Do the Oral and Intravenous Glucose Tolerance Tests Provide Similar Diagnostic Information in Patients with Chemical Diabetes Mellitus?

Jerrold M. Olefsky, M.D., John W. Farquhar, M.D., and Gerald M. Reaven, M.D., Palo Alto

SUMMARY

In order to evaluate the diagnostic reliability of the oral glucose tolerance test (OGTT) and the intravenous glucose tolerance test (IVGTT), the results of these two tests have been compared both to each other as well as to a third test of carbohydrate tolerance termed the pancreatic suppression test (PST), in forty-five subjects. When results of the IVGTT and OGTT are compared, there is a 40 per cent incidence of discordance in the diagnosis of diabetes mellitus. There is no significant correlation between the results of the PST and the IVGTT, but a significant correlation is obtained between results of the PST and the OGTT ($P < 0.01$). Furthermore, the PST could not detect differences between patients classified as normal or diabetic on the basis of the IVGTT, but differences could be detected between subjects divided into diabetic or normal on the basis of the OGTT ($P < 0.001$). Although neither test is an ideal diagnostic tool, our results suggest that the OGTT is more meaningful than its counterpart in estimating the efficiency of glucose disposal in patients with mild abnormalities of glucose tolerance. DIABETES *22*:202-09, March, 1973.

In recent years, increasing efforts have been made to diagnose diabetes mellitus in patients before they have developed symptoms, and when they are still capable of maintaining fasting euglycemia. To accomplish this, clinicians have commonly defined patients as being diabetic on the basis of their response to the challenge of an acute glucose load. The glucose has been administered by either the oral or intravenous route, and depending upon the height and rate of fall of the plasma glucose concentration, the patient is classified as diabetic or normal. Although this approach has obviously led to an increase in the frequency with which diabetes mellitus is diagnosed, it is not equally clear that all patients thus diagnosed have diabetes mellitus.[1-5] For example, it is apparent that considerable difference still exists in terms of how the tests are performed and what the criteria are for normal or abnormal.[1,4] Thus, depending upon the criteria used, the number of individuals with diabetes in a given population can vary from 0.5 to 25 per cent.[4,6-10] Furthermore, it has been shown that a large proportion of patients in whom diabetes mellitus has been diagnosed by an abnormal tolerance test can have subsequent normal tests,[3,4] and that many patients with a "diabetic" glucose tolerance test do not demonstrate significant decompensation of their glucose tolerance with time.[2,4] Thus, the significance of designating asymptomatic individuals with fasting euglycemia as being diabetic on the basis of a glucose tolerance test is not clear. Obviously, the ultimate clinical significance of an abnormal glucose tolerance test will depend upon further study of such patients and it would seem crucial in such studies to use tests that provide the most representative measurement of the phenomenon being tested specifically, the efficiency of an individual's ability to dispose of a glucose challenge. In this regard, it is not clear whether or not the two tests most commonly used—the oral glucose tolerance test (OGTT) and the intravenous glucose tolerance test (IVGTT)—provide similar information about the carbohydrate tolerance of any given individual.

In order to answer this question, we have performed both oral and intravenous tolerance tests on forty-five patients and examined the relationship between these two tests in this group of patients. In addition, we have

From the Stanford University School of Medicine, and the Palo Alto Veterans Administration Hospital, Palo Alto, California 94304.

Address reprint requests to: Gerald M. Reaven, M.D., Veterans Administration Hospital, Medical Service, 3801 Miranda Avenue, Palo Alto, California 94304.

Accepted for publication October 27, 1972.

evaluated the efficiency with which these same patients disposed of a glucose load by a third method, and have compared the results of this method with those of the oral and intravenous glucose tolerance tests. The data to be presented indicate that there was a high incidence of diagnostic disagreement when the results of oral and intravenous glucose tolerance tests were compared, and that estimates of glucose disposal efficiency derived from the oral glucose tolerance tests correlated to a significantly greater degree than did the intravenous tolerance tests with the results of the third test employed.

MATERIALS AND METHODS

Patients. The patient population consisted of forty-five subjects referred to the Metabolism Clinic at Stanford University Hospital, consisting primarily of patients thought to have some form of hyperlipoproteinemia or diabetes, or a family history of atherosclerotic heart disease and/or diabetes mellitus. Thus, the study group was composed of patients in whom the possibility of chemical diabetes could be suspected on clinical grounds, or, in other words, the kinds of patients in whom glucose tolerance tests are usually performed. In addition to these clinical criteria, patients were selected on the basis of their willingness to participate in the study, and absence of fasting hyperglycemia, marked obesity, or other endocrine disease. A summary of some relevant clinical data can be seen in table 1.

Protocol. All studies were performed within a single week on inpatients at the Stanford General Clinical Research Center. Patients consumed at least 240 gm. of carbohydrate for several days prior to any study, and were taking no medication which might affect carbohydrate metabolism. Three different methods were used to evaluate glucose tolerance: the oral glucose tolerance test (OGTT), the intravenous glucose tolerance test (IVGTT) and the pancreatic suppression test (PST). The order of administering the OGTT and IVGTT was randomized, and the PST was always performed last. Details of the test procedures are given below.

OGTT's were performed by the administraton of 40 gm. glucose/m^2 as a lemon-flavored dextrose solution brought to a volume of 300 ml. with distilled water and consumed within ten minutes. Blood was drawn for measurement of plasma glucose concentration before and 30, 60, 120, and 180 minutes after receiving the dextrose solution. The results were expressed in three ways: (a) the two hour plasma glucose concentration (2 hr. PG), (b) the mean weighted glucose response (MWGR),* and (c) classification as normal or diabetic according to the criteria of Fajans and Conn.[6] The latter criteria have recently been adjusted by the American Diabetes Association[10] for measurement of plasma glucose and administration of an oral glucose challenge of 40 gm./m^2. IVGTT's were performed by the administration of 0.5 gm. glucose/kg. as a rapid intravenous infusion within three minutes. Blood samples for determination of plasma glucose concentration were drawn before and 1, 3, 5, 10, 20, 30, 40, 60, and 120 minutes following the end of the infusion. Glucose disappearance constants (K values) were calculated for each patient according to the method of O'Sullivan et al.,[11] in which the K value is calculated by the method of least squares from the log transformed plasma glucose values. With the following exceptions, data points from ten to sixty minutes were used: (a) if the ten-minute sample is 50 mg. higher than would be predicted from the slope of the subsequent values (indicating incomplete mixing), then the twenty-minute value is the first one used;

*MWGR is the area under the OGTT curve calculated by summing the areas of the successive trapezoids described by the curve and then dividing by the time in hours, i.e.

$$\frac{T_0 + T_{30}}{4} + \frac{T_{30} + T_{60}}{4} + \frac{T_{60} + T_{120}}{2} + \frac{T_{120} + T_{180}}{2} \div 3$$

where T_0 = fasting plasma glucose value, T_{30} = thirty-minute value, etc.

TABLE 1
Pertinent clinical data of the forty-five subjects studied

	Subjects	Age	Height (in.)	Weight (lb.)	Relative Weight*
Men	33				
mean		47.6	69.3	179.4	1.02
range		(27-61)	(65-74)	(121-251)	(0.77-1.27)
Women	12				
mean		41.2	64.3	158.8	1.10
range		(24-61)	(59-68)	(121-184)	(0.81-1.20)
Total	45				
mean		45.9	68	174	1.04
range		(24-61)	(59-74)	(121-251)	(0.77-1.27)

* Relative weight is the subject's actual weight divided by his ideal weight (as determined by Metropolitan Life Insurance Tables).

(b) if the plasma glucose concentration returns to the fasting value prior to sixty minutes, then the first value below 100 mg./100 ml. is used as the endpoint; (c) if prior to sixty minutes two successive values show < 5 mg./100 ml. difference, then the first of these is used as the endpoint. K values less than 1.2 were considered to be diagnostic of diabetes mellitus.[12-16] The pancreatic suppression test (PST) is performed by simultaneously infusing constant amounts of crystalline pork insulin (50 mU./min.) and glucose (6 mg./kg. body weight/min.), while endogenous insulin secretion is suppressed by low doses of epinephrine (6 μg/min.) and propranolol (0.08 mg./min.). The infusion is administered via a Harvard pump over a period of 150 minutes. The infusion is begun five minutes after a 5 mg. loading dose of propranolol, and steady state conditions are achieved within sixty minutes. Blood samples for determination of plasma glucose and immunoreactive .insulin concentrations are drawn every ten minutes during the final sixty minutes of the steady state. With this technic, it has been shown that endogenous insulin and glucose production are inhibited,[17] and similar steady state levels of plasma insulin are reached in all subjects. Under these conditions, the steady state plasma glucose (SSPG) concentration reached is a measure of the efficiency of a subject's ability to dispose of a constantly infused glucose load. We have previously suggested the word impedance as an apt term to describe the degree of inefficiency of glucose disposal under steady state conditions.[17] The results are expressed as the mean of the plasma glucose concentration, based on the seven samples drawn during the steady state.

Analytical methods. Samples for plasma glucose were collected in potassium oxalate-sodium fluoride tubes, and measured by the Technicon AutoAnalyzer using the ferricyanide method of Hoffman.[18] Plasma immunoreactive insulin was determined by a modification of the method of Hales and Randle,[19] using I-125 insulin and insulin binding reagent obtained from Schwarz Bioresearch, Orangeburg, N.J.

RESULTS

Table 2 presents the mean (± S.E.) results of both the oral and intravenous glucose tolerance tests when the subjects are divided into normal and abnormal on the basis of either the OGTT (upper rows) or the IVGTT (lower rows). It is apparent that when subjects are divided on the basis of the OGTT, their mean K values are not strikingly different, and just reach statistical significance. Likewise, when the subjects are divided on the basis of the IVGTT, their mean OGTT results reveal no differences at the fasting, thirty minute, and 180 minute intervals and only marginal differences at the sixty minute and 120 minute intervals. This suggests that in a single individual the two tests are not providing precisely the same information. To further examine these relationships, we have looked at the degree of correlation between the four measures of carbohydrate tolerance that were obtained from each patient, and these results are seen in table 3. The highest correlation was noted between the plasma glucose concentration two hours after receiving the oral glucose load (2 hr. PG) and the mean weighted plasma glucose response (MWGR) to oral glucose. This degree of correlation suggested that these two methods of estimating the ability of patients to dispose of an oral glucose load gave comparable information. Somewhat less striking, but statistically significant, correlation coefficients were also noted between the glucose disappearance constant (K value) observed after intravenous glucose and both estimates (2 hr. PG and MWGR) of glucose disposal rates following oral glucose. Furthermore, as is also seen in table 3, both estimates (2 hr. PG and MWGR) of glucose disposal generated by the OGTT had a statistically significant correlation with the steady state plasma glucose (SSPG) concentration. In contrast, the K value did not correlate with the SSPG. There is no obvious explanation for the lack of correlation between estimates of glucose disposal rate derived from an acute intravenous glucose challenge (K) as compared to estimates of glucose disposal based upon the response to a continuous intravenous infusion of glucose (SSPG).

Although the above results indicated that there was an overall correlation between estimates of glucose disposal derived from the use of the OGTT and IVGTT, inspection of the individual test results indicated that there was great variation in the estimates of carbohydrate tolerance provided by these two tests in any single patient. With this in mind, it seemed reasonable to anticipate that there would also be considerable diagnostic disagreement when the IVGTT and the OGTT were used to determine whether an individual patient was normal or diabetic. This prediction is borne out by the data in table 4 and figure 2, which display the relative frequency of concordance and discordance between diagnoses made on the basis of one test as compared to the other. From table 4, it can be seen that both tests were normal in eighteen (40 per cent) of subjects and both abnormal in nine (20 per cent), with an overall con-

TABLE 2

Mean (± S.E.) results of the oral and intravenous glucose tolerance tests when subjects are divided into normal and abnormal on the basis of one of these tests

Subjects divided into normal and abnormal on the basis of the OGTT*						
	Glucose concentration (mg./100 ml.) during OGTT					
	Fasting	30 min.	60 min.	120 min.	180 min.	
Abnormal (N = 15)	103 ± 2.2 ‡	191 ± 6.7 §	220 ± 7.1 §	178 ± 8.4 §	107 ± 8.0 §	
Normal (N = 30)	96 ± 1.4	156 ± 4.6	153 ± 5.4	108 ± 4.2	85 ± 3.1	
	Glucose concentration (mg./100 ml.) during IVGTT					
	10 min.	20 min.	30 min.	40 min.	60 min.	K Value (%)
Abnormal (N = 15)	341 ± 8.5	290 ± 9.8	248 ± 7.4	227 ± 7.2	190 ± 8.4	1.13 ± .08 †
Normal (N = 30)	303 ± 6.9	257 ± 5.7	219 ± 5.5	196 ± 5.4	154 ± 5.2	1.36 ± .07
Subjects divided into normal and abnormal on the basis of the IVGTT‖						
	Glucose concentration (mg./100 ml.) during OGTT					
	Fasting	30 min.	60 min.	120 min.	180 min.	
Abnormal (N = 21)	99.6 ± 2.3 N.S.	168 ± 7.1 N.S.	187 ± 9.8 †	147 ± 10.3 †	95 ± 5.5 N.S.	
Normal (N = 24)	97 ± 1.2	168 ± 5.7	165 ± 8.1	118 ± 6.8	90 ± 5.1	
	Glucose concentration (mg./100 ml.) during IVGTT					
	10 min.	20 min.	30 min.	40 min.	60 min.	K Value (%)
Abnormal (N = 21)	311 ± 9.1	269 ± 7.6	243 ± 7.1	223 ± 6.4	188 ± 5.9	.98 ± .02 §
Normal (N = 24)	320 ± 7.5	266 ± 7.9	216 ± 5.4	192 ± 5.6	147 ± 5.7	1.56 ± .03

* Criteria for abnormality were 1 hr. plasma glucose > 185 mg./100 ml. and 2 hr. plasma glucose > 140 mg./100 ml.[6,10]
† $P < .05$
‡ $P < .01$
§ $P < .001$
‖ K value of 1.2 per cent was considered the lower limit of normal.[12-16]

cordance of 60 per cent. However, six (13 per cent) of the subjects had an abnormal OGTT with a normal IVGTT, and twelve (27 per cent) had a normal OGTT with an abnormal IVGTT for an overall discordance of 40 per cent. Thus in twenty-seven of forty-five subjects the two tests gave similar diagnoses, while in eighteen of forty-five subjects the diagnoses disagreed.

Figure 1 pictorially displays the agreement-disagreement frequency within either group of abnormal tests. It can be seen that if the results of one test are abnormal, then the chance of having the second test ab-

TABLE 3

Correlations between the results of the oral and intravenous glucose tolerance tests and the pancreatic suppression test

Studies compared	Correlation coefficient r	p
2 hr. PG vs. MWGR	0.87	0.001
K value vs. 2 hr. PG	−0.38	0.02
K value vs. MWGR	−0.43	0.005
2 hr. PG vs. SSPG*	0.47	0.005
MWGR vs. SSPG	0.39	0.01
K value vs. SSPG	−0.24	NS

* This number represents the mean plasma glucose concentration of seven samples obtained during the period of the steady state.

TABLE 4

Comparison of diagnoses based upon results of the oral and intravenous glucose tolerance tests in the same subjects

	Number	%
Both tests normal	18	40
Both tests abnormal	9	20
OGTT abnormal, IVGTT normal	6	13
OGTT normal, IVGTT abnormal	12	27
Total Agree	27	60
Total Disagree	18	40

normal is not much different than 50-50. Clearly the results show a great disparity in diagnostic accuracy, and although a statistical correlation was found between the K values and the OGTT results of the group as a whole, for an individual patient a consistent diagnosis cannot be predicted from either test. Finally, this conclusion is not a function of the particular criteria being used. For example, if a K value of 1.0 is used (instead of 1.2), as the lower limit of normal, the results are essentially the same, i.e. 25 per cent of the subjects have an abnormal OGTT and a normal IVGTT, and 10 per cent have a normal OGTT and an abnormal IVGTT. Thus, the overall discordance of 35 per cent is quite similar to the 40 per cent discordance noted in table 4.

These results indicate that patients who dispose of an intravenous glucose load in an abnormal fashion may dispose of an oral glucose load normally, and vice versa. Thus it is apparent that the two tests give conflicting diagnostic information. In an effort to see which one might be providing the more accurate estimate of glucose disposal, we have made the following comparisons. The subjects were divided into two groups, diabetic or normal, first on the basis of the results of the OGTT and then on the basis of the results of the IVGTT. We then compared the plasma glucose response of the two groups to the continuous infusion of exogenous insulin, glucose, epinephrine and propranolol (PST). These results are illustrated in figure 2A, which shows that the mean plasma glucose level during the PST was significantly higher in subjects with abnormal OGTT's as compared to subjects with normal OGTT's. The mean ($\pm$ S.E.) SSPG level of subjects with abnormal OGTT's was 228 $\pm$ 15 mg./100 ml., as compared to a mean of 159 $\pm$ 12 mg./100 ml. for patients with a normal OGTT. This difference was highly significant at the $P < 0.005$ level. Since figure 2B indicates that circulating levels of insulin were similar in both groups of patients, the higher mean SSPG level in patients with diabetic OGTT's can only be due to a decrease in their ability to dispose of a glucose load. In contrast, the mean glucose response during the PST was not significantly different when the subjects with abnormal IVGTT's (186 $\pm$ 18 mg./100 ml.) were compared to those with normal IVGTT's (173 $\pm$ 13 mg./100 ml.). Since insulin levels were comparable (figure 2B), these results indicate that patients diagnosed as being diabetic on the basis of an IVGTT disposed of a glucose load during the PST as well as subjects with a normal IVGTT. As before, these results are not changed by changing the criteria. The mean ($\pm$ S.E.) SSPG of subjects with K values < 1.0 per cent is 194 $\pm$ 28 mg./100 ml. as compared to a mean ($\pm$ S.E.) SSPG of 178 $\pm$ 11 mg./100 ml. for those subjects with K values > 1.0 per cent. These values are not significantly different and re-emphasize the fact that subjects with an abnormal IVGTT (in this instance $K < 1.0$ per cent) dispose of a glucose load during the PST as well as subjects with a normal IVGTT ($K > 1.0$ per cent).

DISCUSSION

It is apparent from our data that there is a high incidence of disagreement when the diagnosis of diabetes mellitus is made on the basis of an OGTT as compared to an IVGTT. Even though there was a statistically significant overall correlation between the two methods of estimating glucose disposal, the two tests gave different diagnostic information 40 per cent of the time. This observation is not unique to us, and several workers have previously documented the high degree of discordance when these two tests are used to make the diagnosis of diabetes mellitus.[14,16,20-22] Although there seems to be some agreement that the two tests give different answers, there is significant disagreement over which test provides the most accurate estimate of efficiency of glucose disposal. To add to the confusion is the observation that in some instances the discordance is attributed to the combination of normal OGTT's and abnormal IVGTT's,[21] while at other times the combination of abnormal OGTT's and normal IVGTT's is said to prevail.[14,16,20,22] Our results seem to fall into yet a third category, in which if one test is abnormal, the likelihood

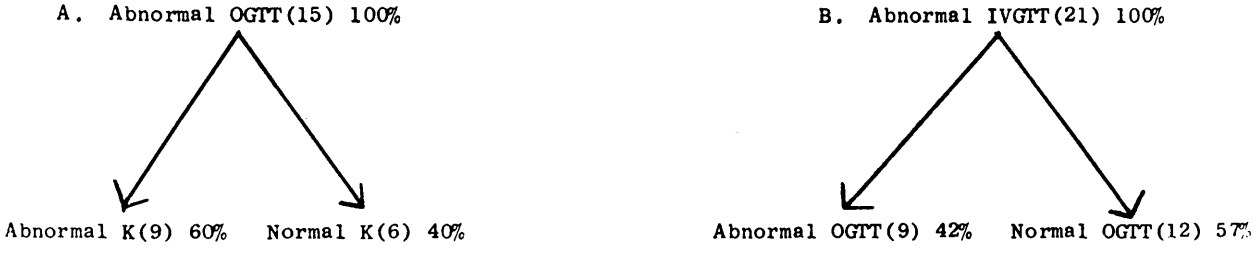

FIG. 1. (A) The diagnostic results of the IVGTT in the fifteen subjects with an abnormal OGTT. (B) The diagnostic results of the OGTT in the twenty-one subjects with an abnormal IVGTT.

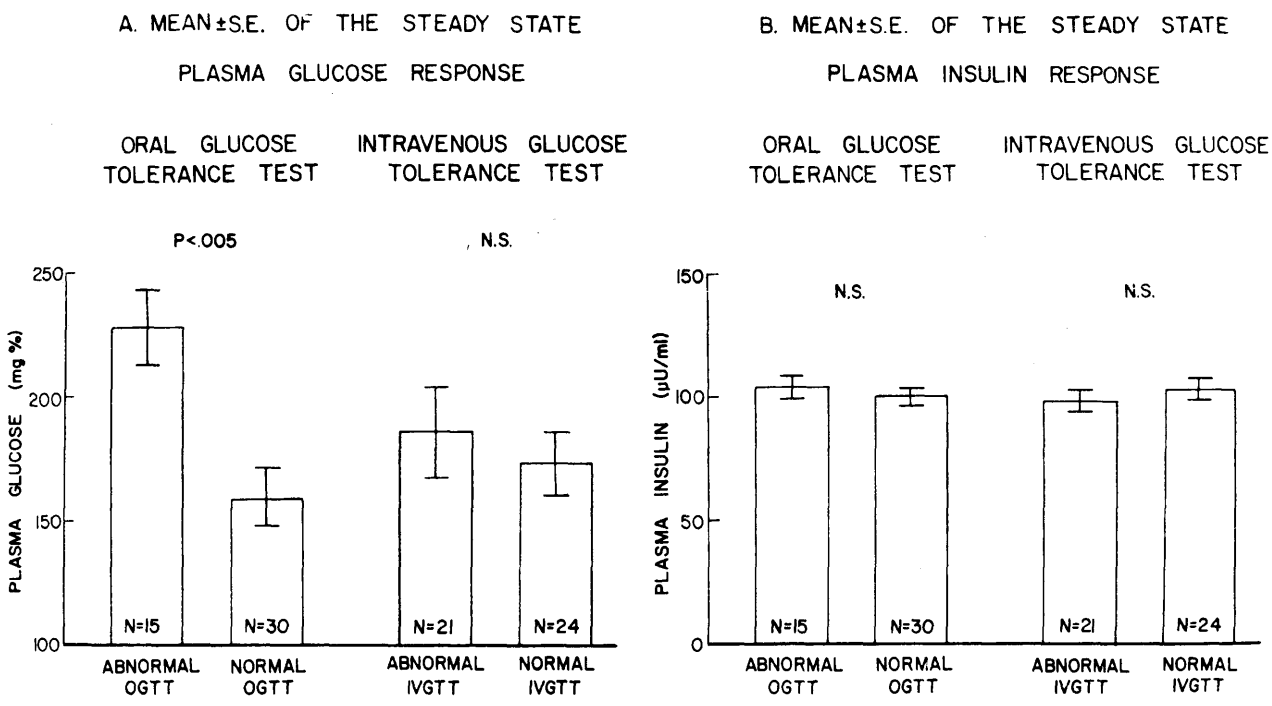

FIG. 2. Summary of the results of the pancreatic suppression tests (PST). (A) The heights of the bars represent the mean steady state plasma glucose (SSPG) responses (± S.E.M.) of the indicated group during the PST. A large, statistically significant, difference between the mean SSPG responses is noted when subjects with positive OGTT's and those with negative OGTT's are compared. On the other hand, no difference can be detected when subjects are similarly divided and compared on the basis of the IVGTT. (B) The heights of the bars represent the mean steady state insulin levels (± S.E.M.) of the indicated group during the PST. It can be seen that essentially identical plasma insulin levels were achieved in all four groups.

that the other test will be normal is almost 50 per cent.

There are at least three explanations for this degree of diagnostic discordance, and it is possible that all three may be exerting some influence on our results. In the first place, it is quite clear that the reproducibility of the oral and intravenous glucose tolerance tests leaves a good deal to be desired,[21,27-30] and it might not be too unreasonable to postulate that they would give opposite diagnostic results 40 per cent of the time. Thus, the simplest explanation might be that the discordance is due to the intrinsic variability of these tests, and that both tests provide equally unreliable estimates of glucose intolerance.

Alternatively, the two tests may indeed be providing reasonably reliable estimates of glucose tolerance, but some unique characteristic of our study group accounts for the discordant results. For example, it has been reported by Doar et al.[23] and Morse et al.[24] that obesity can result in a worsening of the OGTT without a comparable deterioration of the IVGTT. Thus, the discordance we noted could theoretically be due to the effect of obesity. We think this is not likely for several reasons. In the first place, the findings of Doar and Morse were reported in obese subjects whose body weights were greater than 120 per cent[23] or 130 per cent[24] of their ideal weight, respectively. None of our subjects exceeded 130 per cent of ideal weight, and only six exceeded 120 per cent. Furthermore, only two of these six subjects had discordant results. However, to further explore the possibility that obesity might be responsible for the discordance, we subdivided our patients into two groups, a "lean" group and a "heavy" group, on the basis of their relative weight. We found that 56 per cent (10/18) of the discordant results occurred in the "heavy" group, and 44 per cent (8/18) occurred in the "lean" group. Thus, there seems to be no predilection for discordance in either of these groups, and it appears that obesity is not exerting a significant effect on our results.

Finally, the possibility exists that the two tests do not provide comparable estimates of glucose tolerance, and that one cause of the discordance is that one test is better able to measure glucose tolerance than the other. The ideal measure of glucose tolerance would be a test which reproducibly and specifically assessed the subject's ability to dispose of a glucose load. In order to provide such a test, we introduced and validated a

method which is based upon measurement of the plasma glucose response to a continuous infusion of exogenous insulin, glucose, epinephrine and propranolol.[17] This approach is based upon the ability of epinephrine and propranolol to suppress endogenous insulin secretion, and this has been confirmed by finding no rise in plasma endogenous insulin levels during extreme hyperglycemia following an infusion of glucose, epinephrine, and propranolol.[17] During the pancreatic suppression test (PST), comparable steady state plasma insulin levels are achieved in all subjects and thus, we are able to measure the effect of identical circulating levels of exogenous insulin to promote disposal of comparable glucose loads in a variety of subjects. Steady state plasma concentrations of glucose and insulin are reached within ninety minutes of starting the infusion, and we then measure these levels every ten minutes for an additional sixty minutes. If one assumes that endogenous glucose production is inhibited during this steady state period, then the glucose uptake rate should be equal to the glucose infusion rate. We have verified this assumption by directly measuring the irreversible glucose loss rate.[17] Thus, since insulin concentration and glucose uptake (infusion rate) are the same for all subjects at the steady state, the height of the steady state plasma glucose response is a direct reflection of the efficiency of glucose uptake. We think that this provides an excellent technic to directly measure efficiency of glucose disposal, and we have also shown it to be quite reproducible.[17] Therefore, we feel that the excellent correlation between results of the PST and the OGTT, coupled with the fact that patients with abnormal OGTT's had much higher mean SSPG responses than did patients with normal OGTT's, indicates that the OGTT provides a reasonably good estimate of the efficiency of a patient's ability to dispose of a glucose load. On the other hand, no significant correlation was found between results of the PST and the IVGTT. Furthermore, when patients were divided into normal and abnormal on the basis of the IVGTT, no difference could be found in their mean SSPG responses. These findings suggest that the IVGTT is not measuring the efficiency of glucose disposal as well as is the OGTT, and that this difference in the relative ability of the two tests to estimate glucose tolerance may help explain the diagnostic discordance that we have documented.

Additional support for the notion that the IVGTT does not provide a very accurate estimate of the ability of a subject to dispose of a glucose load is found in the work of Butterfield and associates,[25] who found a poor correlation between direct measurement of glucose uptake and the K value obtained during an IVGTT. On the other hand, they found that direct measurements of glucose uptake during an OGTT indicated that decreased oral glucose tolerance in patients with diabetes was associated with decreased glucose uptake.[26] Thus, available evidence also suggests that the OGTT provides a more accurate estimate of glucose disposal than does the IVGTT. It is not clear to us why this is the case; it may be simply because the IVGTT is a relatively acute test (being completed within sixty minutes), and it is possible that the early response to a glucose challenge may not be closely related to the physiologic events which control the efficiency of glucose disposal. Finally, it should be emphasized that the discrepancies between results of the OGTT and IVGTT are not due simply to different routes of glucose administration because the PST, which did correlate with the OGTT, also bypasses the gastrointestinal tract.

Our conclusion that the OGTT is a better measure of glucose uptake than the IVGTT should not be interpreted as defense of the clinical utility of the OGTT. The reproducibility of this test leaves a good deal to be desired;[27-30] factors such as age,[31] diet,[32] activity[33] and various medications[34-36] can profoundly affect the results; whether a patient is classified as diabetic or normal often depends upon which of several sets of criteria are used;[4,6] and the meaning of an abnormal test in the subsequent development of the diabetic syndrome is certainly debatable.[1-5] However, these criticisms are equally applicable to the clinical use of the IVGTT,[21,35,37] and if it is deemed desirable to "diagnose" diabetes mellitus when patients are still capable of maintaining fasting euglycemia, then it is reasonable to use tests which best measure the phenomenon in question, namely, a subject's efficiency in disposing of a glucose load. Our study suggests that when these two tests are used in a patient population in which there is a high risk of chemical diabetes, the OGTT seems to provide a more satisfactory method of estimating efficiency of glucose disposal than does the IVGTT.

ACKNOWLEDGMENT

We wish to thank Miss Janet Wagner, Mrs. Virginia Hunt, Mrs. Louise White, and Miss Phyllis Crapo for their valuable technical assistance.

This work was supported in part by grants from the National Institutes of Health, no. RR70, General Clinical Research Center Branch, no. AM 05021, Training Grant, no. HE 08506, N.H.L.I., HE 14174, N.H.L.I. and no. 71-2161, N.H.L.I.

Dr. Reaven is a Medical Investigator of the Veterans Administration.

REFERENCES

[1] Unger, R. H.: The standard two-hour oral glucose tolerance test in the diagnosis of diabetes mellitus in subjects without fasting hyperglycemia. Ann. Intern. Med. *47*:1138-53, 1957.

[2] Moorhouse, J. A.: A note on prediabetes. Manit. Med. Rev. *40*:693-94, 1960.

[3] O'Sullivan, J. B., and Hurwitz, D.: Spontaneous remissions in early diabetes mellitus. Arch. Intern. Med. *117*:769-74, 1966.

[4] O'Sullivan, J. B., and Mahan, C. M.: Prospective study of 352 young patients with chemical diabetes. N. Engl. J. Med. *278*:1038-41, 1968.

[5] Schwartz, T. B.: Editorial—Who is a diabetic. Ann. Intern. Med. *69*:161-63, 1968.

[6] Fajans, S. S., and Conn, J. W.: The early recognition of diabetes mellitus. Ann. NY Acad. Sci. *82*:208-18, 1959.

[7] The College of General Practitioners: A diabetes survey. Br. Med. J. *1*:1497-1503, 1962.

[8] Butterfield, W. J. H.: Summary of results of the Bedford Diabetes Survey. Proc. R. Soc. Med. 4-10, 1963.

[9] Grant, D. R., and Moorhouse, J. A.: Pilot study for a diabetes detection program based upon rapid glucose microanalysis of postprandial capillary blood. Can. Med. Assoc. J. *94*: 1213-19, 1966.

[10] Committee on Statistics of the American Diabetes Association: Standardization of the oral glucose tolerance test. Diabetes *18*:299-310, 1969.

[11] O'Sullivan, J. B., Snyder, P. J., Sporer, A. C., Dandrow, R. V., Jr., and Charles, D.: Intravenous glucose tolerance test and its modification by pregnancy. J. Clin. Endocrinol. Metab. *31*:33-37, 1970.

[12] Ikkos, D., and Luft, R.: On the intravenous glucose tolerance test. Acta Endocrinol. (Kbh) *25*:312-34, 1957.

[13] Soeldner, J. S., Gleason, R. E., Williams, R. F., Garcia, M. J., Beardwood, D. M., and Marble, A.: Diminished serum insulin response to glucose in genetic males with normal glucose tolerance. Diabetes *17*:17-26, 1968.

[14] Kahn, C. B., Soeldner, J. S., Gleason, R. E., Rojas, L., Camerini-Davalos, R. A., and Marble, A.: Clinical and chemical diabetes in offspring of diabetic couples. N. Engl. J. Med. *281*:343-47, 1969.

[15] Felig, P., Marliss, E., and Cahill, G. F., Jr.: Plasma amino acid levels and insulin secretion in obesity. N. Engl. J. Med. *281*:811-16, 1969.

[16] Alford, F. P., Martin, F. I. R., and Pearson, M. J.: The significance and interpretation of mildly abnormal oral glucose tolerance. Diabetologia *7*:173-80, 1971.

[17] Shen, S. W., Reaven, G. M., and Farquhar, J. W.: Comparison of impedance to insulin-mediated glucose uptake in normal subjects and in subjects with latent diabetes. J. Clin. Invest. *49*:2151-60, 1970.

[18] Hoffman, W. S.: A rapid photoelectric method for determination of glucose in blood and urine. J. Biol. Chem. *120*:51-55, 1937.

[19] Hales, C. N., and Randle, P. J.: Immunoassay of insulin-antibody precipitate. Biochem. J. *88*:137-44, 1963.

[20] Benjamin, F., and Casper, D. J.: Oral versus intravenous glucose tolerance tests during pregnancy. Am. J. Obstet. Gynecol. *94*:566-70, 1966.

[21] Dyck, D. R., and Moorhouse, J. A.: A high-dose intravenous glucose tolerance test. J. Clin. Endocrinol. Metab. *26*:1032-38, 1966.

[22] Benjamin, F., and Casper, D. J.: Comparative validity of oral and intravenous glucose tolerance tests in pregnancy. Am. J. Obstet. Gynecol. *97*:488-92, 1967.

[23] Doar, J. W. H., Wynn, V., and Cramp, D. G.: Blood pyruvate and plasma glucose levels during oral and intravenous glucose tolerance tests in obese and nonobese women. Metabolism *17*:690-701, 1968.

[24] Morse, W. L., Siedorov, J. J., Soeldner, J. S., and Dickson, R. C.: Observations on carbohydrate metabolism in obesity. Metabolism *9*:666-79, 1960.

[25] Butterfield, W. J. H., Abrams, M. E., and Whichelow, M. J.: The 25-gm. intravenous glucose tolerance test: A critical appraisal. Metabolism *20*:255-65, 1971.

[26] Whichelow, M. J., and Butterfield, W. J. H.: Peripheral glucose uptake during the oral glucose tolerance test in normal and obese subjects and borderline and frank diabetics. Q. J. Med. *40*:261-73, 1971.

[27] West, K. M., Wulff, J. A., Reigel, D. G., and Fitzgerald, D. T.: Oral carbohydrate tolerance tests. Arch. Intern. Med. *113*:641-48, 1961.

[28] McDonald, G. W., Fisher, G. F., and Burnham, C.: Reproducibility of the oral glucose tolerance test. Diabetes *14*: 473-80, 1965.

[29] Kosaka, K., Mizuno, Y., and Kuzuya, T.: Reproducibility of the oral glucose tolerance test and the rice-meal test in mild diabetes. Diabetes *15*:901-04, 1966.

[30] McDonald, G. W., Burnham, C. E., and Lewis, W. F.: Reproducibility of glucose tolerance in 101 nondiabetic women. Public Health Rep. *84*:353-57, 1969.

[31] Hayner, N. S., Kjelsberg, M. O., Epstein, F. H., and Francis, T., Jr.: Carbohydrate tolerance and diabetes in a total community, Tecumseh, Michigan. I. Effects of age, sex, and test conditions on one hour glucose tolerance in adults. Diabetes *14*:413-23, 1965.

[32] Conn, J. W.: Interpretation of the glucose tolerance test: The necessity of a standard preparatory diet. Am. J. Med. Sci. *199*:555-64, 1940.

[33] Blotner, H.: Effect of prolonged physical inactivity on tolerance of sugar. Arch. Intern. Med. *75*:39-45, 1945.

[34] Wachman, A., Hattner, R. S., George, B., and Bernstein, D. S.: Effects of decaffeinated and nondecaffeinated coffee ingestion on blood glucose and plasma radioimmunoreactive insulin responses to rapid intravenous infusion of glucose in normal man. Metabolism *19*:539-46, 1970.

[35] Editorial: Drug-induced diabetes. Lancet *2*:328-29, 1965.

[36] Spellacy, W. N., Carlson, K. L., Birk, S. A., and Schade, S. L.: Glucose and insulin alterations after one year of combination-type oral contraceptive treatment. Metabolism *17*: 496-501, 1968.

[37] Crockford, P. M., Harbeck, R. J., and Williams, R. H.: Influence of age on intravenous glucose tolerance and serum immunoreactive insulin. Lancet *1*:465-67, 1966.