, the patient still has no symptoms referable to his metabolic disorder. The diagnosis, however, may be determined by presently accepted lab procedures such as an OGTT. Frank or overt diabetes is the most advanced stage. Classical symptoms such as polyuria, polydipsia and polyphagia may be present. The OGTT is not necessary for diagnosis as these patients manifest fasting hyperglycemia.

Camerini-Davalos[4] has emphasized that the four stages from prediabetes to overt symptomatic diabetes are not necessarily progressive in a forward direction, but may revert spontaneously in some individuals to earlier stages without change in body weight or treatment. In

addition to the usual course of diabetes, neuropathy, retinopathy and coronary artery disease may proceed the abnormalities in carbohydrate tolerance. In this sense, the "complications become the manifestations".[19]

ORAL GLUCOSE TOLERANCE TEST

According to Remein and Wilkerson,[28] the productivity of diagnostic or screening procedures is dependent upon the prevalence of the disease in the group under investigation, the reliability of the test and its efficiency. The latter is measured in terms of sensitivity and specificity. Sensitivity is the ability of a test to identify as positive those individuals who possess the abnormality. Specificity, on the other hand, is the ability of a test to classify as negative only those subjects who do not have the disease. Unfortunately, it is not possible to select a diagnostic procedure which would result in only diabetics being considered positive and nondiabetics negative. Therefore, in screening for diabetes, one must choose between a method which may be more sensitive and yield some false positive results or a procedure which is more specific and accept some false negative tests. This is an important principle and will be applied later on in this paper to evaluate the OGTT and the IVTT.

The convenience of the standard OGTT has led to its widespread use as a means of detecting early derangements in carbohydrate metabolism. In adequately prepared subjects, the failure of the blood sugar to return to 120 mg per cent within two hours after an oral glucose load is commonly interpreted as evidence for diabetes.[44] The height of the curve is far less significant than the rapidity with which the glucose is removed from the blood, i.e., the duration of hyperglycemia.[22, 23] In addition, terminal hypoglycemia, occuring two to five hours after the ingestion of carbohydrate may represent an early manifestation of diabetes.[29] Unger maintains, however, that the diagnostic specificity of a moderate elevation in the two hour blood sugar has never been estimated.[38] In a five to seven year prospective study where OGTTs were repeated on the same subjects, he concluded that the long term diagnostic and prognostic implication of abnormal OGTT curves associated with normal fasting blood sugars had a high degree of nonspecificity. Therefore, the possibility exists for mislabeling normal individuals as diabetics by strict adherence to the above criteria.

FALLIBILITY OF THE OGTT

It is insufficiently recognized that the OGTT can provide only limited information about carbohydrate

metabolism. Much of the unreliability and unwarranted deductions occur when the conditions of the test are not standardized.[1] Exogenous factors such as carbohydrate content of the antecedent diet, exercise, prolonged inactivity, emotional tension, endocrine balance, concentration and amount of the glucose solution, site of the sampling, fever, infection, neoplasia, uremia, drugs and accuracy of the procedure, to mention a few, are all known to affect the OGTT. Unger[34] challenges the physiologic validity of the OGTT on the basis that gastrointestinal factors, unrelated to peripheral utilization of glucose, play too great a role in determining the configuration of the curve. Baird[1] reports that the rate of gastric emptying varied greatly among normal subjects and was affected markedly by the concentration of the solution. If the OGTT, as interpreted by Soskin,[31] may be regarded chiefly as an index of hepatic efficiency in blood sugar regulation, liver disease, as well as the various endocrinopathies may also modify the body's response to a carbohydrate load.

REPRODUCIBILITY OF THE OGTT

Freeman[13] observed a marked variation of results when OGTTs were repeated in the same individuals; this

discrepancy was not resolved by comparing either the maximum levels attained or the maximum increase in blood sugar, irrespective of time. He concluded that the variation in carbohydrate tolerance is too great to give the OGTT any precise diagnostic value. McDonald[21] also experimented with the reproducibility of the OGTT and reported that the results are indeed variable and that one should not assume freedom from this disease when this test is interpreted as normal. He therefore recommended that those classified as suspects on the basis of a screening test should be re-evaluated periodically when the initial study does not indicate active disease.

DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE OGTT

By present criteria for the OGTT, most people develop diabetes mellitus during their advancing years.[32] Consequently, maturity-onset diabetes could be considered, much like that of arteriosclerosis, as a part of the general aging process. One could also say that the significance of the abnormal OGTT in the elderly is not known and that it may not indicate significant disease. If this is the case, it must be admitted that the criteria for the diagnosis of diabetes in the younger age group by the OGTT cannot be used satisfactorily in the diagnosis of diabetes in elderly patients. Wagner[41] reported that

by present standards 18-56 per cent of the elderly population should be classified as being diabetic; however, since none of the patients in his series presented any of the clinical stigmata of diabetes and it was apparently not becoming overt, he was doubtful that the condition existed. Hayner[16] suggested that the criteria for the OGTT be age dependent. Fajans and Conn[10] also observed that the tolerance to carbohydrate diminishes with advancing age and frankly admitted that no reliable criteria exists for subjects greater than fifty years of age.

INTRAVENOUS TOLBUTAMIDE TOLERANCE TEST

The clinical usefulness of any diagnostic test for mild diabetes depends upon its ease of performance, safety and, most important, its ability to differentiate the diabetic without fasting hyperglycemia from the nondiabetic. Any test which measures insulin activity indirectly, as does the OGTT, is bound to yield a specificity and sensitivity less than 100 per cent. Because of the difficulty in interpreting equivocal GTTs, a new parameter for detecting chemical diabetes may be necessary. An alternate method would certainly permit a greater degree of diagnostic confidence in borderline cases.

The intravenous tolbutamide test (IVTT) appears to offer a more direct approach to pancreatic beta cell function since it has been shown that there is a relatively close correlation between the degree of hypoglycemia and the secretion of endogenous insulin after the administration of tolbutamide.[24, 45] Since fewer exogenous factors affect the response to insulin than to carbohydrate, fewer false positive results may occur.[18] In addition to being a valuable supplementary procedure to the various types of carbohydrate-loading tests currently utilized to estimate beta cell function, the IVTT is more convenient to perform than the OGTT in that it requires only thirty minutes, as compared with two or three hours for the latter test. The IVTT is also less unpleasant and avoids the nausea and vomiting which may occur during the OGTT. However, with present knowledge and experience, one cannot diagnose diabetes with confidence using the IVTT. It is the purpose of this paper to compare additional clinical data with accepted standards--as only further experience with the IVTT can establish the ultimate usefulness of this diagnostic test.

METHOD OF INVESTIGATION

The intravenous tolbutamide and standard oral glucose tolerance tests were performed on 35 hospital patients.

Approximately one-half of the studies were compiled on the medicine ward of Douglas County Hospital while the remainder were obtained on the medical and surgical wards at the University hospital. The subjects ranged from 21-89 years in age and all were ambulatory and afebrile. As carbohydrate restriction is known to diminish the magnitude of the hypoglycemic response to sodium tolbutamide, all patients were placed on a general diet which contained at least 200 grams of carbohydrate for approximately three days prior to the test.[2] Before the IVTT was administered, the status of carbohydrate tolerance was evaluated in each patient.

After an overnight fast, a specimen was withdrawn for glucose determination. Then one gram of sodium tolbutamide, as Orinase Diagnostic (Upjohn Company), was dissolved in 20 c.c. of sterile saline and injected into a prominent vein at a constant rate over a two minute time interval. A blood specimen was drawn thirty minutes after the mid-point of the injection; in many cases, an additional sample was taken at sixty minutes. The nature of the response necessitated close attention to the timing of the blood collection. In personal experience, no more than a one to two minute deviation was allowed. The glucose concentration of the two

(or three) blood samples were then determined by means of a "true glucose" method.

Table I contains all of the significant data necessary for an evaluation of the IVTT as a useful procedure in the diagnosis of mild disorders in carbohydrate metabolism. The subjects investigated are similar to those patients found in any general hospital population in that the majority are females (69 per cent) and most (62 per cent) are older than sixty years of age; however, the study is not entirely representative of a true hospital population in that the incidence of cancer was obviously much higher. Only four individuals presented with a close familial history of diabetes; a fifth reported a more distant family history. The major diagnosis of each patient is also tabulated. The standard oral glucose tolerance test was utilized for the preliminary study of carbohydrate tolerance in most patients, but was not performed when the modified form was diagnostic of diabetes.

UNTOWARD RESPONSES

There were no cases of drug sensitivity encountered. Since hypoglycemia is hazardous in patients with either coronary or cerebral vascular disease, the intravenous tolbutamide was administered to these patients with

PT.	SEX	AGE	F.H.	DIAGNOSIS	ORAL GTT				IVTT		
					FBS	30'	60'	120'	FBS	30'	60'
1 FH	M	68	-	ASHD	76	120	167	134	84	95	87
2 IM	F	84	-	HCVD	84	205	195	103	76	74	55
3 LB	F	83	-	ASHD	92	183	124	107	87	76	78
4 AC	M	85	-	CA LUNG	87	116	129	147	50	104	72
5 CM	F	55	+	MI	68			249	116	89	86
6 EV	F	89	-	PYELITIS	96	116	120	147	157	55	41
7 HF	M	69	-	PYELITIS	70		142	142	66	76	
8 GE	M	60	-	CHF	74		209	100	73	78	
9 JR	F	67	-	CVD	162	187	177	134	116	69	75
10 MS	F	63	+	MI	103	162	195	147	80	105	83
11 AT	F	52	-	CVD	76	157	195	152	103	74	56
12 MW	F	33	+	HCVD	85	149	221	290	107	68	71
13 HH	F	73	-	ASHD	87	107	116	124	103	71	61
14 LB	F	52	-	CVD	56	124	142	177	107	86	
15 EK	F	74	-	CA BREAST	82	206	188	134	114	63	61
16 GR	F	56	+	CA LUNG	94			104	104	89	
17 DS	F	54	-	CVD	76	134	117	66	72	71	
18 HJ	M	67	-	DERMATITIS	70	127	158	132	66	64	
19 EV	F	45	-	ANEMIA	82			123	75	83	
20 AC	F	68	-	CA CECUM	80			119	80	63	
21 AW	F	47	-	CA BREAST	77	116	122	130	73	74	62
22 MP	F	75	-	CA RECTUM	81	158	104	98	90	57	
23 LS	M	50	+	PVD	75	97	108	78	68	38	80
24 WG	M	21	-	NEUROSIS	74	140	178	135	67	72	90
25 SD	F	24	-	GB DISEASE	64	147	150	226	64	81	
26 PF	F	61	-	CA LUNG	88			215	98	102	
27 LB	F	59	-	ADENO-CA	78	148	201	226	71	82	
28 VO	F	78	-	GB DISEASE	106	184	208	128	83	77	
29 ES	M	65	-	CA COLON	80	126	106	132	76	69	
30 WN	M	62	-	CA RECTUM	78			136	75	76	
31 CR	M	84	-	CA SINUS	85	180	279	290	101	90	
32 EF	F	73	-	ASHD	130	372	420	474	133	98	
33 IT	F	72	-	BILROTH II	70	110	185	230	84	73	
34 LK	F	74	-	CA CECUM	132	191	245	248	73	60	
35 RS	M	22	-	EPILEPSY	72	110	112	80	73	79	

Table I represents a compilation of data taken from 35 patients in the current investigation. IVTT values for 30 and 60 minutes are expressed as per cent of the pretest value.

Abbreviation key:

ASHD=arteriosclerotic heart disease
HCVD=hypertensive cardiovascular disease
CA =carcinoma
MI =myocardial infarction
CVD =cerebral vascular disease
PVD =peripheral vascular disease
GB =gall bladder
CHF =Congestive heart failure

caution. Although transitory mild hypoglycemia did occur, more severe manifestations were rather rare. Some complained of hunger and weakness during the test, but nervousness, perspiration and trembling were uncommon. These symptoms were observed only in nondiabetics since the blood glucose levels in diabetics seldom reach the hypoglycemic range. In any event, the possible deleterious effects of lowered blood sugar were circumvented by the ingestion of a glass of fruit juice immediately after the thirty (or sixty) minute specimen was obtained. In addition, the subjects were cautioned about skipping any meals for the remainder of the day.

This diagnostic procedure was not performed on patients known to have hepatic dysfunction or on a regimen requiring the use of salicylates.[33] The injection of tolbutamide occasionally resulted in a transient burning sensation along the course of the vein, attributed to venospasm, which occasionally radiated to the shoulder. Such episodes were rare and considered insignificant. Side reactions similar to those described above have also been encountered by Unger[35] and Kaplan.[18]

CLINICAL DATA

Table 2 represents a modified version of Unger's criteria used in the present study for the interpretation

Intravenous Tolbutamide Test	Twenty Minutes	Thirty Minutes
Normal	<75%	--
Diabetes	>89%	>76%
Probable Diabetes	85-89%	77-80%
Nondiagnostic		
Subgroup I	80-84%	>77%
Subgroup II	75-79%	<77%

Table 2. A modified version of Unger's criteria[37] for interpretation of the intravenous tolbutamide tolerance test with the responses expressed as a percentage of the pretest level.

of the IVTT; the results are simply expressed as the percentage of change from the pretest level.[39] As can be readily seen, the vast majority of nondiabetics exhibit a prompt fall twenty minutes after injection to a level of 75 per cent or less. A corresponding determination in diabetics remains at 90 per cent or greater. The probability of diabetes is 90 per cent in the 85-89 per cent range, 50 per cent in the 80-84 per cent range and only 20 per cent in the 75-79 per cent range. A thirty minute specimen is also diagnostic if the glucose concentration is 76 per cent or greater; however, a value below 75 per cent at this time period is not significant in ruling-out diabetes.[35] As stated earlier, only thirty minute specimens were drawn in this study. Whitehouse and Lowrie feel that the wide range of values at twenty minutes in nondiabetics vitiates this determination--even though 80 per cent of all diabetics will not demonstrate a 20 per cent decrease from fasting levels at this time.[43]

Figure 2 demonstrates the mean normal and diabetic responses during the IVTT in this particular series. Normal and diabetic patients exhibit distinctly different responses thirty minutes after injection. By this time the mean value in the nondiabetic group had decreased

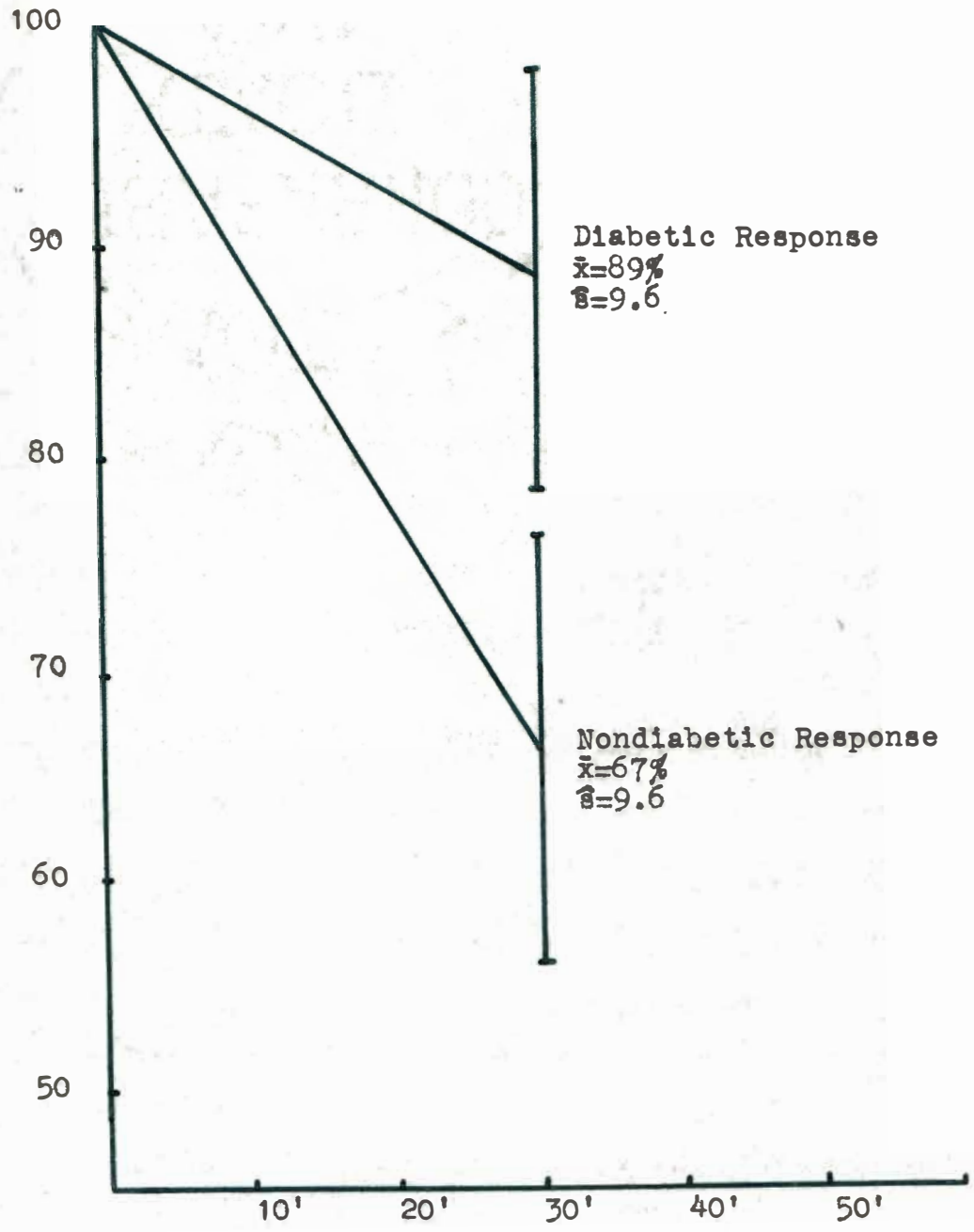

Figure 2. Comparason of normal and diabetic IVTT responses at thirty minutes; the results are expressed as the percentage of the pretest level. One standard deviation is drawn for each mean response.

33 per cent; the range in this same group was from 76 to 38 per cent. The standard deviation calculated to be 9.6. Thus, in this study, at least two-thirds of all nondiabetic values can be shown to fall below 80 per cent of the pretest level at thirty minutes. The diabetic group, on the other hand, demonstrated a mean descent to only 89 per cent during the same time interval. Individual values ranged from 105 to 77 per cent with the standard deviation of 9.6.

SIGNIFICANCE OF 20, 30, AND 60 MINUTE VALUES

Whitehouse and Lowrie[43] state that a 20 per cent drop in the blood glucose at thirty minutes following the injection of tolbutamide will maximally separate those patients with diabetes from the normal group. Voll[40] and Unger[37] also believed that the greatest separation occurred at twenty and thirty minutes and were more specific. Voll regarded the thirty minute value as being most significant in differentiating from the diabetic and nondiabetic state. He reported that a drop of less than 25 per cent of the pretest level constituted a diabetic response. In addition, this investigator cast some doubt on the necessity of the twenty minute specimen because he found that none of his subjects showed a diabetic response at thirty minutes and a

nondiabetic result at the twenty minute determination. The converse was apparently also true, as in no case did a normal thirty minute value coincide with a diabetic twenty minute value. When borderline values occurred, for example, a 15-19 per cent drop at twenty minutes, a normal response required a 25 per cent fall of the fasting blood sugar at thirty minutes. Unger and Madison[39] fully expected a "zone of overlap" to exist between diabetic and nondiabetic responses. Strict adherence to recommended criteria could lead to diagnostic errors, but they assumed that these misinterpretations could be minimized by evaluating the values in terms of probability of diabetes--as discussed earlier.

Unger and Madison[35] stated that the thirty minute specimen appears to be diagnostically more specific as 99 per cent of all nondiabetics are below 77 per cent of the pretest level by this time; this sample is too insensitive to be of value in exclusion of diabetes since approximately 15 per cent of mild diabetics will have also reached this point. The present study confirms this observation; at 2.6 standard deviations from the diabetic mean, it can be shown that 13 per cent of the diabetic population will have a calculated response below 77 per cent. Thus the blood glucose level at thirty

minutes is more specific, but less sensitive than the twenty minute specimen. Only the diabetic zone is of any importance since negative values have little significance. This finding has led Unger to regard the thirty minute determination as being of value only when it is abnormal in that it gives added significance to an elevated twenty minute specimen.[39]

Zarowitz and Eis[46] found that the greatest fall in blood sugar of nondiabetics occurred forty minutes after the injection of the tolbutamide; the mean percentage drop was 40 per cent of the fasting level. At sixty minutes the mean rose to 26 per cent. From this observation, these investigators concluded that the normal response to tolbutamide consists of a prompt fall in the blood sugar within forty minutes of injection and then later demonstrates an appreciable degree of hypoglycemic responsiveness. Those patients with decreased beta cell function exhibit a delayed response to tolbutamide which is characterized by a more gradual fall, reaching a nadir at sixty minutes or more, and demonstrating no significant hypoglycemic responsiveness. It is important to note that the zone of overlap between normal and elevated values become broader after forty minutes, and less diagnostic, as the blood sugar of normal individuals returns to fasting levels while that of

diabetics continues to decline.[37] Unger[39] also took note of the high frequency of rebounds in the nondiabetic group, but regarded the phenomenon as being secondary to a more rapid decline in blood sugar resulting in counter-regulatory forces being brought into play. In other words, the rebound effect was attributed to the rate and extent of drop in blood glucose rather than beta cell function and therefore is less diagnostic than twenty and thirty minute determinations. However, Unger is ready to advise a prolongation of the IVTT if examination of the rebound phase provides an unmistakable increase in diagnostic acuity. Recant,[27] in addition, finds it of value to carry out the IVTT for ninety minutes because she feels that valuable diagnostic features in the shape of the curve are missed with the thirty minute test currently advocated.

The hypoglycemic responsiveness observed in non-diabetic subjects was not as readily apparent in this current investigation. Probably the over-all age of the patients in this series had a significant effect on the general response to the sulfonylurea. As presented in figure 3, the degree of response to the tolbutamide was roughly proportional to the severity of the metabolic disorder, i.e., the more severe the diabetes, as evidenced by fasting hyperglycemia, the more diminished and delayed

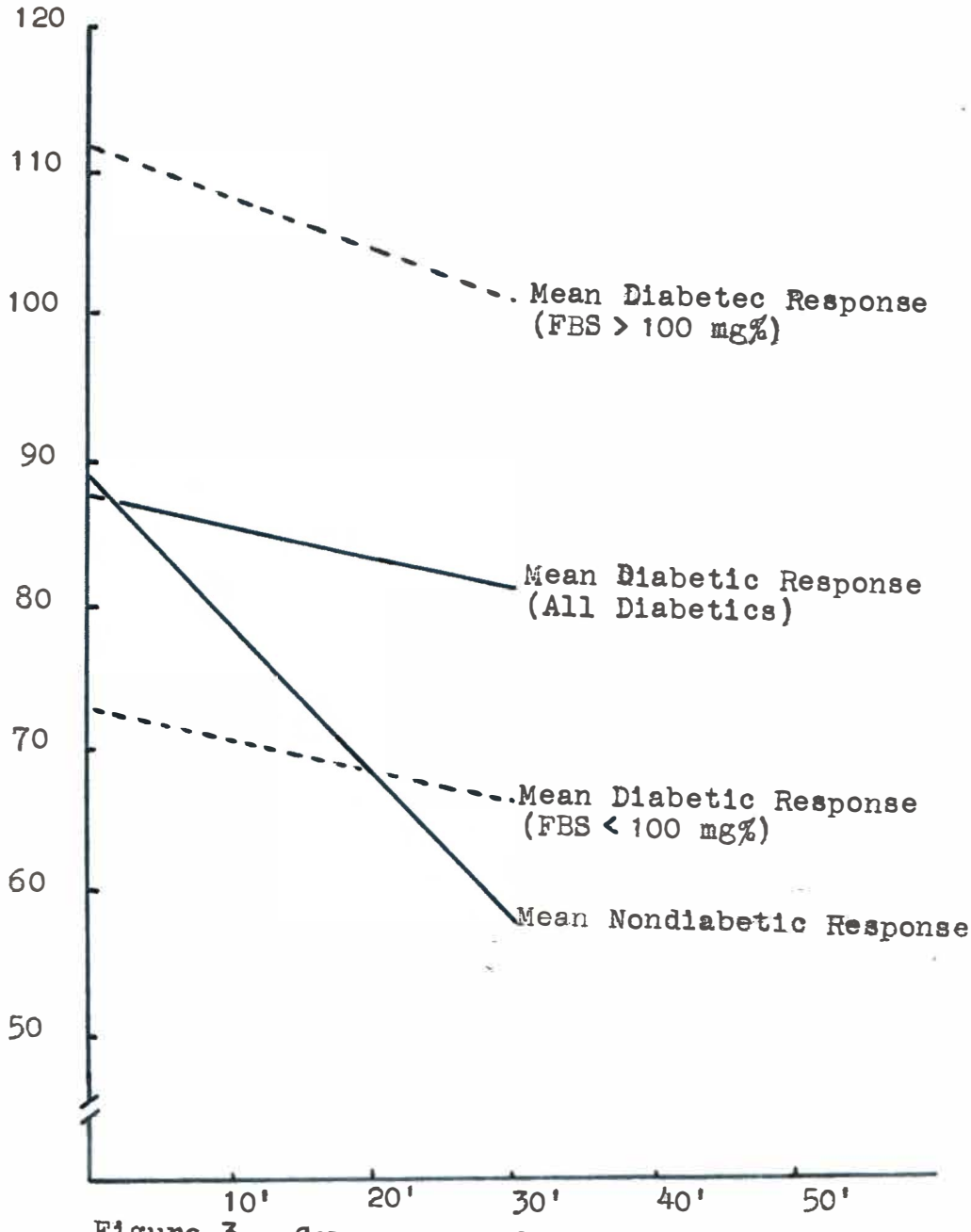

Figure 3. Comparason of normal and diabetic IVTT responses at thirty minutes; the results are expressed as milligrams of glucose per 100 c.c. of whole blood. Also correlated are diabetic responses with fasting normoglycemia and hyperglycemia.

was the response of the test. More significant is the fact that the values of those diabetics with fasting normoglycemia appear to parallel the curve found in overt diabetes. If the IVTT can differentiate the diabetic without fasting hyperglycemia from the nondiabetic, this procedure may become particularly useful in verifying borderline oral glucose tolerance results since the diagnosis would be more certain if this adjunctive test were also abnormal.

Unger and Madison[35] find it tempting to attribute the striking similarity of the normal tolbutamide response curve to the rapid release of insulin stored in the beta cells. Pfeiffer[24] states that the prompt and significant fall of glucose in the nondiabetic group after the administration of tolbutamide is associated with a marked increase in "insulin-like activity" in the peripheral blood. This finding is taken as indicative of functionally active islet cell tissue. If such a generalization is true, the more gradual decline in blood sugar in both latent and overt diabetics might be ascribed to a diminished release of insulin from the pancreatic beta cells due to a deficiency of stored insulin or a slower rate of release.[8] Fajans[11] and Hasselblatt,[15] however, would probably include extrapancreatic factors in the serum and at the cellular level to attribute for at least part of the decreased responsiveness to this drug.

EFFICIENCY OF IVTT COMPARED WITH OGTT

In this present investigation, an attempt was also made to correlate the effectiveness of the intravenous tolbutamide test with that of the oral glucose tolerance test as a screening measure for the detection of diabetes. Table 3 represents a modification of the criteria advocated by Conn and Fajans[10] which was utilized for evaluating the oral glucose tolerance tests. Table 4 then tabulates the diagnostic results of the various methods of investigating carbohydrate metabolism. Since twenty minute specimens were not obtained in this study, Unger's criteria for nondiagnostic results could not be compared with its counterpart in the OGTT. The tolbutamide screening procedure indicated that 43 per cent of the patients under investigation were diabetic whereas 51 per cent of the same group were diabetic when evaluated by the oral glucose tolerance method. This finding is consistent with the conclusion that the IVTT results in a higher percentage of false negative results when compared with the OGTT. As a certain number of diabetic individuals will be missed in this procedure, the IVTT cannot be considered as valid as the OGTT in the exclusion of diabetes mellitus.[21]

Standard Glucose Tolerance Test	One Hour	Two Hour
Normal	<160 mg%	<110 mg%
Diabetes	>160 mg%	>120 mg%
Probable Diabetes	>160 mg%	110-120 mg%
Nondiagnostic		
Subgroup I	>160 mg%	<110 mg%
Subgroup II	<160 mg%	>120 mg%

Table 3. A modification of the criteria advocated by Conn and Fajans[10] for interpretation of the oral glucose tolerance test.

	Intravenous Tolbutamide Test		Oral Glucose Tolerance Test	
	Number	Percent	Number	Percent
Normal	20	57	7	20
Diabetic	12	34	17	49
Probable Diabetic	3	.9	1	2
Nondiagnostic				
Subgroup I			2	8
Subgroup II			8	23

Table 4. IVTT compared with standard OGTT in 35 subjects: measured in individuals tested and percentile of total.

Table 5 compares the results of the intravenous tolbutamide test with a breakdown of the glucose tolerance test into subdivisions ranging from positive (groups I-IV) to probable (group V) and nondiagnostic (groups VI and VII) for diabetes. As indicated, only 50 per cent of the tolbutamide tests were positive for the first four classes of glucose tolerance curves; 40 per cent of the tolbutamide tests were positive when the standard oral glucose level fell to the probable diabetic or nondiagnostic zone. Kaplan[18] observed that one-third of his patients with fasting normoglycemia, but an abnormal OGTT and no known cause for a derangement in carbohydrate metabolism had a normal IVTT. More than half of his patients with varying conditions which may affect carbohydrate metabolism (advanced age, obesity, pregnancy, liver disease, steroid treatment and thyrotoxicosis) had a normal reactivity to tolbutamide in the presence of an altered glucose tolerance. Therefore, he concluded that the IVTT possesses, in addition to "adequate sensitivity" for the diagnosis of diabetes, an important specificity for this disease in comparason to glucose-loading techniques.

Fajans[21] is among those who express some skepticism to the variable response of the IVTT in patients with normal fasting blood sugar, but an abnormal OGTT. He has performed studies comparing the sensitivity of the IVTT

GROUP	BLOOD GLUCOSE	NUMBER of SUBJECTS	POSITIVE for DIABETES	NEGATIVE for DIABETES	PROBABLE DIABETES
I	FBS>120 mg%	3	1	2	
II	FBS<110 mg% OGTT: 1hr>220 mg% 2hr>180 mg%	2	1	1	
III	OGTT: 1hr>180 mg% 2hr>140 mg%	5	2	2	1
IV	OGTT: 1hr>160 mg% 2hr 120-140	3	1	2	
V	OGTT: 1hr>160 mg% ahr 110-120	0			
VI	OGTT: 1hr>160 mg% 2hr<110 mg%	2	0	2	
VII	OGTT: 1hr<160 mg% 2hr>120 mg%	8	3	4	1
VIII	MGTT: 2hr>110 mg%	5	3	2	

Table 5

Comparason of oral glucose tolerance test and intravenous tolbutamide test.

with the OGTT in patients with varying degrees of carbohydrate intolerance. Instances have been clearly demonstrated where the IVTT has reverted to normal with treatment, but the diabetic OGTT responses have remained. Kaplan[18] suggested that the groups investigated may be composed of two populations: one truly diabetic and responding abnormally to tolbutamide, the other actually nondiabetic and reacting normally to tolbutamide, but for some obscure reason are unable to handle a carbohydrate load. Unger[27] attempted to explain the discrepancies by the poor reproducibility of the OGTT, the relatively high frequency of false positives in nondiabetics with the OGTT, and the fact that glucose and tolbutamide may have different effects on beta cells of the pancreas and hence one may not be measuring the same function.

It is significant that false positive results may also occur in a certain number of nondiabetics. This must be expected if there is any alteration in carbohydrate metabolism which involves either a diminished pancreatic reserve or a decreased responsiveness to insulin.[18] Such alterations may be important in patients with advanced age as was probably the case in this particular series. It should be pointed out that, with exception of those patients having either a positive or nondiagnostic OGTT curve, only one additional patient (number 35) demonstrated

a "probable diabetic" IVTT. The chances of an abnormal IVTT response in a nondiabetic, through laboratory error, would appear to be greater in those patients with relatively low fasting blood sugars because the degree of change to be measured falls within a much more narrowed range. Thus, a minor error would exert a greater effect. This would constitute one of the disadvantages of the IVTT.[7]

In the present study, only five patients presented with a positive history for diabetes. The IVTT appeared to have an equal sensitivity with the OGTT when compared in those patients with an inherited susceptibility. Pote and Paucher[25] found that the IVTT unveiled more positive responses in those patients with a close family history than with a distant or no family history for diabetes. Although this conclusion is logical, the series in the present study was too small to enable one to make similar predictions.

IVTT RESPONSE IN PREDIABETES

Several investigators have experimented with the IVTT as a means of detecting subclinical diabetes. Silver and Matchor[30] report that when the thirty minute response is between 77 and 50 per cent the patient is labled a potential diabetic. Barreto[2] noted that repeating the IVTT in a susceptible individual after eliminating carbohydrate

from the diet for three to seven days may uncover previously unrecognized diabetes. Jackson[17] administered tolbutamide intravenously to subjects believed to be "prediabetic" by various criteria and found increased levels of plasma insulin activity when compared with normal controls. He concluded that the results were consistent with large and probably overactive islet cells during the prediabetic phase.

STEROID PROVOCATIVE IVTT

Barreto and Recant[2] found that two types of distinctly different responses were seen when the IVTT was repeated in normal patients after steroid provocation: (1) one termed normal since it closely resembled the curve of the original response and (2) an abnormal curve faithfully reproducing that seen most often in diabetics. In both groups the initial blood glucose is increased in all cases; the degree of response in the normal steroid-IVTT curve is as great as the original one. These investigators suggested that the term "prediabetic" might be used for those responses indicating decreased insulin stores. This criteria for an abnormal test result includes two of the following three findings: (1) fasting blood sugar greater than 113 mg per cent, (2) a fall of glucose at thirty minutes less than 16 per cent of the pretest level,

and (3) failure of the glucose level at ninety minutes to rise 4 mg per cent above the lowest recorded point.[20] Long, Kito and Recant found an increase in abnormal responses in young subjects with a positive family history for diabetes, in those who were older than sixty years and in patients with peripheral vascular disease or significant obesity. The fact that a positive history was less important in determining the response to an IVTT after the age of forty is pertinent to the present study. Perhaps, as imparted earlier, aging per se results in a progressive impairment of pancreatic or insulin responsiveness. They interpreted the abnormal results as representing already existing diabetes not yet apparent by the OGTT.[20]

ORAL TOLBUTAMIDE TOLERANCE TEST

Boshell, et al,[3] has experimented with the use of oral tolbutamide as a diagnostic test for diabetes to circumvent occasional bouts of syncope and local thrombophlebitis following the IVTT which apparently may happen, but was not experienced in the present study. Four grams of bicarbonate was administered along with the two grams of Orinase to enhance absorption and thereby reduce the likelihood of a false positive test. The blood samples were drawn at thirty and forty minutes since the response

to oral tolbutamide has been shown to lag behind the intravenous route by approximately ten minutes. After making allowances for the time discrepancy, the responses were found to compare favorably with the IVTT curves of Unger and Madison.[39] Boshell advises caution in interpretation of results in those cases with various endocrinopathies, liver disease and starvation.[3]

IVTT IN YOUNGER AGE GROUPS

Di George and Chiowanich[9] experimented with the IVTT in infants and children to evaluate this procedure as a means for discovering early onset of diabetes. They found that the maximal fall in blood glucose occurs at twenty minutes in this younger age group; this result differs from that usually encountered in adults. The difference may be due to the test dose (20mg/kgm) or more likely represents a more rapidly responsive insulin secretory mechanism in the child. Frawley,[12] in earlier experiments, observed no significant hypoglycemia after tolbutamide administration in juvenile diabetics.

IVTT IN PREGNANCY

The occurence of false positive results in the non-diabetic during the last trimester of pregnancy were reported by Chesley, Kaufmann and Pauersteen.[5] This

diabetic response to the IVTT is manifested by a significantly smaller decrease in blood glucose, greater lag in hypoglycemic effect, and absence of significant rebound within one hour. In every case, the hypoglycemic responsiveness to the sulfonylurea is greater during the postpartum period. These authors feel that the placental insulinase (proteolytic) may negate the pancreatropic effect of the tolbutamide.

SUMMARY

Additional experience with the IVTT is necessary before the ultimate usefulness of this diagnostic tool may be ascertained. It constitutes a new parameter for the diagnosis of latent diabetes mellitus and could be a significant supplementary procedure to the various types of carbohydrate-loading tests currently in vogue; the IVTT would seemingly be particularly useful in verifying borderline results obtained with the OGTT. The tolbutamide tolerance test at least permits an evaluation of carbohydrate tolerance unobscurred by the caprices of gastrointestinal absorption which beset the OGTT and is free of the unphysiologic, mass-action effects induced by the rapid intravenous injection of glucose.

At present the IVTT appears to qualify as a reasonably accurate, safe, rapid and not too unpleasant diagnostic

procedure for latent diabetes; it is less sensitive, but more specific (except during pregnancy) than other methods now commonly used to evaluate carbohydrate metabolism. It is naive to expect the IVTT to provide a sharp demarcation between diabetics and nondiabetics since elements of the two groups are bound to overlap. Ultimately, the rigid division in percentile fall, as suggested by Unger[35] and used in this present study, may not stand. With an accumulation of further experience, an alteration in the diagnostic criteria may be desirable.

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