

## Detection of Diabetes Mellitus *In Situ* (Occult Diabetes)

by Joseph R. Kraft, M.D.

In recent years, further development and refinement of technique has permitted reproducible serum insulin determinations to become available for correlation, with plasma glucose levels during tolerance testing. In earlier presentations,<sup>1,2</sup> five basic insulin patterns were identified indicating the absence or presence of diabetes through a wide range of insulin response (diabetic state).

In a number of cases, normal glucose tolerances were associated with abnormal insulin patterns. Such situations, in which the glucose tolerance curve was normal and correlated insulin pattern was abnormal, were considered indicative of pre-diabetes or occult diabetes. In order to focus greater attention upon this, the earliest detectable phase of diabetes mellitus, the term diabetes mellitus *in situ* has been proposed and used interchangeably with occult diabetes throughout this report.

It is the primary purpose of this paper to review basic insulin patterns which develop in the course of standard glucose tolerance testing and indicate the significance of each.

### Methods and Materials

Blood glucose and insulin levels were obtained on 3650 patients randomly referred for glucose tolerance

testing. Specimens were collected after fasting and ½, 1, 2, and 3 hours after a 100 gram oral glucose meal or equivalent in children. Early in the study, the procedure was extended to include fourth-hour specimens. In many cases, the study included fifth-hour examinations upon referring physician request.

Plasma glucose was determined via AutoAnalyzer (ferricyanide method) on the day collected. For the last 500 tolerances, AutoAnalyzer glucose measurement was made by the plasma glucose oxidase method. Specimens for insulin determination were frozen and assayed the following day utilizing the Phadebus Insulin radioimmunoassay test<sup>3</sup> with a 1185 series Automatic Gamma Counting System (Searle Analytic). In our laboratory, frozen insulin specimens provided reproducible results for at least six months. The Phadebus Insulin Test had duplicate procedure precision of 1 Standard Deviation =  $\pm 5$  microunits in measurements up to 150.

Each glucose insulin tolerance assay was plotted graphically and correlated with specimen collection time. The Wilkerson Point System for plasma glucose values as recommended by the American Diabetes Association<sup>4</sup> was used as a reference base for classifying and grouping results (Table 1).

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Time	Mg per 100 ml	Wilkerson Points *
Fasting	130 or more	1
1 hour	195 or more	1/2
2 hour	140 or more	1/2
3 hour	130 or more	1

\* Wilkerson point system. Two or more points are judged diagnostic of diabetes.

### Age, Obesity and Sex Distribution

Of 3650 glucose/insulin tolerances performed, there were 2345 females and 1305 males, ranging in age from 3 to 87 years (mean age of 46.52 years). Two hundred-nineteen were 20 years or younger (mean age = 16.37). There were 1825 in 21-49 age group, with a mean age of 34.48. Of 1606 who were 50 years and older, the mean age was 63.87. Subsequent studies concerning age and detectable phases of diabetes mellitus are pending.

Obesity was considered present in male patients whose actual weight exceeded 115% of their adjusted ideal weight, and in female patients whose actual weight exceeded 66.3kg. (146lbs).<sup>5</sup> Twenty-nine percent of males and 40% of females were obese by these criteria (Table III). Increased incidence of obesity was noted in females at the 3-point range on the Wilkerson scale. Review of the total number of cases failed to demonstrate a significant causal relationship between obesity and diabetes mellitus in this study.

Wilkerson Scale	Male	(Obese)	%	Female	(Obese)	%	Total	(Obese)	%
0	559	(139)	25	1154	(384)	33	1713	(523)	31
1/2	204	(57)	28	301	(139)	46	505	(196)	39
1.	220	(66)	30	276	(132)	48	496	(198)	40
1 1/2	86	(19)	22	140	(65)	46	226	(84)	37
2	139	(60)	43	349	(137)	39	488	(197)	40
3	97	(41)	42	125	(76)	61	222	(117)	53
Total	1305	(382)	29	2345	(933)	40	3650	(1315)	36

Male: Obese: Actual weight >= 115lbs of adjusted ideal weight.  
Female Obese: Actual weight >=146lbs

### Family History of Diabetes

Family history was considered positive when any diabetic relative was noted, regardless of kinship and without differentiation as to age, intensity, duration and/or therapy. When the first several hundred tolerances yielded only 35% positive family histories, less than anticipated, poor family history documentation was suspected. In order to avert this possibility, trained medical technologists were utilized as diabetes history reporters during multiple patient contacts of the tolerance procedure. This evolved as our routine, but such duplicate history inquiry failed to alter significantly the earlier, unassisted findings. There was a positive diabetic family history in 37% of the 3650 patients studied (Table III).

Family history and normal glucose tolerance was judged insufficient to categorize normal in this study.

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Wilkerson Points	N	Positive
NORMAL ZERO (0)	1713	38%
GLUCOSE/INSULIN NORMAL	(568)	(28)%
OCCULT DIABETES	(862)	(34)%
Equivocal (1/2—1 1/2)	1227	35%
Diagnostic (2 and 3)	710	36%
	Total 3650	37%

Wilkerson Glucose Points	Number	Insulin Value	Number	Mean Insulin Value
0	1713*	16.47 (103)	1610*	12.35
1/2	505	8.63 (26)	479	13.87
1	496	17.83 (117)	479	13.56
1 1/2	226	18.98 (13)	213	13.60
2	488	16.60 (20)	468	14.17
3	222	17.79 (198)**	3452	17.68
Total	3650**	17.79(198)**	3452	13.37

\*Includes 568 Normals Mean = 7.52  
\*\*Includes 198 Cases High Fasting >50 Mean = 92.90

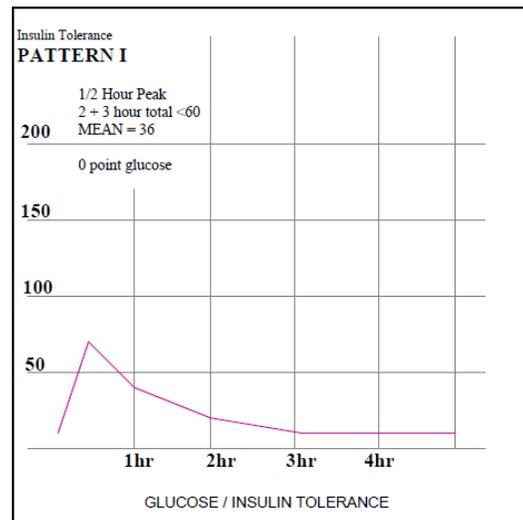
## Results

### *Pattern I – Normal*

Before abnormal patterns could be identified, it was necessary, first, to define the normal fasting insulin range and normal insulin response to glucose. When data on all 3650 cases in our series were analyzed, it became apparent that a small but significant number in each Wilkerson point grouping showed considerably higher fasting insulin values. Accordingly, cases with fasting values greater than 50 microunits (198 or 5%) were separated and will be examined as a group later constituting abnormal pattern IV.

The remaining 3452 cases had a mean fasting value of 13.37 microunits

(Table IV) with a mean range of 7.52 to 17.68 which closely approximated the results of an earlier study examining the initial 2500 tolerances.<sup>1</sup> Applying  $\pm 3$  standard deviations of the procedure (3SD =  $\pm 15$  microunits) to a mean of 15, the selected fasting insulin range was again between 0 and 30 microunits.



**Figure 1A:** Maximum insulin peak occurred at 1/2 hour in 234 (40%) of the normals identifying Pattern I.

Under normal circumstances, insulin peaks within the first hour (either at 1/2 or 1 hour) following glucose loading and this typical pattern was found in cases displaying zero (0) Wilkerson point tolerances (Figs. 1 A and 1B). Thereafter, insulin levels declined sequentially at 2 and 3 hours, returning to fasting range. Thus, the normal insulin pattern seen associated with a normal glucose tolerance test demonstrated the following basic features, which are also graphically displayed in figure 2A:

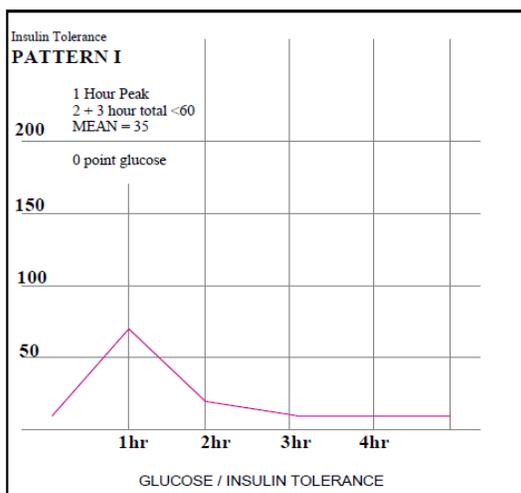
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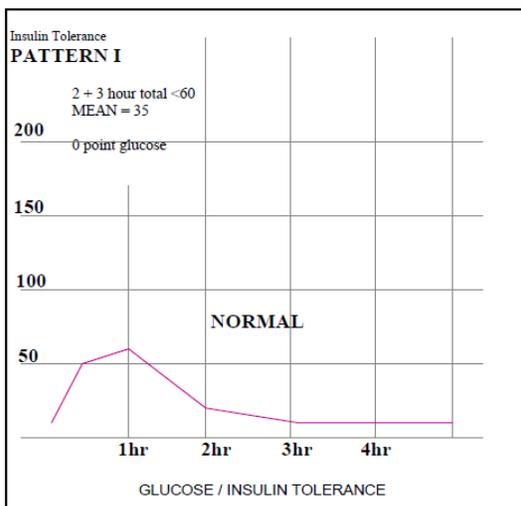
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1. Fasting level between 0 and 30 microunits
2. Peak insulin production at ½ to 1 hour
3. Sequential return to fasting range at 2 to 3 hours
4. Stabilization on the fasting range beyond 3 hours



**Figure 1b:** maximum insulin peak occurred at 1 hour in 334 cases (60%) of the normals identifying Pattern I.



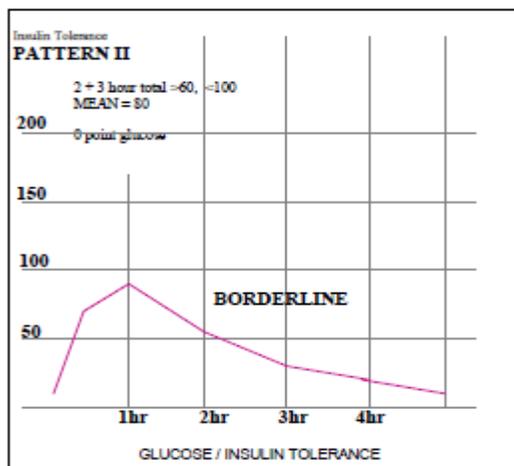
**Figure 2A:** Normal 568 cases with : a. fasting level between 0 and 30 microunits; b. peak insulin at ½ or 1 hour; and c. return to fasting range at two to three hours.

Since variance at second and third hours is also critical in diagnosis of diabetes,<sup>6,7</sup> limits were developed and defined specifically to cover that segment of insulin response. Following normal insulin peak production at ½ to 1 hour, the sum of second and third hour insulins should be 60 microunits or less (i.e., twice the maximum fasting range of 30) in order for the entire response (curve) to be judged unequivocally normal. This was seen in 568 of 1713 cases with zero (0) Wilkerson point tolerances and is illustrated by figure 2A.

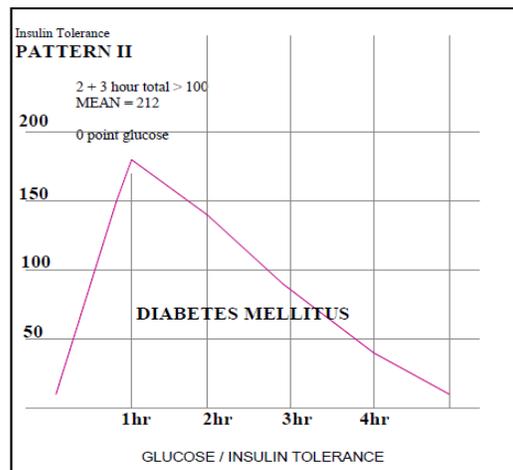
When the sum of second and third hour insulins exceed 60 microunits, but remained below 100 microunits, such responses were considered borderline, and 240 of the zero (0) tolerance cases fell into this category (see Fig 2B). Two and three hour sums greater than 100 microunits were judged to be abnormal insulin delay responses constituting abnormal Pattern II.

### ***Pattern II – Normal Insulin Peak, Delayed Return***

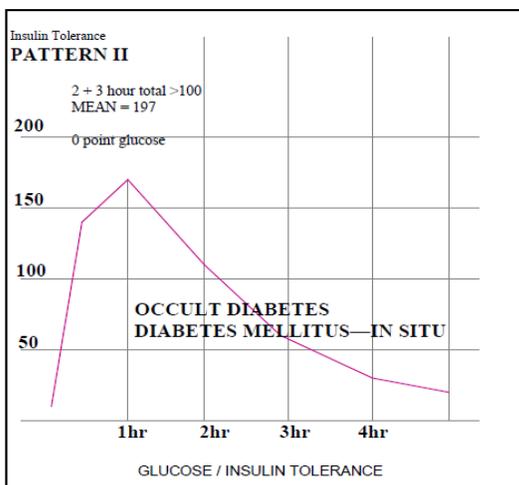
In 1713 cases with zero (0) Wilkerson point tolerances and normal insulin peaks within the first hour, 401 had abnormal second and third hour delay responses with sums greater than 100 microunits (Fig 3A). This same delay insulin response was seen in 595 cases in which ½ or more Wilkerson points were present (Fig 3B). Of the total number of cases examined, 996 or 27% displayed this abnormal pattern diagnostic of diabetes mellitus.



**Figure 2B:** of 1713 zero point tolerances, 240 had borderline delay values with 2 plus 3 hour insulin total values between 60 and 100microunits.



**Figure 3B:** Pattern II- normal peak delayed return: a. demonstrates 2 plus 3 hour insulin total greater than 100 microunits; b. identifies 595 cases of diabetes mellitus with abnormal tolerances (1/2 to 3 Wilkerson points); c. basic pattern display by 996 of 3650 tolerances.

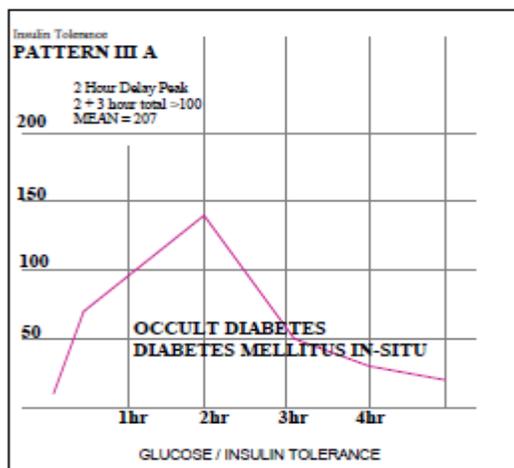


**Figure 3A:** Pattern II- normal peak delayed return: a. demonstrates insulin delay with 2 plus 3 hour insulin total greater than 100 microunits; b. identifies 401 occult diabetics with normal zero point tolerances.

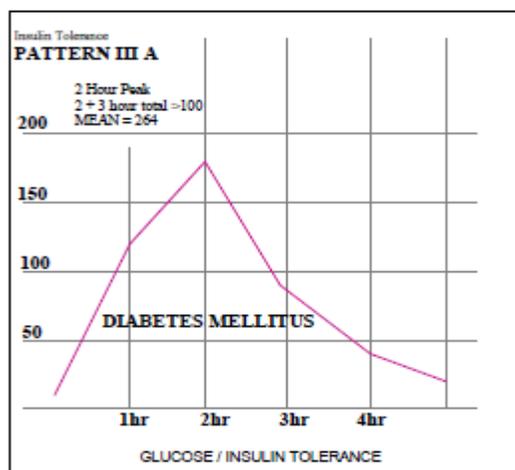
### **Pattern III – Delayed Insulin Peak**

#### **A. Second Hour Peak**

Insulin peaks appearing later than one hour are always abnormal and associated with diabetes mellitus. In our series, 1220 (33%) demonstrated maximum insulin response at the second hour; 292 with zero (0) Wilkerson tolerance points, and 928 with ½ to 3 Wilkerson tolerance points (see Fig. 4A and 4B).



**Figure 4A:** Pattern IIIA- two-hour delayed peak; a. insulin peaks after one hour always are abnormal and associated with diabetes mellitus; b. identifies 292 occult diabetics with normal zero point tolerances.

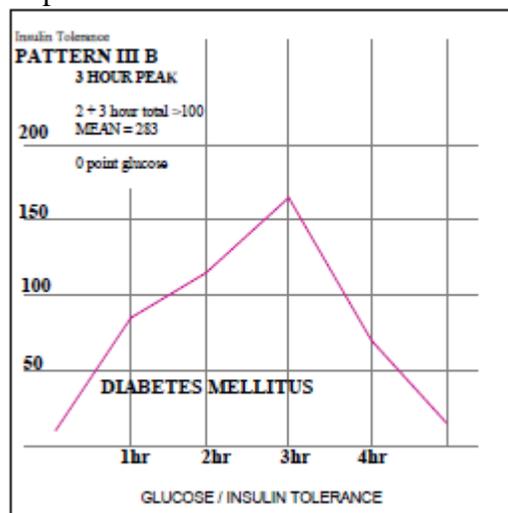


**Figure 4B:** Pattern IIIA- two-hour delayed peak; a. identifies 928 cases of diabetes mellitus with abnormal tolerances (1/2 to 3 Wilkerson points); b. of 3650 tolerances, 1220 displayed this basic pattern.

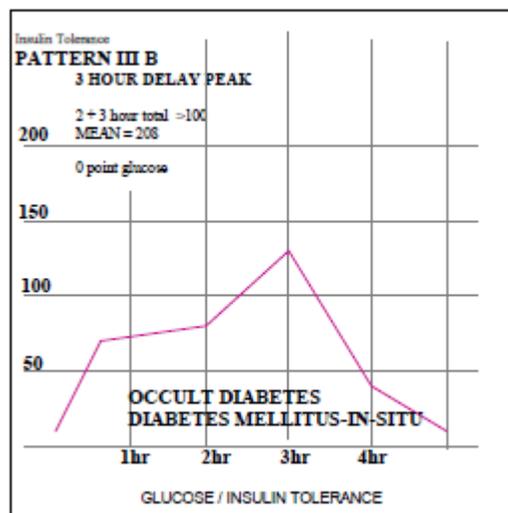
### B. Third Hour Peak.

Of the 3650 cases examined, 297 (8%) with zero (0) or greater Wilkerson tolerance points displayed delay in maximum insulin response until the third hour. Although much less frequent than the two hour delay peak pattern, it was considered equally definitive as a

diagnostic diabetic pattern. This insulin pattern (Figs. 5A and 5B) demonstrated the value of expanding the procedure beyond three hours (four or five hours) in order to illustrate complete insulin response.



**Figure 5B:** three-hour delayed peak; a. although less frequent than Pattern IIIA- two-hour delayed peak, it is equally diagnostic of diabetes; b. identifies 66 occult diabetics with normal zero point tolerances.



**Figure 5A:** Pattern IIIB- three-hour delayed peak; a. identifies 231 cases of diabetes mellitus with abnormal tolerances (1/2 to 3 Wilkerson points); b. of 3650 tolerances, 297 displayed this basic pattern.

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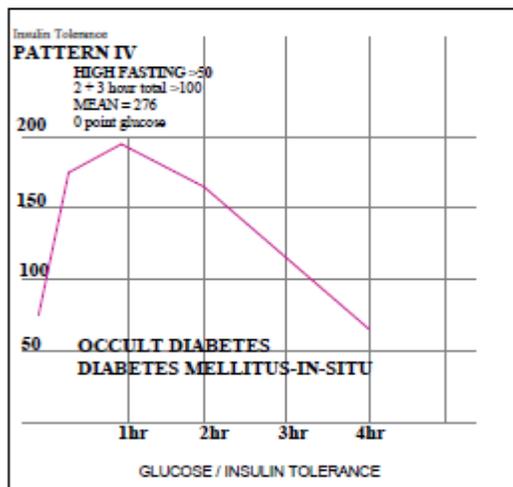
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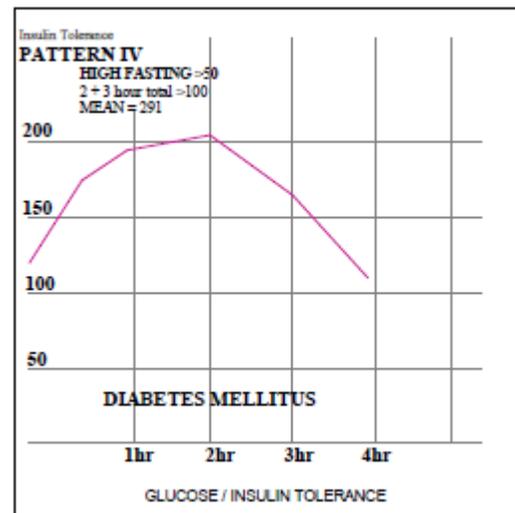
In rare cases (seven), peak insulin response occurred later than three hours after the glucose load was given and were included in this group.

### ***Pattern IV – High Fasting***

In 198 cases (5%) of the total studied, fasting insulin levels were greater than 50 microunits – well above the selected normal range 0 to 30. Slightly more than half (103) were associated with zero (0) Wilkerson tolerance points (Fig. 6A). With exception of two cases having values between 50 and 55 microunits, all demonstrated elevated two and three-hour insulin responses (Figs. 6A and 6B). High fasting insulin levels alone are consistent with diabetes mellitus, and this conclusion was further reinforced by the remarkably high incidence of associated delay insulin return after two and three hours.



**Figure 6A:** Pattern IV- high fasting: a. high fasting is an abnormality, per se, and when associated with increased two-hour and/or three-hour insulins becomes distinctive and thereby a basic pattern; b. identifies 103 occult diabetics with normal zero point tolerances.



**Figure 6B:** Pattern IV- high fasting: a. high fasting may be associated with all basic delay patterns; b. identifies diabetes mellitus in 95 cases with abnormal tolerances (1/2 to 3 Wilkerson points); c. of 650 tolerances, 198 displayed this basic pattern.

### ***Pattern V – Low Insulin Response***

In our series, 131 (4%) of the assays had insulin responses in which all values were below 30 microunits, e.g., within the designated normal fasting range. Low insulin response was further subdivided on the basis of respective glucose tolerances into two groups – those associated with 2 and 3 Wilkerson points and those with zero (0) to 1 ½ Wilkerson points.

#### **A. Low Insulin, High Glucose.**

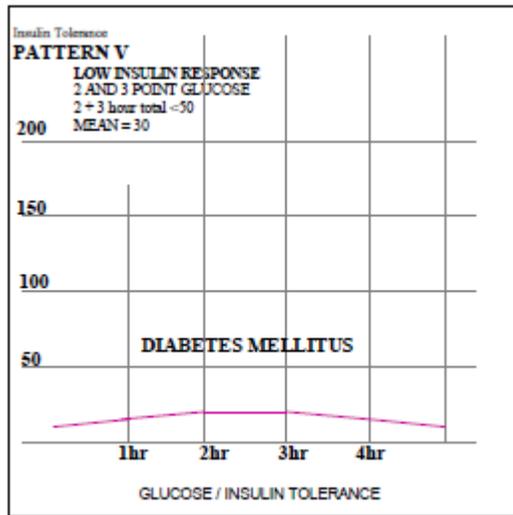
Approximately one-half (62) of the low insulin cases were associated with clearly abnormal glucose tolerances according to the Wilkerson point system (Fig. 7A). This situation was consistent with the insulinopenic or so-called “juvenile” response pattern indicative of significantly reduced insulin production and requiring insulin replacement therapy.

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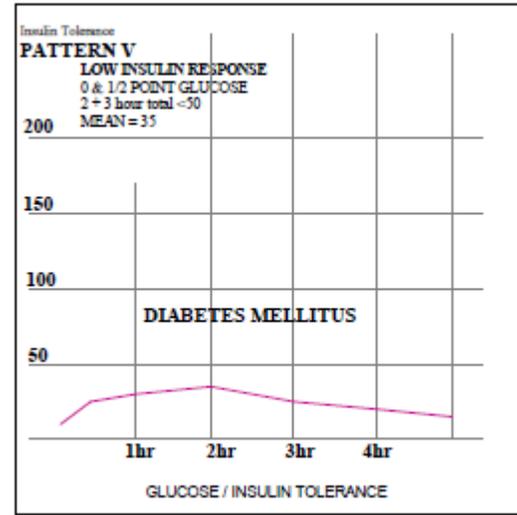
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**Figure 7A:** Pattern V- low insulin response: a. insulinopenic or so-called juvenile response pattern in Wilkerson point 2 and 3; b. indicative of significantly reduced insulin production.



**Figure 7B:** Pattern V- low insulin response: a. all assay values are within normal fasting range of 0 to 30 microunits; b. in the absence of pancreas gland dysfunction, low insulin is indicative of low caloric/carbohydrate diet preparation and/or management.

## B. Low Insulin, Normal to Borderline Glucose.

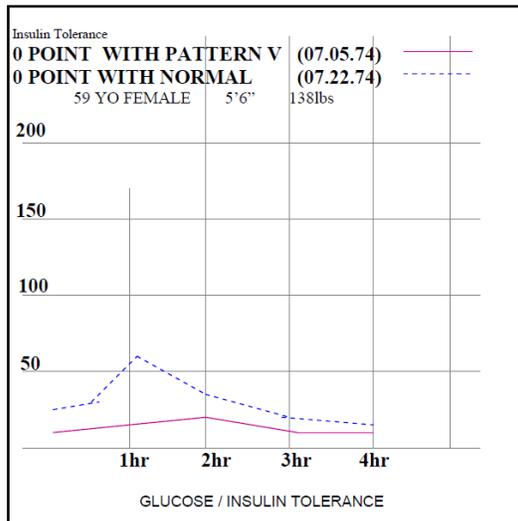
The remaining low insulin cases were divided between those with normal glucose values (43) and borderline glucose elevations (26) (Fig. 7B). The apparent paradox of insulinopenic pattern associated with normal to borderline glucose tolerance did not allow immediate differentiation into either normal or diabetic state. In the absence of pancreatic gland dysfunction, such as insulin pattern suggested low carbohydrate diet preparation and/or management.

In these cases, standard high carbohydrate diet preparation for two or more weeks followed by repeat tolerance examination was necessary to uncover the true insulin response pattern. Figure 8A illustrates a flat insulin response pattern which became normal following high carbohydrate preparation. It was not possible purely on the basis of the initial tolerance test to predict whether the subsequent insulin response would be normal, borderline or delayed.

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**Figure 8A:** Dietary response/ Low insulin response, Pattern V to normal.

***Standard Glucose Tolerance vs  
Combined Glucose/ Insulin Tolerance  
(Table V)***

Table V—Standard Glucose Tolerance. Glucose/ Insulin Tolerance		
Standard Glucose Tolerance	Glucose / Insulin Tolerance	
N = 3650		
Normal (0 Wilkerson Point) 47% N = 1713	2.5%	Low Insulin N = 43
	33%	Normal N = 568
	14%	Borderline N = 240
	50%	Diabetes N = 862
Equivocal (1/2, 1, 1 1/2 Wilkerson Point) 34% N = 1227	10%	Non-Diabetes N = 122
	90%	Diabetes N = 1105
Diabetes (2 and 3 Wilkerson Point) 19% N = 710	100%	Diabetes N = 710

A. Normal Glucose Tolerance (0 Wilkerson Points).

Of 1713 tolerances which would have been considered normal on the basis of Wilkerson points, 50% (862) demonstrated insulin patterns consistent with diabetes mellitus in situ. One-third (568) had completely normal insulin values, 14% (240) were in the borderline range and 2.5% (43) were associated with low insulin response patterns.

B. Equivocal Glucose Tolerance ( 1/2 - 1 1/2 Wilkerson points).

In 1227 cases with equivocal glucose tolerances, correlated insulin determination differentiated between typically non-diabetic and diabetic insulin responses. All 1 1/2 point glucose tolerances were associated with clearly diabetic insulin patterns. The remaining cases with abnormal glucose values ( 1/2 to 1 Wilkerson point) and normal insulin patterns were most frequently associated with “gastric dumping” seen in connection with gastric resection, nonsurgical upper gastrointestinal pathology, and functional alimentary hyperglycemia. Additional cases with equivocal glucose tolerances and normal insulin response occurred in the presence of hepatopathy (hepatitis).

C. Diabetic Glucose Tolerance.

For every positive glucose tolerance (2 to 3 Wilkerson points) the correlated insulin pattern confirmed the diagnosis of diabetes. In these cases, as in the Wilkerson normal and equivocal tolerances, insulin assay provided information regarding:

1. The character of initial insulin response

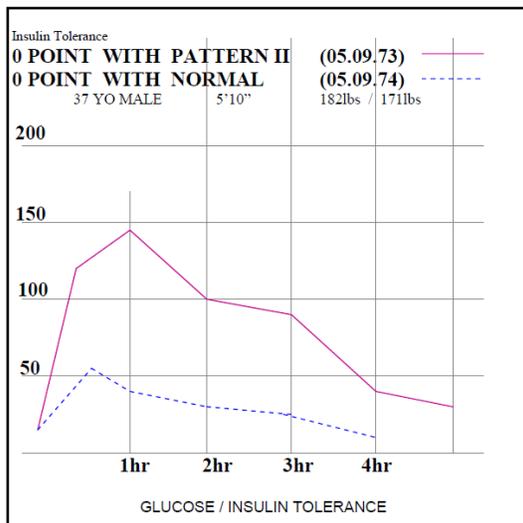
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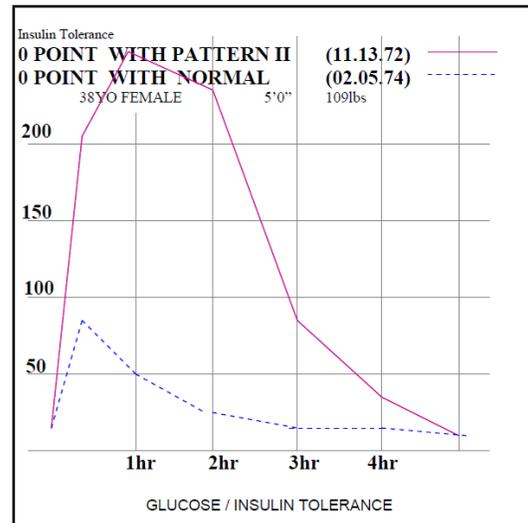
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2. Baseline data for rational classification, therapy and prognosis
3. Evaluation of dietary and/or oral hypoglycemic management.

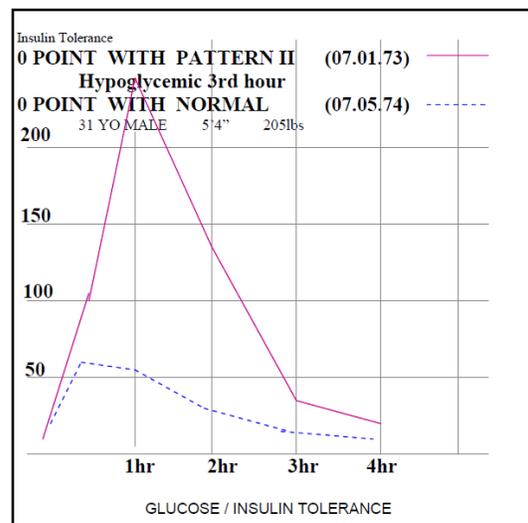


**Figure 8B:** Dietary management. Diabetes mellitus in situ to normal.

Demonstration that alteration of carbohydrate intake could affect insulin response has been used to monitor effectiveness of diet in diabetic management programs. Figs. 8B, 9A and 9B are examples taken from patients with diabetes mellitus in situ who were placed on low carbohydrate diets and re-evaluated after one year. All changed to an entirely normal pattern and only in one instance was there appreciable weight reduction [5kg (11lb.)]. The fact that diet alters insulin pattern was further supported by the case illustrated in Fig. 10A in which a low carbohydrate diet was followed by a typical low insulin response.



**Figure 9A:** Dietary management. Diabetes mellitus in situ to normal.



**Figure 9B:** Diabetes mellitus in situ to normal.

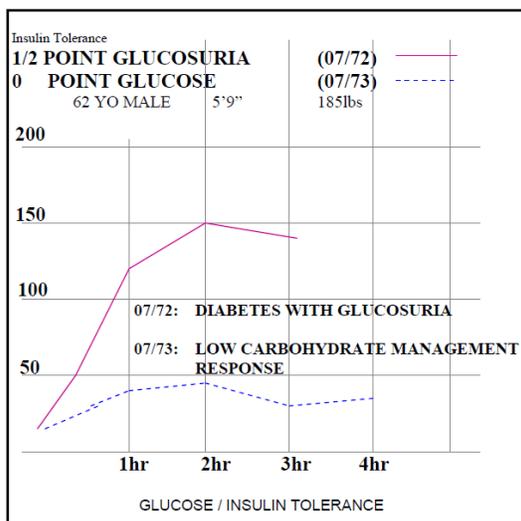
This study consistently failed to support the classification of diabetes mellitus into juvenile or adult (maturity) onset types based on patient's age at onset. Classification based upon glucose/insulin tolerance testing utilizing Wilkerson points and insulin pattern scoring (Table VI) is proposed as a more

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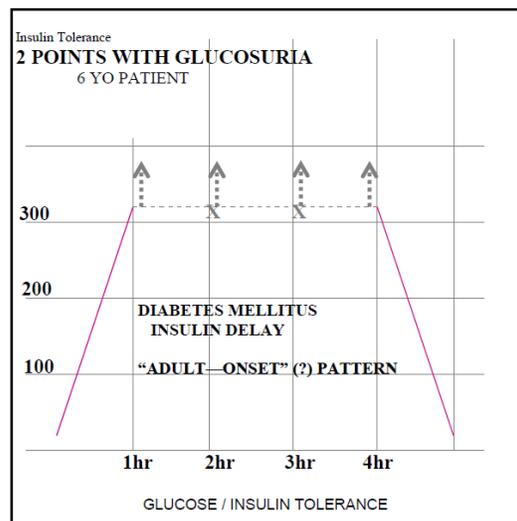
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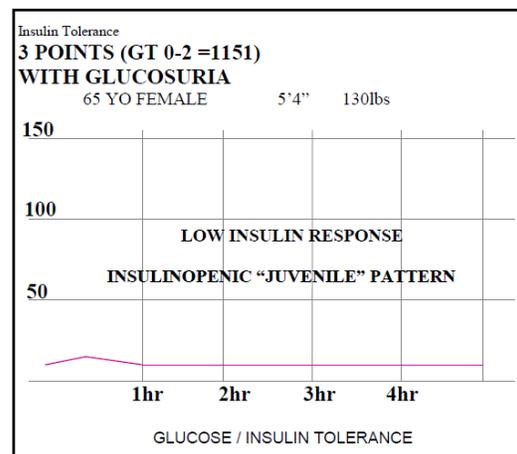


**Figure 10A.** Dietary management. Diabetes mellitus ½ point glucose/insulin Pattern IIIA to 0-point glucose/insulin Pattern V.

reliable means of assessing insulin dependency. This is best illustrated in Figs. 10B and 10C in which glucose/insulin tolerance studies of a six-year-old male with insulin delay (diabetes mellitus – 2 point glucose/insulin Pattern II) and a 65yo female with insulinopenia (diabetes mellitus – 3 point glucose/insulin Pattern V) are presented. Two-year follow-up of the child revealed a glucose/insulin tolerance of 1 ½ points Pattern II.



**Figure 10B:** Diabetes mellitus. Two-point glucose/insulin Pattern II.



**Figure 10C:** Diabetes mellitus. Three-point glucose/insulin Pattern V.

Table VI—Insulin Patterns.	
<p><b>Pattern I—Normal</b></p> <ul style="list-style-type: none"> <li>• 30min or 1 hour peak value</li> <li>• 2nd hour less than 50 microunits</li> <li>• 3rd hour less than 2nd hour</li> <li>• 2nd hour plus 3rd hour values sum less than 60 microunits</li> <li>• Subsequent hour values at fasting range (0-30 microunits)</li> </ul>	<p><b>Pattern III—A</b></p> <ul style="list-style-type: none"> <li>• Second Hour Delay Peak</li> </ul> <p><b>Pattern III—B</b></p> <ul style="list-style-type: none"> <li>• Third Hour Delay Peak</li> </ul> <p><b>Pattern IV</b></p> <ul style="list-style-type: none"> <li>• High Fasting &gt;50 microunits</li> </ul>
<p><b>Pattern II—Normal Peak, Delayed Return</b></p> <ul style="list-style-type: none"> <li>• 3 hour total &gt;60 and &lt;100 = borderline value range</li> <li>• 3 hour peak &gt; 100 = abnormal value</li> </ul>	<p><b>Pattern V</b></p> <ul style="list-style-type: none"> <li>• Low Insulin Response</li> <li>• High Value &lt; 30 microunits</li> </ul>

The glucose/insulin tolerance test also has assisted in evaluating patient cooperation, failure of dietary and/or hypoglycemic management, and biologic progression of the disease. Fig. 11 A illustrates progression in a 60yo female from normal (0 point Pattern I) to diabetes mellitus in situ (0 point Pattern II) to diabetes mellitus (½ point Pattern IIIA).

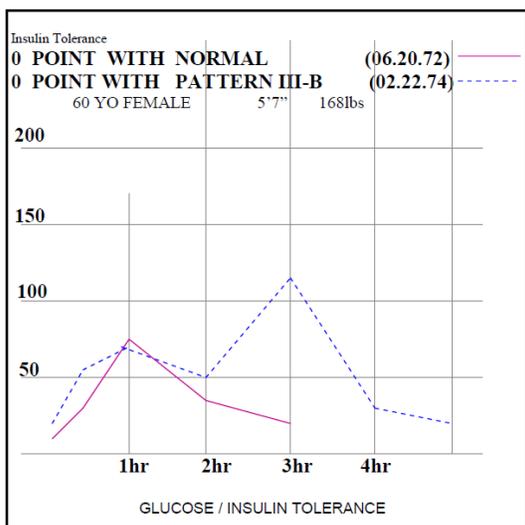
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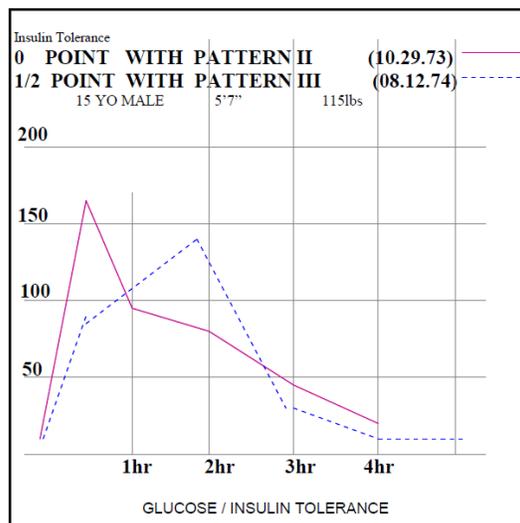
In patients who have received insulin therapy, glucose/insulin tolerance testing may be clinically useful. However, patients who have insulin antibodies may have false high results, greater than 320 microunits in all measurements including fasting. Procedures utilizing adsorption to charcoal for separation conversely give false low (0) results. A method for determining plasma insulin in the presence of endogenous insulin antibodies has been described.<sup>8</sup>



**Figure 11A:** Progression. Normal 0-point glucose/insulin Pattern I to diabetes mellitus in situ.

## Discussion and Conclusions

In order for the glucose/insulin tolerance test to provide the greatest yield, the procedure should be conducted at least over a four-hour period. In selected cases, five-hour testing may be of benefit.



**Figure 11B:** Progression. Diabetes mellitus in situ, 0-point glucose/insulin Pattern II, to diabetes mellitus 1.2 point glucose/insulin Pattern IIIa.

No causal relationship between obesity and diabetes mellitus was shown in this study.

Although stringent pedigree studies were not applied, duplicate historical information revealed a positive family diabetic history in 37% of all cases while 73% demonstrated diabetic insulin patterns. It should be noted that the random population studied was heavily weighted with patients suspect of diabetes referred specifically for identification. Prospective evaluation of relatives of known diabetics is in progress.

Negative family history and a normal tolerance was judged insufficient to identify normal in this study. Normal was clearly defined on the basis of insulin response patterns (Pattern I) correlated with a normal glucose tolerance.

Insulin Patterns II, III and IV are diagnostic of diabetes mellitus. Pattern V

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(low insulin response) when seen in association with clearly abnormal glucose tolerances unequivocally established insulinopenic (“juvenile”) diabetes requiring replacement therapy.

Patterns V, when seen associated with normal or borderline glucose tolerance, suggested low carbohydrate diet. These cases did not allow categorization into diabetic or non-diabetic state. Such differentiation was possible if the glucose/insulin tolerance was repeated after two weeks of high carbohydrate diet.

Diabetes mellitus in situ was characterized by normal glucose tolerance associated with abnormal insulin tolerance. Identification of this phase of diabetes has far-reaching clinical implications.

The ability to rationally interpret insulin response to a glucose load, separating normal and abnormal patterns, has distinct investigative merit, but has practical clinical significance as well. For this reason the term “diabetes mellitus in situ” has been adopted

because it embodies the concept of disease detection at its earliest identifiable point – a period during which maximum potential benefit might be anticipated through appropriate management. This study has shown that dietary carbohydrate control alone can change the insulin response pattern in cases of diabetes mellitus in situ.

Recent observations with animals<sup>9,10</sup> and humans<sup>11,12</sup> lend support to the concept that adequate diabetes control during early phases can reverse vascular changes. Additional investigations in our laboratory are concerned with determining whether or not normalization of insulin response is associated with delay in vascular changes and progression of the disease.

Finally, since a significant number of patients with normal glucose tolerances were shown to have diabetes mellitus in situ, the reliability of the glucose tolerance test alone as a means of assessing presence or absence of disease must be reevaluated.

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