# THE GLUCOSE TOLERANCE TEST

## Appraisal of Criteria for Interpretation, Based on Laboratory Results

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A recent increase in the number of standard oral glucose tolerance tests done in our laboratory prompted an investigation of the validity of the generally accepted criteria for the interpretation of these studies. The results of all glucose tolerance tests performed in this laboratory during a representative 12-week period were categorized and tabulated. With glucose tolerance tests, as with most laboratory studies, the most meaningful interpretation rests on correlation with clinical findings. This study, however, concerns analysis solely of laboratory results.

### Method

The glucose tolerance test, for the purpose of this study, is defined as the determination of the blood sugar level at a specified interval or intervals after administration of a standardized amount of glucose. Results of tests that included two or more blood sugar determinations were considered *tolerance curves.* The results of all the glucose tolerance tests performed in our laboratory from April 8, 1963, through June 28, 1963, were reviewed. Glucose tolerance tests were administered to 630 patients at the Cleveland Clinic during this 12-week period, an average of 52.5 such studies each week. The results of each individual test were interpreted as normal, abnormal, or equivocal. These categories were based on the ranges of normal established for our laboratory, and were modified in some instances by consideration of the patient's overall response.

Blood sugar levels were determined on venous blood samples by an automated procedure, using the potassium ferricyanide — potassium ferrocyanide oxidation reduction method[1] as modified[2,3] for use on the AutoAnalyzer.† The glucose administered to the fasting patients was a commercial solution‡ containing 100 gm. of glucose in a total volume of 200 ml. of solution.

### Results

Under the conditions outlined, normal fasting levels of blood sugar for our laboratory range between 65 and 105 mg. per 100 ml.; one hour after ingestion of glucose, the normal range is from 90 to 160 mg. per 100 ml. By the second hour, the blood sugar concentration normally returns to the fasting range. These particular limits of normal are similar to the criteria set forth by others.[4-7]

Those levels or curves in our series which were within these limits were cate-

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*†Manufactured by Technicon Instruments Corporation.*
*‡Dextol, available from Scientific Products, Division of American Hospital Supply Corporation.*

gorized as *normal* glucose tolerance tests, together with those tests in which the deviations from the normal range were judged insignificant. Results well outside the normal range or of clearly abnormal pattern were designated *abnormal*. Results that deviated from normal so slightly or so inconsistently that definite interpretation was impossible were considered *equivocal*. Curves with little rise in blood sugar concentration during the tolerance study (<20 mg. per 100 ml. during the first hour) or no significant variation in blood sugar concentration from the fasting level were designated *flat* and were included in the equivocal category.

Of the 630 patients tested, glucose tolerance curves were determined on 540 (86 percent of the series) and 75 tests were single determinations performed two hours after ingestion of glucose.* Of the 630 patients, abnormal glucose tolerance was demonstrated in 353 (56 percent). For an additional 69 patients (11 percent) results were equivocal. Of the 540 tolerance curves, 161 (29.8 percent) were normal (*Fig. 1*). The tolerance curves of 257 patients (48 percent) were abnormally high

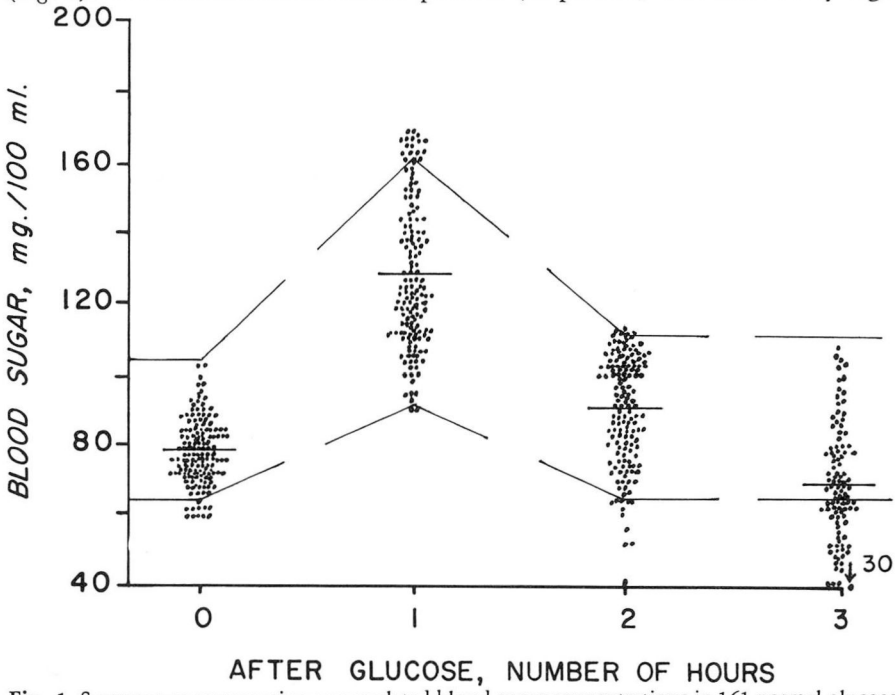


**Fig. 1.** Scattergram representing accumulated blood sugar concentrations in 161 normal glucose tolerance curves. The means of the values at each interval inscribe a typical normal curve.

(*Fig. 2*). Of these high curves, 241 included fasting determinations, and in 197 (82 percent) of these, the fasting levels were within normal limits. Among the 540 tolerance curves, there were 50 (9 percent) flat curves.

**Fifteen studies were not completed.*

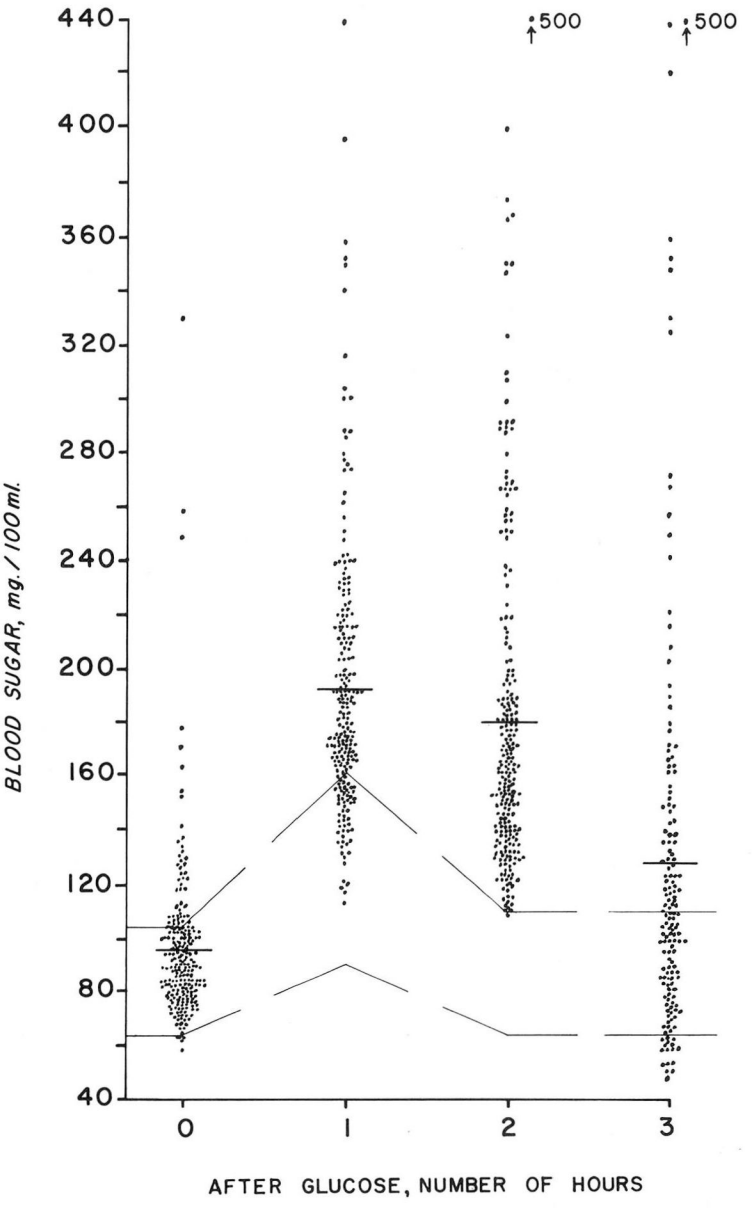


**Fig. 2.** Scattergram representing accumulated blood sugar concentrations in 246 elevated glucose tolerance curves. The means of the values at each interval inscribe a typical prolonged hyperglycemic curve well above the normal range. Note the preponderance of normal fasting blood sugar concentrations.

## Discussion

The high incidence of altered glucose tolerance in our series represents a high yield for the time and effort expended in the tolerance studies. This high proportion of abnormal results reflects the clinical selection of patients for tolerance testing. The recent increase in the number of glucose tolerance tests apparently represents an increase in the number of clinical situations confronting our staff, which include alterations in carbohydrate metabolism. The increasing use of these tests also reflects the expanding indications for efficacious application of tolerance studies even to certain asymptomatic persons, with promise of still earlier detection of diabetes mellitus.

Of the 257 patients with diminished tolerance to a glucose load, 82 percent had normal fasting blood sugar levels. Even in the 105 curves judged typical of diabetes mellitus, 61 (63 percent) still included normal fasting values. This finding clearly emphasizes that one cannot rely on an isolated fasting blood sugar determination for detection of early or mild diabetes mellitus.[8, 9] This preponderance of normal fasting levels in this series of clinically selected subjects is in keeping with the generally accepted principle that formal glucose tolerance studies should be reserved primarily for the evaluation of patients with normal or nearly normal postabsorptive blood sugar levels.

The interval of two hours after ingestion of glucose is the critical time in separating normal and abnormal metabolic responses as gauged by the blood sugar concentration.[5, 6, 10] It seems probable that a glucose tolerance test consisting only of blood sugar determinations one and two hours after giving glucose can constitute as reliable a test for the detection of diabetes mellitus as the longer tests covering several hours and including fasting blood sugar determinations. The two-hour blood sugar value is so crucial that some authorities[3, 5] suggest that even this single determination alone constitutes a simplified but still meaningful test,[3, 6, 10, 11] since a diminished glucose tolerance is manifested by a prolonged hyperglycemia and more than two hours is required to return the blood sugar level to normal.[8, 12]

The test results, in our study, for the 75 patients who were evaluated by means of single two-hour determinations of blood sugar, are depicted in the first column of *Figure 3*. The single determinations served to segregate these patients into groups: one group of 33 patients (44 percent) with two-hour after-glucose blood sugar levels higher than 125 mg. per 100 ml.; another group of 33 patients with two-hour levels of 110 mg. per 100 ml. or less. The remaining 9 (12 percent) of the 75 patients had two-hour concentrations ranging between 110 and 125 mg. per 100 ml. These two levels were selected with the thought that two-hour concentrations below 110 mg. per 100 ml. and above 125 mg. per 100 ml. should represent, respectively, normal and diminished glucose tolerance. The greater the deviation from these limits, the more certain is the implication. These designated levels conform to the general experience with glucose tolerance tests, and to the established normal

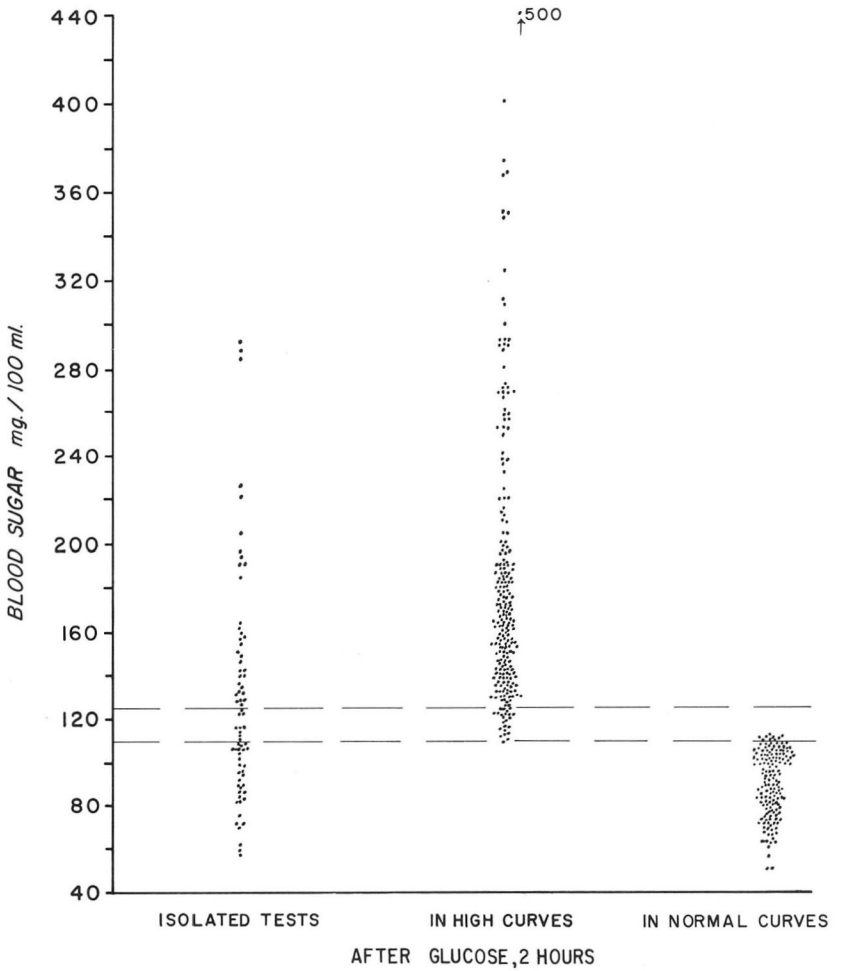


**Fig. 3.** Scattergram representing isolated blood sugar determinations in 75 random patients two hours after ingesting glucose, compared with the two-hour levels in 161 normal and 246 elevated glucose tolerance curves.

ranges of this laboratory. The intermediate range from 110 to 125 mg. per 100 ml. then could represent an equivocal zone, allowing for physiologic variations[13, 14]

and for inherent error in chemical determinations of blood sugar. Single two-hour blood sugar determinations in this range would be of indefinite significance and would indicate the need for more elaborate studies.

The two-hour blood sugar levels in the more complete curves of our series, normal and abnormal, corroborate the critical value of the two-hour blood sugar concentrations (*Fig. 3*). Of the 158 two-hour levels included in 161 normal curves, 149 (94 percent) were 110 mg. per 100 ml. or less; none were higher than 125 mg. per 100 ml.; and only 9 (6 percent) were in the equivocal zone between 110 and 125 mg. per 100 ml.*

Of the 257 high tolerance curves, 11 were of the fairly distinct type observed in reactive hypoglycemia (see below). When these 11 curves are eliminated, along with two curves altered by emesis after the first hour, the two-hour blood sugar levels in the remaining 244 high curves were above 125 mg. per 100 ml. in 221 (91 percent), and only 21 (9 percent) were in the equivocal zone between 110 and 125 mg. per 100 ml.

A single determination of blood sugar two hours after a dose of glucose is more reliable and meaningful in the detection of early or mild diabetes than the usual random fasting or postprandial tests, because of the better controlled and standardized conditions. This single determination is capable of eliciting good evidence of diabetes mellitus, but it would be advisable to corroborate abnormal results in this single test by repeating the test or by further studies such as a one- and two-hour tolerance test.

Longer glucose tolerance studies may be necessary, particularly in evaluating patients with equivocal results in abbreviated tolerance studies, or in those suspected of having such problems as reactive hypoglycemia. With the latter patients, a complete tolerance curve can demonstrate the characteristic rapid, high-peaked blood sugar response that is followed by a phase of hypoglycemia usually within two or three hours. Such responses are frequently seen after partial gastrectomy (dumping syndrome). Similar curves may be elicited from patients who have not undergone gastric resection. The response in these instances has generally been ascribed to states such as hyperthyroidism, in which there is rapid gastric emptying and an accelerated rate of intestinal absorption. However, the occurrence of hypoglycemia within a few hours after ingestion of glucose does not rule out the presence of diabetes mellitus. In fact, symptomatic spontaneous hypoglycemia may be one of the earliest manifestations of diabetes mellitus.[9, 15, 16] It must be emphasized that curves of this type typically show normal or subnormal blood sugar levels at two hours, and a single determination at this interval may be misleading unless consideration is given to the clinical history. Seven of the 11 curves of this type in our series had two-hour blood sugar levels less than 110 mg. per

**A statistical analysis of these data (standard deviation) verified that at least 90 percent of all normal persons should have two-hour posttest blood sugar levels less than 110 mg. per 100 ml.*

100 ml., and three of these were less than 70 mg. per 100 ml. Some of these situations may be best clarified by an intravenous glucose tolerance test, which has the advantage of completely eliminating the variable factor of glucose absorption from the intestine.[3, 11]

Flat glucose tolerance curves may be the result of various pathologic conditions;[17] flat curves comprised a high proportion (more than 9 percent) of our series. However, as all but 3 of these 50 flat curves included normal fasting levels, we believe that many of these responses were not due to truly abnormal absorptive or metabolic function. These flat curves may instead reflect misleading physiologic mechanisms. For example, pylorospasm and/or prolonged gastric retention (and delayed enteric absorption) of glucose can result from administering an excessively hypertonic solution.[8] The 50 percent solution employed in our laboratory was routinely given undiluted. This may be the cause of some of the flat glucose tolerance curves in our series, as several authorities believe that a 20 percent glucose solution is the ideal concentration for the most reliable physiologic response.[10]

For the oral glucose tolerance test, it is not necessary to adjust the glucose dosage to an individual's weight,[4] inasmuch as doses greater than 25 gm. usually are sufficient to give the maximal rise in blood sugar level.[18] As much as 50 gm. of an orally administered 100-gm. dose of glucose may even remain in the stomach during the first hour of a two-dose glucose tolerance test.[19] The 100-gm. dose, more or less standard in the United States, provides ample carbohydrate for maximal and reproducible response of the blood sugar concentration. The glucose solution is usually better tolerated when chilled.[20]

The results were considered equivocal in 11 percent of the glucose tolerance tests in this series. Such a proportion of equivocal results is justifiable, since physiologic variations, plus the inherent error in determinations of blood glucose, prevent the designation of a sharp dividing line between normal and definitely abnormal glucose tolerance.[5, 7, 13] Such minor variations from the normal range, not diagnostic in themselves, may nonetheless, in some instances, be early indications of altered carbohydrate metabolism, which eventually will emerge as unequivocal diabetes mellitus.[21]

Although mild variations of glucose tolerance do occur, a high degree of reproducibility is achieved with the oral test when attention is given to the adequate preparation of the patient and the careful performance of the test.[5] The accuracy and validity of all tests of carbohydrate tolerance depend to a great extent on the prior dietary intake and nutritional state of the patient.[12, 22, 23] The average American diet usually constitutes satisfactory preparation for the test.[4, 8, 10] A low level of carbohydrate intake, including therapeutic or self-imposed diets, for even a few days preceding a glucose tolerance test, may result in a diminished tolerance in normal persons, and a false indication of diabetes mellitus.[4, 22] It is advisable to verify abnormal results by a repeated test after a period of good dietary preparation.

Although the results of the urine tests for sugar during glucose tolerance studies were reviewed for only 231 of the patients in our series, an abnormally low renal threshold for glucose (renal glycosuria) was suggested in at least eight instances (3.5 percent). This finding emphasizes the value of including determinations of urine sugar in glucose tolerance studies. Such urine tests may substantiate the blood sugar values, and aid in establishing alterations of the renal threshold for glucose. It is now believed that in many instances, renal or nondiabetic glycosuria is an early indicator of potential diabetes.[5, 24] Conversely, the absence of glycosuria does not rule out the presence of diabetes mellitus. The renal threshold for glucose may become elevated in some diabetics,[9] particularly those diabetics who have renal vascular disease.[25]

## Summary

The 630 consecutive glucose tolerance tests performed in our laboratory during a typical 12-week period were reviewed. In 56 percent of these patients abnormal glucose tolerance was demonstrated; whereas, in 11 percent the results were equivocal. The glucose tolerance test is particularly useful in evaluating patients, clinically suspected to be diabetic, who have normal or borderline results in screening tests. In our series, the high proportion of abnormal results, despite a preponderance of normal fasting blood sugar levels, emphasizes this value of glucose tolerance tests.

The data support the belief of some authorities that a single determination of blood sugar two hours after administration of a standard glucose dose can, in many instances, differentiate between a normal and an abnormal carbohydrate tolerance, and more reliably so than the usual screening tests. Blood sugar levels of 110 mg. per 100 ml. or less two hours after giving glucose can be considered normal; those exceeding 125 mg. per 100 ml. at this same interval indicate a diminished glucose tolerance. Of the patients in our series tested in this manner, 88 percent could be categorized on this basis. An analysis of 405 glucose tolerance curves in this series (161 normal, 244 abnormal) corroborates the value of the two-hour determination and the validity of the suggested criteria for interpretation of this test. The single two-hour blood sugar level after glucose deserves consideration as a means for evaluating carbohydrate metabolism, intermediate in significance between random screening tests and formal glucose tolerance studies.

The data suggest that the standard glucose tolerance test need not include the fasting blood sugar level, and that the one-hour and two-hour levels will be adequate for the diagnosis of diabetes mellitus. Inclusion of the fasting level offers little or no additional information when glucose tolerance studies are performed on appropriately selected patients.

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