Reproducibility and Comparative Analysis of Repeated Intravenous and Oral Glucose Tolerance Tests

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SUMMARY

We have developed a methodology for measuring the reproducibility of the oral glucose tolerance test (OGTT) and the intravenous glucose tolerance test (IVGTT) in normal subjects and in offspring of conjugal diabetic parents.

Both groups of subjects revealed more striking correlations of several parameters of blood glucose and insulin secretion between two IVGTTs than between two OGTTs. Employing arbitrary criteria, we calculated a "reproducibility index" as a quantitative measure of blood glucose variability in each subject. No significant difference was found in the reproducibility of OGTT versus IVGTT, nor in normals versus the offspring. Only about 50 per cent of the tests in normals and in the offspring could be considered to be "reproducible."

The offspring revealed greater correlations of several parameters, particularly insulin secretion, between the two IVGTTs and between the two OGTTs as compared with the normal group. However, the blood glucose variations tended to be considerably greater in the offspring from one to the other test. DIABETES *27*:715-25, July, 1978.

The clinical value of a test in comparative analysis depends upon its reproducibility. Glucose tolerance tests have been employed widely in the early diagnosis of disorders of carbohydrate metabolism. Several studies have indicated considerable variability in the oral glucose tolerance test (OGTT) in the same individual when multiple tests were performed.[1-12] An important consideration raised by such studies is whether one would miss a sizable number of "mild" diabetics by performing the test only once,[8-10] thus limiting its clinical value. The American Diabetes Association has recommended standard test conditions to minimize variability, yet considerable variability necessitates the "criteria for normality to be arbitrary."[13] The quantitation of reproducibility of multiple glucose tolerance tests in the same individual by conventional statistic methods presents a complex problem, since the test consists of several sampling times.

While the limitations of the intravenous glucose tolerance test (IVGTT) in the diagnosis of an abnormal response are also well appreciated,[14-16] scant information is available regarding its reproducibility and, thus, its value in comparative investigations.

In the studies reported here, two oral and two intravenous glucose tolerance tests were performed in normal subjects and in offspring of conjugal diabetic parents. Comparisons of glucose and insulin concentrations were made between the two tests in each group, and correlations of several measures of glucose utilization and insulin secretion were examined. In addition, the reproducibility of the tests was quantitated by developing a "reproducibility index" from normal subjects.

MATERIAL AND METHODS

Two groups of subjects were studied. The normal subjects were healthy, nonobese individuals with no history of drug intake and no family history of diabetes. Forty-two normals received two IVGTTs and 26 received two OGTTs. None of the offspring were obese or on any drug known to affect carbohydrate

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metabolism. Table 1 shows that age and body weights (expressed as percentage of ideal weight as determined by Metropolitan Life Insurance Tables, 1959) in the two groups were comparable. Body weights did not change significantly during the time between the two tests. Seventeen of the normals and nine of the offspring received all four tests, i.e., two IVGTTs and two OGTTs.

All subjects were on a diet containing about 250 gm. of carbohydrate for three days before each tolerance test. The tests were performed in postabsorptive state, after an overnight fast, starting between 8 and 9 a.m. For OGTT, 100 gm. glucose was administered as a carbonated, flavored drink (VWR Scientific, California). For IVGTT, rapid glucose infusion, as 0.5 gm. glucose per kilogram body weight, was administered over three minutes as a standard procedure.[17]

Samples were drawn for glucose and insulin in the fasting state and at 1, 3, 5, 10, 20, 30, 40, 50, 60, 90, 120, and 180 minutes after intravenous glucose and 15, 30, 45, 60, 90, 120, 180, 240, and 300 minutes after oral glucose.

Whole blood glucose (BG) was determined by the ferricyanide method[18] as modified for the AutoAnalyzer and serum immunoreactive insulin (IRI) by a two-antibody technique.[19] For both BG and IRI determinations, standard specimens were run concurrently in each assay. Insulin determinations were in duplicate and the reproducibility and sensitivity of the assay have been described previously.[19] The normal criteria for OGTT and IVGTT have also been presented elsewhere.[18]

Statistics

For each test, early and total areas under the curve above the baseline were calculated for BG and IRI. The early area is defined as the 0 to 10 minute segment for the IVGTT and the 0 to 60 minute portion of the OGTT. The total area is the 0 to 60 minute area and the 0 to 300 minute area for the IVGTT and the OGTT, respectively. Ratios of early to total areas and of insulin to glucose areas were also calculated. In each test, linear regressions were computed between the insulin and glucose responses, and the slope of the regression line was expressed as microunits per milliliter insulin per milligram per 100 ml. glucose ('B').

For each IVGTT, rate of blood glucose disappearance (Kg) was determined from the slope of the linear regression (least square analysis) of log blood glucose on time from 10 to 60 minutes after glucose injection.

Student's *t*-test was employed for paired comparisons between the repeated tests. Pearson's correlation coefficients were calculated for individual responses at each time interval and for all the other derived indices between the repeated tests.

Reproducibility Index

IVGTTs from 27 normal men and OGTTs from 20 normal men were analyzed further in order to quantitate and develop a reproducibility index. A series of BG differences (Δ) were obtained for each subject at each time interval (13 for IVGTT and 10 for OGTT) by subtracting the BG levels during test 2 from those obtained at the corresponding time intervals during test 1. These BG Δ were ranked from low to high within each sampling time and the ranked distribution divided into quartiles. The range of BG Δ for each quartile was thus obtained. The first quartile (Q_1) contained the largest negative Δ, i.e., BG in test 2 were higher than in test 1. The fourth quartile (Q_4) contained the largest positive Δ, i.e., BG in test 2 were lower than those in test 1. Zero Δ occurred in either Q_2 or Q_3.

Since, for a given subject, Δ occurring within Q_2 or Q_3 would indicate greater reproducibility than those occurring in Q_1 or Q_4, the reproducibility index was defined and calculated as follows. For each subject, the BG Δ (test 1 minus test 2) at each time interval was obtained and the quartile in which each fell was

TABLE 1

Description of study groups

Group	Age (yr.) (test 1)	Interval between tests 1 and 2 (yr.)	Weight (% of ideal body wt.) Test 1	Weight (% of ideal body wt.) Test 2
Normals				
IVGTT, n = 42	29.7 ± 1.4	1.0 ± 0.14	103.1 ± 1.7	102.7 ± 1.8
OGTT, n = 26	24.8 ± 0.98	1.3 ± 0.20	100.5 ± 2.1	100.3 ± 1.9
Offspring				
IVGTT, n = 34	28.5 ± 2.1	1.8 ± 0.15	102.0 ± 1.8	103.4 ± 1.8
OGTT, n = 32	32.9 ± 1.5	2.3 ± 0.23	102.2 ± 1.8	103.1 ± 1.9

All values are means ± S.E.M.

tabulated. The reproducibility index was defined as the number of BG Δ that occurred in Q_2 or Q_3. Any individual with an index equal to one-half or greater of the total number of sampling times was arbitrarily classified as having a "reproducible" test. For IVGTT, this number would be 6 and for OGTT, 5 (the quartile for fasting BG Δ was excluded).

RESULTS

Comparison of BG and IRI Concentrations in Test 1 and Test 2 at each Time of Sampling

The mean BG and IRI responses during the two IVGTTs in normal subjects and in the offspring are plotted in figures 1 and 2, respectively. The fasting BG levels were virtually identical in the two tests for both groups, the corresponding values for test 1 and test 2 being 75 and 74 mg. per 100 ml. for normals and 75 and 75 mg. per 100 ml. for offspring. Similarly, fasting IRI values for test 1 and test 2 were identical, being 14 and 14 μU. per milliliter for the normals and 19 and 16 μU. per milliliter for the offspring. After glucose administration, comparable mean BG concentrations were seen at most of the time intervals, there being no significant difference except at 20, 30, 40, and 120 minutes in the normal group (figure 1) and except at 1, 3, 5, and 10 minutes in the offspring group. However, the IRI values were nearly superimposable throughout the two tests in both groups, there being no significant difference between the two tests at any time interval.

The mean BG and IRI responses during the two OGTTs are plotted in figures 3 and 4 for the normal and the offspring, respectively. While the curves for the two tests appear comparable, the BG differences and IRI differences between the two tests reached significant levels at a few time intervals. It is worth pointing out that even though there was a significant difference ($p = 0.03$) between fasting BG in the two tests in offspring, the mean BG values differed by only 2.6 mg. per 100 ml., being 77.9 and 75.3 mg. per 100 ml., respectively.

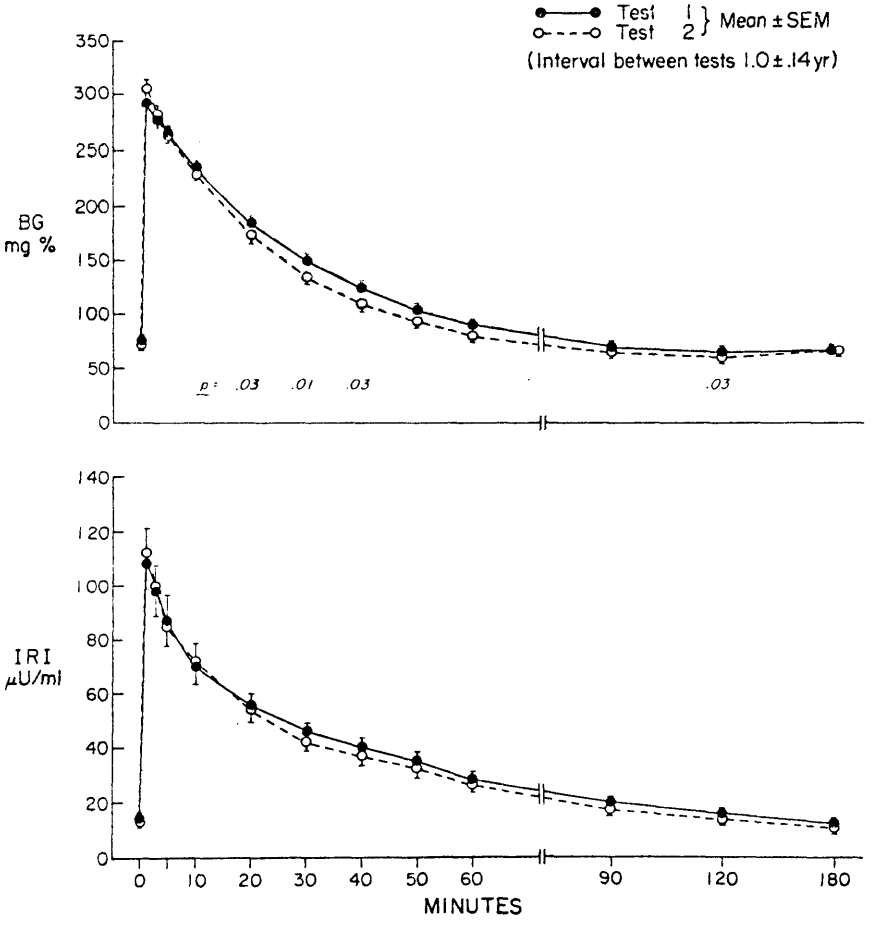

FIGURE 1

Blood glucose (BG) and serum immunoreactive insulin (IRI) during IVGTT (0.5 gm. per kilogram body weight) in normal subjects (n = 42).

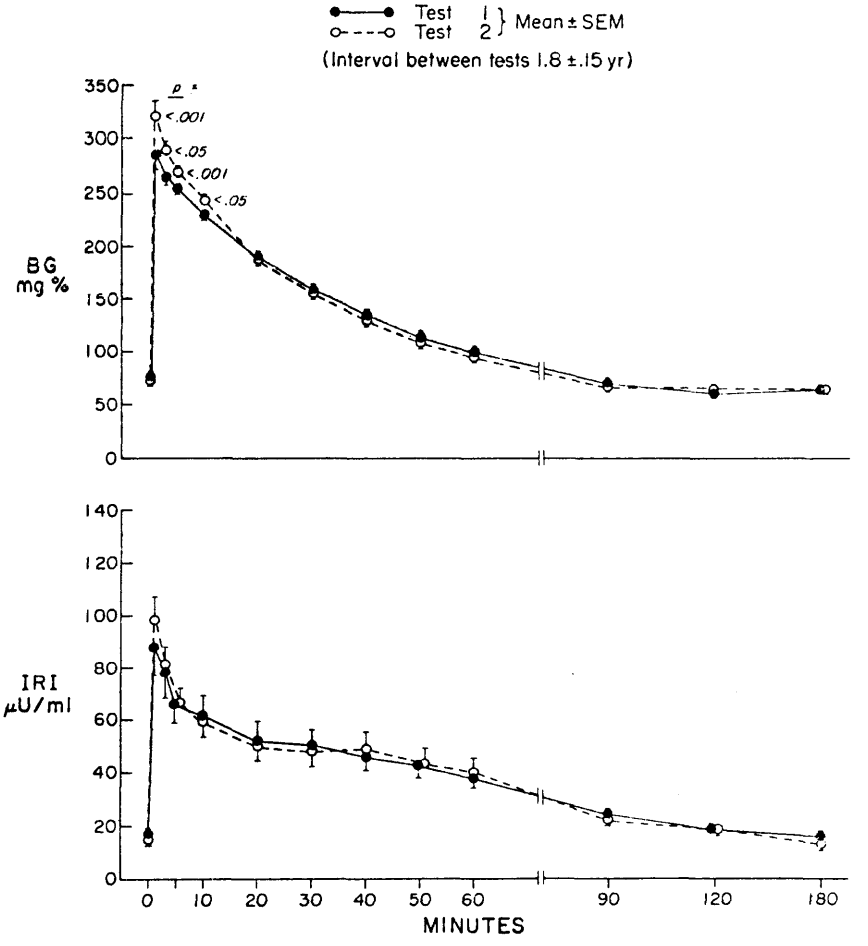

FIGURE 2

Blood glucose (BG) and serum immunoreactive insulin (IRI) during IVGTT (0.5 gm. per kilogram body weight) in offspring (n = 34) of conjugal diabetic parents.

Further comparisons of BG and IRI responses for the two IVGTTs and the two OGTTs at each time interval were done by calculating correlation coefficients. The following salient features emerged from these analyses:

(a) More striking correlations existed at each time interval for both BG and IRI during IVGTTs than during OGTTs. Significant correlations existed for BG at eight out of 13 time intervals in normals and eight out of 13 time intervals in offspring groups during IVGTTs compared with only two out of 10 and four out of 10 time intervals during the OGTTs, respectively. Similarly, for IRI, all 13 samples showed significant correlations in each group during IVGTT whereas only six out of 10 and seven out of 10 samples during OGTT reached significant values in normals and the offspring, respectively.

(b) Both for IVGTTs and OGTTs, the mean IRI concentrations were more often and more strikingly correlated ($p < 0.01$ at each time interval) than those of BG in both normals and the offspring.

(c) Of the two groups, the offspring showed a tendency for greater correlation, particularly of BG responses, at each time interval. To take fasting BG itself, the offspring had a correlation coefficient of 0.57 ($p < 0.001$) and 0.62 ($p < 0.001$) for the IVGTTs and OGTTs, respectively, whereas the corresponding values for normals were 0.37 ($p < 0.05$) and 0.26 (p = N.S.), respectively.

(d) When the responses of BG and IRI were expressed as the insulin-glucose (I/G) ratios, once again more striking correlations were seen for IVGTTs than for OGTTs in both normals and offspring.

Correlations of Secondary Parameters Derived from BG and IRI Responses

For more detailed comparison of the two tests, peak IRI response, early and total IRI area, early and total BG area, ratios of early to the total IRI and BG areas, respectively, ratios of early and total IRI areas to the corresponding BG areas and the slope of regression line of serum IRI upon blood glucose ('B') for each subject was evaluated. Tables 2 and 3 present the

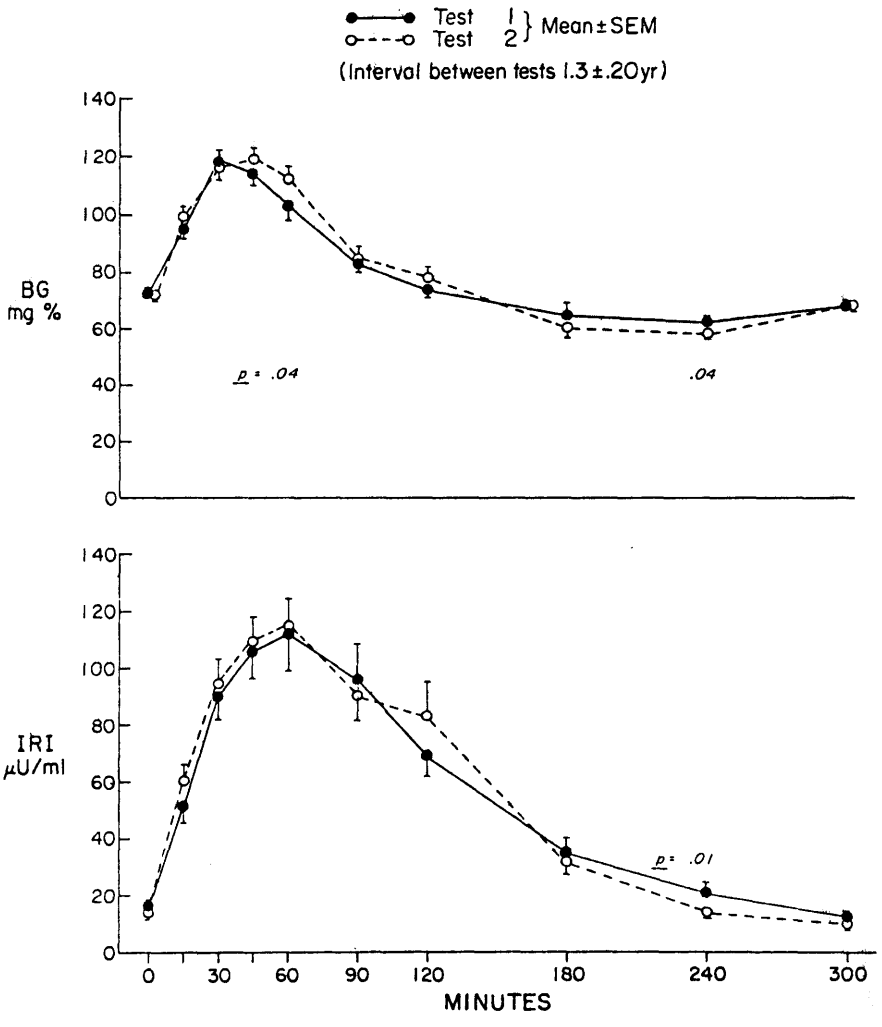

FIGURE 3

Blood glucose (BG) and serum immunoreactive insulin (IRI) during OGTT (100 gm.) in normal subjects (n = 26).

mean responses of these in the two groups of IVGTTs and OGTTs, respectively.

There were only sporadic significant differences between the two tests among all these parameters. Interestingly during the second OGTT (table 3) the offspring group revealed greater insulin release, as depicted by significantly higher peak IRI, greater insulin area during the first 60 minutes, and greater increment of IRI per unit rise of glucose ('B'). However, this was not accompanied by any significant difference in early (0 to 60 minute) or total (0 to 300 minute) BG area or in BG area ratio. This would suggest that factors other than the BG concentration per se are responsible for insulin release.

Correlation coefficients derived from all the secondary parameters for the two tests are presented in table 4. Like the correlations for the mean BG and IRI levels at each time interval, the following patterns of correlation become apparent.

(a) More striking correlations were apparent between most of the parameters in IVGTTs than in OGTTs for both the normals and the offspring.

(b) The offspring tended to show a better correlation between the two IVGTTs, again, for BG responses in particular, when compared with normals. There was no significant correlation between the early or total BG areas in normals whereas in the offspring a significant correlation existed for both the BG areas.

(c) The single most highly correlated index in both groups for both type of tests was the slope of regression line between insulin and glucose ('B').

Correlation of IVGTTs with OGTTs

Table 5 reveals correlations between several parameters in 17 normals and nine offspring who received two intravenous as well as two OGTTs. The offspring group showed striking correlation between peak IRI response, total insulin response, and insulin incremental response ('B') when either the first or the

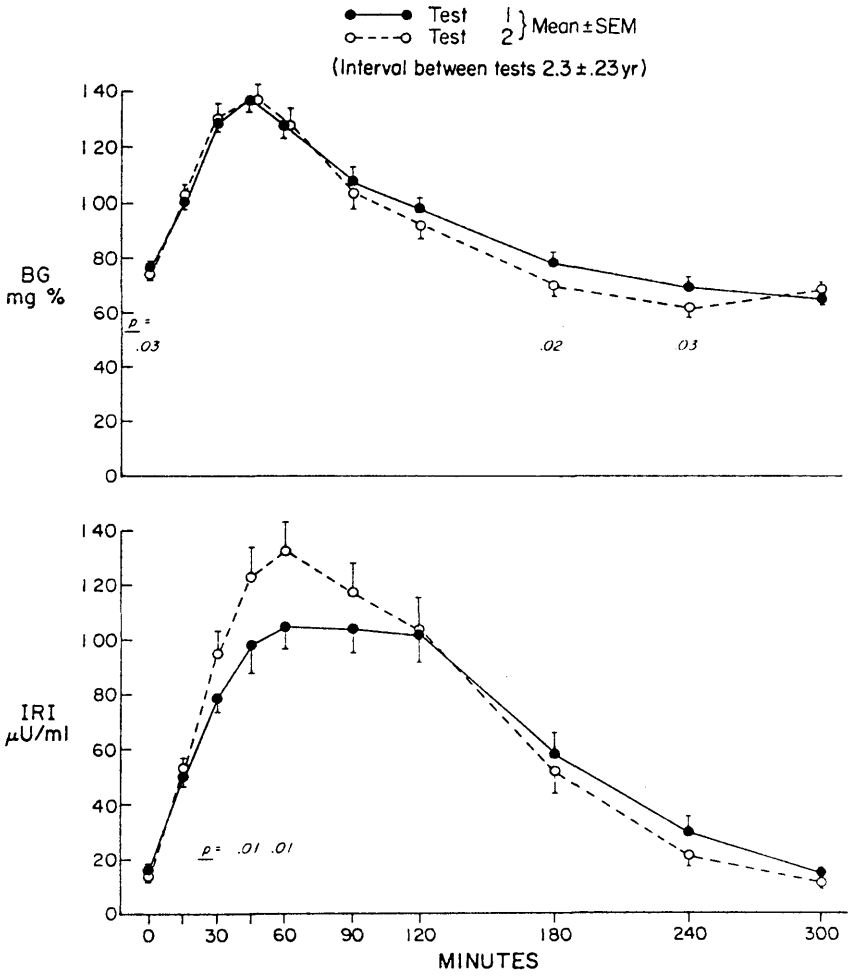

FIGURE 4

Blood glucose (BG) and serum immunoreactive insulin (IRI) during OGTT (100 gm.) in offspring (n = 32) of conjugal diabetic parents.

second IVGTT and the corresponding OGTT were compared. However, there was no correlation when the BG responses during OGTT were compared with the K_g value during IVGTT. None of the parameters showed a significant correlation in the normal subjects.

Distribution of Abnormal Tests in the Offspring

As depicted in table 6, considering both OGTTs and both IVGTTs, about 53 per cent were classified as chemical diabetics by OGTT whereas only about 12 per cent were detected by IVGTT. Significantly more OGTT than IVGTT were abnormal ($p < 0.001$) by chi-square analysis.

Reproducibility Analyses

Tables 7 and 8 display the quartile distributions of BG in normal men for each sampling time during OGTTs and IVGTTs, respectively. These normal quartile distributions were employed for subsequent determinations of the reproducibility index for each subject (vide supra). Tables 9 and 10 present the distribution of BG in quartiles for each normal subject and the offspring, respectively, during OGTT and their corresponding reproducibility indices based on test 1 and test 2. Similarly, reproducibility indices for IVGTTs were derived for each subject in the two groups (details not shown). As indicated above (see Methods section), for IVGTT, a reproducibility index of 6 or greater was required for a test to be classified as "reproducible."

Tables 11 and 12 present a comparative analysis of the quartiles of BG distribution in the offspring and normals for the OGTTs and IVGTTs, respectively. The aggregates of the quartiles during the entire test were also compared. The latter revealed a somewhat uniform distribution for OGTT quartiles but significantly nonuniform distribution for IVGTTs in the offspring ($p < 0.02$).

Table 13 presents a chi-square analysis of the reproducibility of the two types of GTTs within each subject group and between the two subject groups. No

TABLE 2

IVGTT — Test 1 versus test 2

	Normals (n = 42)					Offspring (n = 34)				
	Test 1		Test 2			Test 1		Test 2		
	Mean	S.E.M.	Mean	S.E.M.	P	Mean	S.E.M.	Mean	S.E.M.	P
Peak IRI	110	9.8	116	9.4	—*	90	11.5	107	9.9	—
0-10 min. IRI†	703	78	908	215	—	477	77	533	59	—
0-60 min. IRI†	2,236	169	2,709	581	—	2,035	290	2,255	306	—
0-10/0-60 min. IRI‡	30.5	1.7	34.5	2.1	—	23.6	1.9	27.1	2.7	—
0-10 I/G§	0.40	0.05	0.37	0.03	—	0.28	0.05	0.27	0.03	—
0-60 I/G§	0.46	0.06	0.70	0.20	—	0.37	0.05	0.38	0.04	—
'B'//	0.38	0.05	0.39	0.03	—	0.27	0.05	0.26	0.03	—
0-10 min. BG†	1,799	36	2,101	279	—	1,735	52	1,908	55	<0.01
0-60 min. BG†	5,352	218	5,447	525	—	5,835	240	5,772	194	—
0-10/0-60 min. BG‡	35.5	1.4	40.1	1.8	0.01	30.6	0.86	34.0	1.4	<0.05
K_g**	2.24	0.1	2.52	0.2	—	1.77	0.08	2.01	0.10	<0.05

*Not significant.
†Area above the baseline over the specified time period (IRI, μU./ml./min.; BG, mg./100 ml./min.).
‡Ratio of the areas for the specified time periods.
§Ratio of insulin area to the glucose area for the specified time period.
//Slope of linear regression equation of serum IRI upon blood glucose (μU./ml./mg./100 ml.).
**Rate of disappearance of BG during IVGTT (%/min.)

TABLE 3

OGTT — Test 1 versus test 2

	Normals (n = 26)					Offspring (n = 32)				
	Test 1		Test 2			Test 1		Test 2		
	Mean	S.E.M.	Mean	S.E.M.	P	Mean	S.E.M.	Mean	S.E.M.	P
Peak IRI	127	12.2	135	10.4	—*	136	12.2	167	12.6	0.01
0-60 min. IRI	3,727	392	4,041	324	—	3,315	269	4,510	315	0.01
0-300 min. IRI	11,545	1,283	12,152	1,172	—	14,971	1,438	16,456	1,612	—
0-60/0-300 min. IRI	32.9	2.1	35.4	2.2	—	24.8	1.6	30.4	1.6	0.03
0-60 I/G	2.50	0.38	2.08	0.14	—	1.43	0.14	1.97	0.22	—
0-300 I/G	4.50	0.91	3.60	0.33	—	2.74	0.27	3.33	0.40	—
'B'	1.40	0.14	1.60	0.14	—	1.19	0.11	1.47	0.13	0.01
0-60 min. BG	1,899	155	2,092	147	—	2,486	149	2,722	204	—
0-300 min. BG	3,317	295	3,679	354	—	6,089	472	5,930	639	—
0-60/0-300 min. BG	62.0	3.6	59.5	2.41	—	45.6	2.8	52.2	3.4	—

For explanation of abbreviations, see footnotes to table 2.
*Not significant.

TABLE 4

Comparison of serum immunoreactive insulin (IRI) responses during the two IVGTTs and the two OGTTs in normal subjects and the offspring

	IVGTT — Test 1 versus test 2					OGTT — Test 1 versus test 2			
	Normals (n = 42)		Offspring (n = 34)			Normals (n = 26)		Offspring (n = 32)	
Parameter	r	P	r	P	Parameter	r	P	r	P
Peak IRI	0.74	<0.001	0.70	<0.001	Peak IRI	0.47	<0.05	0.63	<0.001
0-10 min. IRI	0.33	<0.05	0.70	<0.001	0-60 min. IRI	0.49	<0.05	0.28	—
0-60 min. IRI	0.23	—*	0.75	<0.001	0-300 min. IRI	0.58	<0.01	0.60	<0.001
0-10/0-60 min. IRI	0.64	<0.001	0.62	<0.001	0-60/0-300 min. IRI	0.39	<0.05	0.23	—
0-10 I/G	0.79	<0.001	0.69	<0.001	0-60 I/G	0.27	—	0.41	<0.05
0-60 I/G	0.23	—	0.74	<0.001	0-300 I/G	0.60	<0.01	0.60	<0.001
'B'	0.82	<0.001	0.77	<0.001	'B'	0.58	<0.01	0.61	<0.001
0-10 min. BG	−0.07	—	0.35	<0.05	0-60 min. BG	0.43	<0.05	0.27	—
0-60 min. BG	0.23	—	0.52	<0.01	0-300 min. BG	0.25	—	0.39	<0.05
0-10/0-60 min. BG	0.54	<0.001	0.15	—	0-60/0-300 min. BG	0.19	—	0.26	—
K_g	0.36	<0.05	0.37	<0.05					

For explanation of abbreviations, see footnotes to table 2.
*Not significant.

TABLE 5

Comparison of IVGTT with OGTT variables

	Test 1 (normals) n = 17		Test 2 (normals) n = 17		Test 1 (offspring) n = 9		Test 2 (offspring) n = 9	
Parameter	r	P	r	P	r	P	r	P
Peak IRI	0.20	—*	0.23	—	0.82	<0.01	0.83	<0.05
IRI_1†	0.17	—	0.39	—	−0.17	—	0.91	<0.01
IRI_2†	0.13	—	0.39	—	0.91	<0.001	0.89	<0.01
IRI_1/IRI_2	−0.32	—	0.06	—	0.56	—	0.88	<0.01
I/G_1§	0.26	—	0.36	—	−0.02	—	0.86	<0.05
I/G_2§	0.20	—	0.08	—	0.52	—	0.89	<0.01
'B'	0.33	—	0.21	—	0.93	<0.001	0.88	<0.01
BG_1‡	0.15	—	0.12	—	−0.10	—	0.05	—
BG_2‡	0.42	—	0.03	—	−0.23	—	0.16	—
BG_1/BG_2	0.20	—	−0.23	—	−0.03	—	0.40	—
Kg/BG_1//	−0.40	—	0.05	—	−0.56	—	−0.19	—
Kg/BG_2//	−0.45	—	0.07	—	0.27	—	−0.19	—

*Not significant.

†IRI_1 represents 0-10 min. IRI area and 0-60 min. IRI area during IVGTT and OGTT, respectively. IRI_2 represents 0-60 min. IRI area and 0-300 min. IRI area during IVGTT and OGTT, respectively.

‡BG_1 and BG_2 represent BG areas corresponding to the IRI areas.

§I/G_1 represents 0-10 min. IRI/0-10 min. BG area for IVGTT and 0-60 min. IRI/0-60 min. BG area for OGTT. I/G_2 represents 0-60 min. IRI/0-60 min. BG area for IVGTT and 0-300 min. IRI/0-300 min. BG area for OGTT.

//Kg represents glucose disappearance rate during IVGTT. BG_1 and BG_2 are BG areas during OGTT.

significant differences were noted when the reproducibility of OGTTs was compared with that of IVGTTs in either group nor when either test was compared with the corresponding test in the other group, i.e., normal versus offspring. Of note, only about 50 per cent of OGTTs or IVGTTs in both groups were reproducible. For the IVGTTs, when K_g values alone were considered, 13 of 27 normals and 11 of 22 offspring were reproducible, considering K_g in quartile 2 or 3 as reproducible (data not shown).

Of the normal subjects, eight were restudied with both types of GTTs only three days apart. Similar analyses of reproducibility in these were compared with those obtained for tests repeated at long intervals (table 14). However, no significant differences in the reproducibility were observed.

TABLE 6

Pattern of abnormality in offspring of diabetic parents during two IVGTTs and two OGTTs

	IVGTT	OGTT
No. tested	34	32
No. abnormal in test 1 only	3	6
No. abnormal in test 2 only	1	6
No. abnormal in both tests	0	9
% with chemical diabetes	4/34 = 11.8%*	17/32 = 53.1%*

*Abnormal IVGTT versus abnormal OGTT — $p < 0.001$ (chi-square analysis).

DISCUSSION

Based on blood glucose concentrations, intraindividual variability in the OGTT has been documented in the literature.[1-12] Considerable variability has been found irrespective of sex,[12] age, family history of diabetes, weight status, race, drug addiction,[6] and chemical diabetes.[7] Similar studies of reproducibility of IVGTT are not available; however, it is recognized that this test is significantly less often abnormal than the OGTT.[8,15,16] Such studies underscore the limitations of both OGTT and IVGTT in detection of abnormality in a given individual.

TABLE 7

Quartile distributions of blood glucose changes in normal male subjects (n = 20): OGTTs (test 1 minus test 2)

	Time (min.)									
Quartile	F	15	30	45	60	90	120	180	240	300
1	−14 to − 5	−16 to −46	− 8 to −53	−25 to −53	−19 to −46	−25 to −56	−29 to −19	−34 to − 9	−7 to − 4	−14 to − 6
2	− 4 to 0	−15 to − 5	− 7 to 3	−24 to 5	−18 to −11	−24 to − 4	−18 to − 4	− 8 to 2	−3 to − 2	− 5 to 1
3	1 to 4	− 4 to 8	4 to 24	6 to 9	−10 to 5	− 3 to −21	− 3 to 6	3 to 18	−1 to 3	2 to 6
4	5 to 15	9 to 41	25 to 45	10 to 22	6 to 26	22 to 40	7 to 39	19 to 42	4 to 29	7 to 25

TABLE 8

Quartile distributions of changes in blood glucose concentrations and glucose disappearance rates (Kg) in normal male subjects (n = 27): IVGTT (test 1 minus test 2)

	Time (min.)						
Quartile	F	1	3	5	10	20	30
1	−10 to − 3	−132 to − 33	−183 to − 32	−52 to −24	−52 to −16	−59 to −22	−83 to −18
2	− 2 to 2	− 32 to − 2	− 31 to 4	−23 to − 4	−15 to 2	−21 to − 3	−17 to − 5
3	3 to 5	− 1 to 44	5 to 31	− 3 to 27	3 to 23	− 2 to 29	− 4 to 26
4	6 to 16	45 to 102	32 to 110	28 to 58	24 to 96	30 to 69	27 to 94

Quartile	40	50	60	90	120	180	Kg
1	−95 to −20	−107 to − 21	−91 to −19	−39 to −10	−11 to − 8	−16 to − 8	−2.18 to −0.35
2	−19 to − 3	− 20 to − 6	−18 to 1	− 9 to − 3	− 7 to − 2	− 7 to − 1	−0.34 to 0.05
3	− 2 to 28	− 5 to 19	2 to 18	− 2 to 4	− 1 to 4	0 to 6	0.06 to 0.43
4	29 to 96	20 to 101	19 to 81	5 to 29	5 to 31	7 to 14	0.44 to 2.17

TABLE 9

Distribution of blood glucose changes in quartiles for individual subjects at each time interval of OGTTs (test 1 minus test 2): Normal males (n = 20)

	Time (min.)										
Patient	F	15	30	45	60	90	120	180	240	300	Reproducibility index
172	1	2	2	3	2	1	2	3	2	1	7
173	3	3	3	4	3	4	2	3	3	1	6
181	3	4	3	4	4	3	2	3	1	4	4
185	3	4	4	3	4	4	4	4	4	4	1
186	4	—	4	3	1	3	4	2	3	3	5
190	3	3	3	1	3	3	1	2	2	2	7
191	3	3	2	3	3	4	3	1	4	3	7
193	3	3	1	2	4	3	3	4	4	3	6
231	1	2	4	2	1	2	4	1	4	3	4
258	2	2	4	2	2	2	3	1	3	4	6
316	1	1	1	1	1	1	1	2	1	1	1
322	2	3	4	3	3	1	1	2	1	1	4
334	3	4	2	1	2	3	3	4	2	2	6
337	1	2	1	1	1	2	1	1	3	2	4
349	2	1	1	4	3	1	2	2	1	2	4
372	2	1	1	2	1	1	2	3	1	3	4
383	3	2	2	2	2	2	2	1	3	1	7
385	4	3	3	4	4	4	4	3	4	—	3
395	2	1	3	4	4	4	4	3	1	1	3
412	1	1	1	1	2	2	1	4	1	—	2

Total subjects = 20.
Number of subjects with reproducibility index ≥ 5 = 9.

In the present study, we compared the variability in OGTT and IVGTT by correlating the mean BG and IRI responses as well as several other parameters of glucose disposal and insulin secretion between the two tests. As stated, these results indicate greater correlation between IVGTTs than between OGTTs. Furthermore, of the various parameters analyzed, IRI responses reveal greater correlation than do BG responses, when individual values as well as areas under the curve are considered. The better correlations of IRI may be due to the fact that in both types of tests, IRI is near maximally stimulated whereas BG values are far from maximal. This is of interest in view of a greater coefficient of variation (S.D./x × 100) for insulin than for glucose during the same assay.[20,21] A plausible explanation for greater variability of OGTT appears to be that certain ill-defined and nonquantifiable physiological and psychologic factor(s) could influence the gastrointestinal motility, glucose absorption, and the release of gut factor(s) known to account for a major fraction of insulin release during OGTT.[22]

Somewhat surprising and of even greater interest was the observation that the offspring of two diabetic parents tended to reveal greater correlation between the two consecutive tests (particularly the insulin responses) than the normal controls, despite the fact that the mean interval between the two tests was about two years in the offspring and only about one year in the normals. We have previously shown that the incidence of overt diabetes in this apparently

TABLE 10
Distribution of blood glucose changes in quartiles for individual subjects at each time interval of OGTTs (test 1 minus test 2): Male offspring (n = 20)

	Time (min.)									
Patient	F	15	30	45	60	90	120	180	240	300	Reproducibility index
229	4	2	1	2	3	2	3	3	4 (5)	4	6
244	4	3	2	4	3	2	4	1	3	4	5
254	4	3	3	4	4	4	4	2	3	2	5
258	3	3	3	4 (7)	4	3	4	3	3	2	6
276	3	3	1	1	1	1	1 (1)	1 (4)	4	2	2
282	4	2	4	4 (22)	4 (9)	3	4	3	1 (3)	1 (4)	3
283	3	1	1	2	3	3	4	4	4	2	4
326	2	1	1	1	1	2	4	4	1 (14)	1 (4)	1
327	4	3	2	2	2	1	3	1 (19)	4	2	6
329	4	2	1	2	1	1	2	3	2	4	5
338	1	4	2	2	3	1	1 (2)	1	4	—	3
351	1	1	2	2	3	2	1 (1)	1	4	3	5
355	1	2	1	1 (11)	1	3	2	3	3	—	5
372	2	2	1	2	3	3	3	3	4	1	6
405	3	2	1	2	4 (18)	4 (28)	4	3	4 (6)	—	3
414	4	2	2	4	4	3	4	4	4	—	3
424	3	4	3	2	1	1	4	4	4	4	2
427	3	4	3	2	1	2	3	2	4	—	5
436	4	3	4 (15)	4 (31)	4 (26)	4 (22)	4 (6)	4	2	—	2
452	4	2	1	1	1	4	4	3	4 (35)	3	3

Total subjects = 20.
Number of subjects with reproducibility index ≥ 5 = 10.
Numbers in parentheses indicate the deviations of blood glucose concentrations beyond the normal quartile ranges (in mg. per 100 ml.).

"high-risk" "prediabetic" group is rather small.[8] However, by repetitive testing, many more of the offspring are found to have chemical diabetic patterns of glucose tolerance than by doing a single test.[8,10,23] About half of the 32 offspring in this study showed either the first or the second or both OGTTs to be abnormal. It is likely that with relatively diminished glucose tolerance, despite normal fasting blood glucose values, these offspring exhibit a near-maximum stimulation of the beta cell, resulting in a greater correlatibility of IRI secretion on repetitive testing.

It must be noted that, in contrast to the greater

TABLE 11
Comparison of patterns of distribution of blood glucose changes in quartiles in offspring (n = 20) with those in normal subjects (n = 20): OGTTs (test 1 minus test 2)

	Quartiles (offspring)				Quartiles (normals)				
Time	1	2	3	4	1	2	3	4	P*
F	3	2	6	9	5	5	8	2	<0.1
15	3	8	6	3	5	5	5	5	—
30	9	5	4	2	6	4	5	5	—
45	4	10	0	6	5	5	5	5	<0.1
60	7	1	6	6	5	5	5	5	—
90	5	5	6	4	5	5	5	5	—
120	3	2	4	11	5	6	4	5	—
180	5	2	8	5	5	5	6	4	—
240	2	2	4	12	7	3	5	5	—
300	3	5	2	4	6	4	5	3	—
Total	44	42	46	62	54	47	53	44	—

*P by chi-square analysis.

TABLE 12
Comparison of patterns of distribution of blood glucose changes in quartiles in offspring (n = 22) with those in normal subjects (n = 27): IVGTTs (test 1 minus test 2)

	Quartiles (offspring)				Quartiles (normals)				
Time	1	2	3	4	1	2	3	4	P*
F	8	7	5	2	8	6	8	5	—
1	11	7	3	0	7	7	7	6	<0.05
3	9	9	4	0	7	7	7	6	<0.1
5	9	7	6	0	7	8	6	6	—
10	10	3	7	1	7	8	7	5	—
20	2	11	6	3	8	7	6	6	—
30	3	6	9	3	7	7	7	6	—
40	5	7	6	4	7	7	6	6	—
50	5	4	8	5	7	8	6	6	—
60	8	3	8	3	7	7	6	6	—
90	6	2	5	7	6	6	7	5	—
120	5	5	5	5	6	6	7	5	—
180	5	4	6	2	6	6	7	5	—
Total	86	75	78	35	90	90	87	73	<0.02

*P by chi-square analysis.

TABLE 13
Comparison of reproducibility for OGTTs and IVGTTs between normal subjects and the offspring (chi-square analysis)

	Normals		Offspring	
	OGTT	IVGTT	OGTT	IVGTT
Total	20	27	20	22
Reproducible*	9	16	10	15
	P = N.S.		P = N.S.	
	P = N.S.			
		P = N.S.		

*Subjects with reproducibility indexes ≥ 5 in OGTTs and ≥ 6 in IVGTTs.

TABLE 14

Comparison of reproducibility for OGTTs in normal subjects at short and long intervals (chi-square analysis)

	Interval = 3 days		Interval = 1.3 + 0.20 yr.	
	OGTT	IVGTT	OGTT	IVGTT
Total	8	8	20	27
Reproducible*	3	7	9	16
	P = N.S.		P = N.S.	
	P = N.S.			
			P = N.S.	

*Subjects with reproducibility index ≥ 5 in OGTTs and ≥ 6 in IVGTTs.

correlatibility of repeated IVGTTs compared with that of OGTTs and of each type of test in the offspring compared with that of the normals, the reproducibility of the tests was no different in either group. Only about 50 per cent of either type of glucose tolerance test in either group could be considered reproducible. Although several investigators have described the variability of OGTT among the same group of subjects, the quantitation of variability has not been assessed in detail in those studies.[1-12] An assessment of reproducibility of OGTT or IVGTT must take into account the variability of BG at each time interval during the test. We have, therefore, developed a reproducibility index for each subject, taking into account variability of BG through the entire test, rather than at selected time intervals.

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