Reproducibility of the Oral Glucose Tolerance Test

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SUMMARY

Results are presented of a study undertaken to explore the reproducibility of the 100 gm. oral glucose tolerance test. Over 400 male volunteers from an institutional population, who were not known to be diabetic, participated in a program which included a series of six tests for each individual over a period of one year. Ten men were tested daily, and each retested at intervals of approximately two months. Bloods were drawn at fasting, one, two and three hours after the administration of a 100-gm. glucose drink and duplicate determinations were obtained on the Auto-Analyzer. Average blood glucose levels for the total group remained stable over time. However, blood glucose levels for individuals varied considerably. On single tests, some of the men exhibited borderline or diagnostic test readings, but in no case was this consistent over all tests. Some of the factors which contribute to individual variance are considered briefly. Implications of the data on interpretation of the results of oral glucose tolerance tests are presented. DIABETES *14*:473-80, August 1965.

I. *U.S. Public Health Service Interest in Oral GTT*

A procedure frequently recommended in the diagnosis of diabetes is the oral glucose tolerance test (GTT). Furthermore, this test or a modification thereof is used as a retest in an increasing number of diabetes screening programs. After an initial test, those individuals with an abnormal glucose reading are retested, using the GTT. The increasing use of this test is based on the experience that a diagnosis is more likely to be made when a well-chosen screening test is positive and confirmed by a GTT before referral to a physician for definitive diagnosis and treatment. In recent years, the retesting of positive screenees, which often involves one or more blood samples, has become more practical due to the availability of automated technics.

Since many of the persons who have received the oral glucose tolerance test through a screening program or through their private physicians have had only a single test, some concern about the adequacy of a single result has been raised. This has been true particularly when a negative result is obtained on a person who was positive at screening, and who may have characteristics associated with diabetes, such as obesity or a family history of the disease.

Thus, we must ask ourselves: Can we be confident that such persons do not require further observation?

The problem is being explored in several ways. First, observations are being made, over a period of time, of people who were positive to screening tests but who were not referred to their physicians when an oral glucose tolerance test was interpreted as negative. Second, a review of the literature has indicated that there are variations in individual test results.[1-4] The latter information stimulated a further study of the tolerance test itself. Interest has been directed toward certain questions. To what degree is the test reproducible in the same individual? Is the variation in the normal individual less than that in the abnormal? Is variation significant in the interpretation of the test? Is it typical for persons progressing into a diabetic state to exhibit vacillation between abnormal and normal blood glucose levels? If such vacillation is characteristic of impending or early diabetes, can one rely on a single test result for the very group that should be identified through use of the test? The answers to such questions are not well defined.

II. *Objective*

Data presented in this paper are preliminary and directed toward further definition of the reproducibility of the oral glucose tolerance test in males not known to have diabetes or any other condition that might affect their blood sugar levels.

III. *Description of study*

A group of male prisoners at a federal prison who volunteered for the project comprised the study population. Subjects were not accepted for the project if they were expected to leave the prison within one year, or if they were known to have diabetes, or if other chronic conditions were present which might affect glucose tolerance.

Four-hundred and forty-three males were included in the initial population. Information was collected as to age, race, height, weight, prison occupation, smoking status, family history of diabetes, and prior drug ad-

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diction. Before each test, individual participants reported the time of their last food intake. Also, any illness, medication, changes in eating pattern or changes in physical activity were recorded for the previous two-week period. Weight was measured prior to each test.

A prescribed diet was not administered to volunteers before the day of the test. Review of the menus and observation of the portions that were served to the prisoners, by a nutritionist, revealed that the prison menu provided an average of 475 gm. of carbohydrate per man per day. It was the investigator's impression from these observations, that the subjects in the study consumed well above the daily average of 250 to 300 gm. of carbohydrate generally recommended for three days prior to a glucose tolerance test.[5,6] (When the urine is tested for acetone, an indication is given of inadequate carbohydrate in the diet.[7] Positive acetone tests were obtained in three volunteers while fasting.) Though occasionally a man may have had an inadequate preparatory diet, there is greater assurance of proper diet for this population than for a noninstitutionalized group.

Ten men were tested each day. Each man was scheduled to receive six 100-gm. oral tests, with a period of approximately two months between tests. On the evening prior to the test, the men were locked in a separate cell block to insure that they would be in a fasting state the next morning. At 7:00 a.m., fasting blood samples were drawn using Becton Dickinson vacutainers, No. 3204, 7 cc. These contained 50 mg. of sodium fluoride as a preservative and 5 mg. of EDTA as an anticoagulant. Then a 100-gm., 50 per cent glucose solution was administered. Venous blood samples were drawn at one, two, and three hours after the glucose loading. During the testing period, the volunteers remained in the special cell block.

Blood samples were taken immediately to the prison laboratory and processed on the Technicon AutoAnalyzer, on whole blood, according to the procedures recommended by the manufacturer at the time of the study (1962-63).[8,9] Most of the determinations were made within two hours after the blood samples were drawn. Each specimen was separated into two sample cups and two readings were obtained. In this analysis, means of the two readings were used.

The standard deviation of duplicates, as measured by the differences between the first sample and the second sample, using one-hour post glucose specimens, was 1.5 mg. per 100 ml.* (See footnote, column two).

All blood samples were obtained and processed in as uniform a manner as possible. Quality control procedures in the laboratory were precise and were rigidly maintained. Water standards and reagents were prepared in the laboratory. A control serum was prepared for use in several batches by our research laboratory; its value was 150 mg. per 100 ml. Standards and one control serum were processed before each set of ten unknowns.

RESULTS

1. *Study variables.* Six complete tests were administered to each of 334 men. During the course of the project, 109 men were dropped from the study. Nineteen only were dropped from the study at their own request; seventy were transferred or paroled, and twenty were dropped for various other reasons.

The men ranged in age from eighteen to sixty-three years. Distribution by age is given in table 1, along with the frequencies of other characteristics. The men's weight status was obtained by comparing heights and weights to those in standard tables prepared by the Metropolitan Life Insurance Company.†[10] The percentage who were overweight and who were underweight was calculated. Those 10 per cent or more overweight were classified as overweight and those 10 per cent or more underweight were classified as underweight.

2. *Population distribution of glucose values.* Table 2 shows the group averages expressed as means and the variation of values around the group average expressed as standard deviations for the four readings of the six tests. It should be noted that the means and the standard deviations are stable over the six tests for the same reading. This indicates that reliable estimates of group averages and group variability can be obtained

*This measure of precision by glucose level was as follows:

Glucose Level mg. per 100 ml.	*Standard Deviation* Sp
<80	1.16
80-99	1.44
100-119	1.50
120+	1.70
Total	1.49

$$\text{Where: } S_p = \left(\frac{\Sigma d^2}{2N}\right)^{1/2}$$

d = Sample 1 — Sample 2.

†These standard tables are based on life expectancy rather than average weights by height and sex.

TABLE 1

Characteristics of study population consisting of 334 men

Characteristics	Number	Per cent
Age:		
Under 25	30	9.0
25-29	119	35.6
30-34	83	24.8
35-39	57	17.1
40-44	23	6.9
45 and over	22	6.6
Total	334	100.0
Weight Status*		
Underweight	29	8.7
Normal	167	50.0
Overweight	138	41.3
Total	334	100.0
Prison Occupation:		
Industrial	108	32.3
Clerical	47	14.1
Other	179	53.6
Total	334	100.0
Race:		
Caucasian	238	71.3
Non-Caucasian	96	28.7
Total	334	100.0
Other Factors:		
Nonsmokers	40	12.0
Family history of diabetes	40	12.0
History of drug addiction	84	25.1

*Based on data presented in Statistical Bulletin, Metropolitan Life Insurance Company, Vol. 40, November-December 1959.

from the administration of a single test to a group. However, it should not be inferred from these results that the test is reproducible for each individual, over a period of time.

3. *Variation of results in individuals.* Administration of six tests to each individual in this study has permitted the investigators to obtain each man's average over all tests separately, for fasting, and for one, two, and three hours after glucose. These averages can be used as an estimate of his "true" glucose values over the year. In addition, we have measured the variability of the individual's test results around his own average by computing his standard deviation. These can be used as a measure of the reproducibility of the test for individuals.

The standard deviations, averages, and values for each test, one hour after glucose, are presented for cases 172 and 034. Case 172 illustrates the individual who is highly variable. Case 034 represents an individual whose one-hour values are stable over the six tests. In each case, the reproducibility of the test is reflected by the standard deviations.

Blood sugar levels one hour after glucose

Case 172	Case 034
Mean 146.9	Mean 96.3
S.D. = 47.1	S.D. = 4.0
(mg. per 100 ml.)	(mg. per 100 ml.)
Test 1 = 148.0	Test 1 = 93.0
Test 2 = 142.5	Test 2 = 100.0
Test 3 = 108.0	Test 3 = 94.5
Test 4 = 215.0	Test 4 = 102.0
Test 5 = 86.0	Test 5 = 96.5
Test 6 = 182.0	Test 6 = 92.0

Figure 1 shows the distribution of the averages for the individuals, based on six tests, by hour, after glucose load. The range of the averages and the median values are:

	Range of individual means (mg. per 100 ml.)	Median values
Fasting	66.4 to 103.8	76.8
One hour	63.4 to 199.6	100.5
Two hours	46.0 to 148.8	84.0
Three hours	29.4 to 116.8	64.8

Figure 2 shows the distribution of the standard deviations of the individuals, based on six tests, by hour, after glucose load. The range of the standard deviations

TABLE 2

Group means and standard deviations for 334 men who completed six glucose tolerance tests, by time after glucose load and test number—whole blood (AutoAnalyzer)

Test	Number of Men	Fasting $\bar{X}$ (mg.)	Fasting S (mg.)	1st Hour $\bar{X}$ (per 100 ml.)	1st Hour S (per 100 ml.)	2nd Hour $\bar{X}$ (per 100 ml.)	2nd Hour S (per 100 ml.)	3rd Hour $\bar{X}$ (per 100 ml.)	3rd Hour S (per 100 ml.)
1st	334	77.0	5.28	106.1	30.16	86.0	20.42	66.5	18.24
2nd	334	76.0	5.44	105.6	29.81	85.9	22.29	65.8	18.33
3rd	334	76.1	5.28	104.7	29.34	87.6	22.45	64.9	17.21
4th	334	76.6	5.22	108.1	31.10	87.1	20.35	67.2	16.86
5th	334	78.2	5.22	106.5	30.04	88.1	20.28	66.9	15.37
6th	334	77.4	5.85	101.9	30.68	84.7	19.73	64.7	16.60

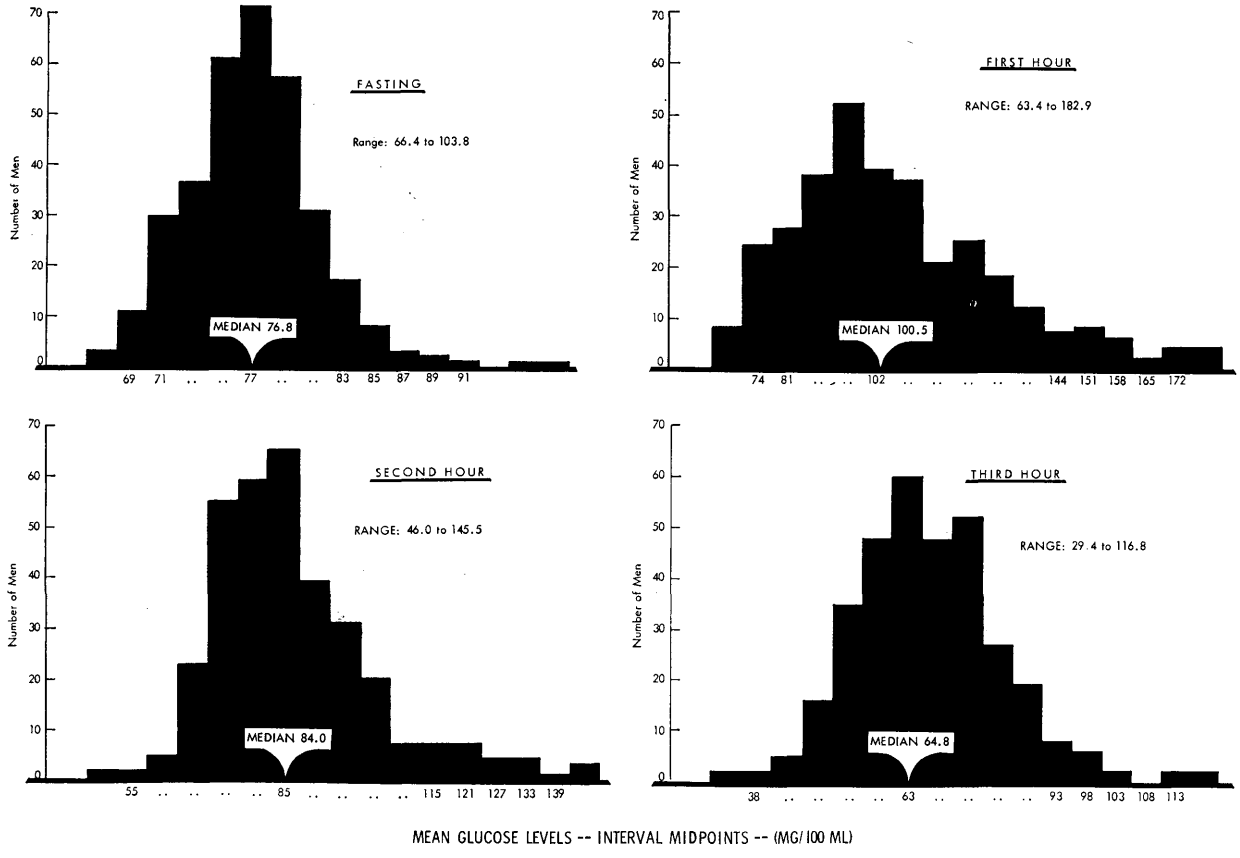

FIG. 1. The distribution of individual averages for 334 men based on six tests for fasting one, two, and three hours after glucose—whole blood (AutoAnalyzer).

and the median values are as follows:

	Range of individual standard deviations (mg. per 100 ml.)	Median values
Fasting	0.6 to 19.9*	2.8
One hour	4.0 to 47.1	17.2
Two hours	2.6 to 43.0	12.2
Three hours	2.7 to 30.1	10.9

This wide range of variability was found at all glucose levels in this population of nondiabetic men. The observed absence of homogeneity of variance in individuals is the basis for the lack of reproducibility of the test in individuals.

It was typical for a man's test result to vary within the interval of his average, plus or minus 34 mg. per 100 ml. (± two times the median individual standard deviation), at one hour after glucose. However, more than 20 per cent of the population varied beyond the interval of their average plus or minus 34 mg. per 100 ml. at one hour. With variations of this magnitude, as well as those exhibited at the other readings, it is difficult to interpret with any degree of confidence, single glucose tolerance tests that show abnormalities which are not extreme. It was possible, and it did occur in our population, for a man to vary from normal readings to those considered abnormal over several tests.

If the persons who show extreme variation or stability of test results could be identified by other characteristics, single glucose tolerance tests would be easier to interpret.

4. *Factors associated with individual variability.* A preliminary review of the results has been made to examine the relationship between individual variability and those factors for which we had collected information. The procedure has been to define those persons whose variability places them in the upper and lower

*The value of 19.9 was extreme; the next highest value was 9.7 mg. per 100 ml.

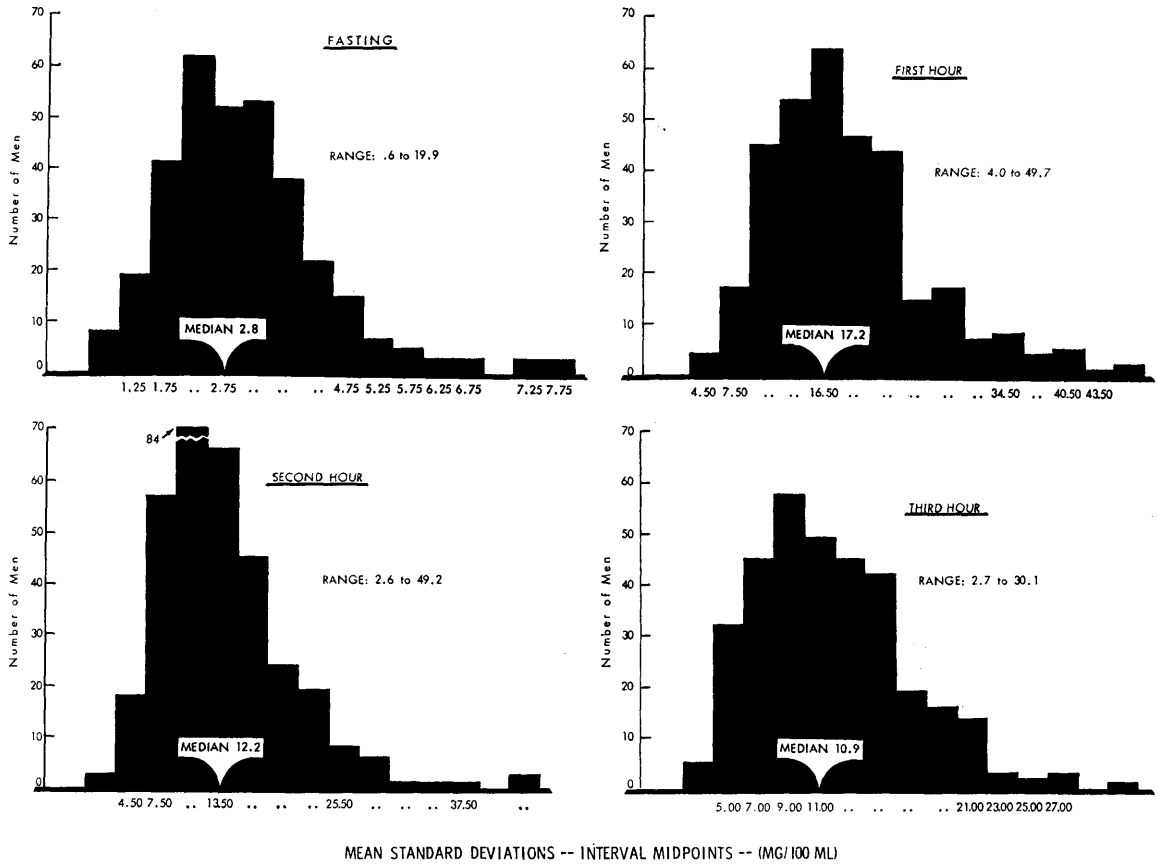

FIG. 2. The distribution of individual standard deviations for 334 men based on six tests for fasting one, two, and three hours after glucose—whole blood (AutoAnalyzer).

25 per cent of the total group. In defining an individual's over-all variability, equal weight was given to relative position at fasting and at one, two, and three hours after glucose. Persons in the upper and lower quartiles were then compared.

We found no significant differences (using chi-square) between the high and low variability groups when compared by age (less than thirty, thirty to thirty-nine, and forty and over); race; weight status classified as normal, underweight, and overweight; diabetes in the family; and a history of drug addiction.

The subjects who were identified as employees of the industrial program within the prison were found more frequently in the group with low variability. This might have been a reflection of greater physical activity on the part of these men; we cannot verify this since our classification for the item was relatively crude.

The strongest relationship was found between the rank of mean blood glucose values and individual variability. The following table indicates this relationship for those in the upper and lower quartiles of variability.

	Rank of blood sugar levels*			
	Upper 25 per cent	Middle 50 per cent	Lower 25 per cent	
High variability 25 per cent	37	31	16	84
Low variability 25 per cent	13	45	26	84
Total	50	76	42	168

While a relationship is apparent, there are individuals with high blood sugar levels and low variability and with low blood sugar levels and high variability. The relationship is not close enough to predict values for individuals. This is confirmed by a rank correlation coefficient of .28 between blood glucose values and standard deviations for the 334 men. Although this is a significant correlation, prediction for individuals cannot be made with precision.

Further examination of our data may show that a

*In defining the individual's rank for blood glucose values, equal weight was given to his relative position at fasting, and at one, two, and three hours after glucose.

combination of factors might permit identification of the highly variable or the highly stable individual. The data that we have presented, however, were not encouraging in this regard.

5. *Abnormal glucose tolerance test results.* Some of the test results for the 334 men indicated abnormality of glucose tolerance. The results have been examined by various criteria that have been used to interpret the glucose tolerance test. The reproducibility of the various criteria is considered in table 3.

The first column lists the case numbers of men who were positive at least once to one or more of the indicated criteria for interpreting test results. Interpretations include those recommended by a consulting committee to the U.S. Public Health Service, by Fajans and Conn, and by the American Diabetes Association.

TABLE 3

Cases positive to various criteria by case number and number of tests positive

	Case Number	Number of tests positive by criteria of: Criteria Recommended to USPHS by Consultants: Elevated at 2 or more readings	Diagnosable	Fajans* and Conn	American Diabetes Association
1	003	2	1	2	1
2	010	5	1	5	3
3	017	2	0	1	0
4	027	1	0	3	2
5	037	1	0	1	1
6	039	0	0	1	0
7	090	1	0	2	0
8	093	2	0	3	1
9	102	0	0	1	0
10	103	1	0	1	0
11	123	1	0	1	1
12	127	4	0	4	3
13	172	2	0	2	0
14	196	4	1	2	0
15	197	1	1	1	1
16	237	4	0	4	1
17	251	1	1	1	1
18	259	1	0	1	0
19	280	4	0	4	1
20	292	4	0	1	1
21	301	1	0	1	0
22	329	2	0	2	0
23	350	1	0	3	1
24	367	2	2	3	3
25	368	1	0	1	0
26	374	1	0	1	0
27	392	1	0	1	0
28	405	3	0	4	2
29	459	2	1	3	1
30	465	3	0	4	3
31	469	5	0	0	0
Total men positive		29	7	30	17
Total tests positive		63	8	64	27

*Modification of the criteria of Fajans and Conn explained in text.

Twenty-nine of the men, or 9 per cent, had elevations for two or more readings on at least one test, according to criteria recommended by a committee of consultants of the U.S. Public Health Service.[11,12] The critical levels, according to this method, are 110 mg. per 100 ml. in the fasting state and 170 at one hour, 120 at two hours, and 110 at three hours after glucose. Examination of the second column of table 3 shows that none of the men consistently exhibited elevations at these levels on two or more readings of the test. In a few cases, four or five of the six tests that were given to each man showed such elevations, but in no case did all six tests show these results.

None of these men had fasting blood sugar levels of 110 or more, although some showed values of 100 to 107. Since the fasting blood sugar values did not exceed the critical level, test results would have had to be elevated at one, two, and three hours in order to be classified as diagnostic by the criteria recommended to the Public Health Service. Diagnostic test results were obtained for seven men. For six of these men the results were diagnostic on only one of their six glucose tolerance tests. One man had two tests that were diagnostic. It should be noted in table 3 that some of the men who had a diagnostic test (column 3) did not even show reproducibility of an elevation at two or more readings (seen in the second column).

Positive results according to a modification of the diagnostic criteria recommended by Fajans and Conn[13] are indicated in column 4. The modification is necessary since one- and one-half hour blood samples were not drawn in this study. Critical levels used were 160 mg. per 100 ml. at one hour, and 120 at two hours after glucose. Thirty men had elevated test results on one or more tests according to these criteria. Still, in no case were positive results obtained on all six tests for the same man.

The following text table shows the distribution of the values of the sixty-four tests interpreted as positive according to the described modification of the criteria of Fajans and Conn.

Distribution of sixty-four tests positive to a modification of the criteria of Fajans and Conn by blood sugar levels.

Two hour reading (mg./100 ml.)	One hour reading (mg./100 ml.) 160-179	180-199	200 or more	Total
120-139	16	12	5	33
140-159	8	9	1	18
160 or more	4	5	4	13
Total	28	26	10	64

Diagnostic criteria recommended by the American Diabetes Association[14] are 160 mg. per 100 ml. at one

hour, and 140 mg. at two hours after glucose. Results according to these criteria are listed in column 5, table 3. Positive results were obtained for seventeen men. Interpretation, again, was not consistent over all of the tests for any of these men.

It may be said that the numerical reproducibility of the test is not as critical as the reproducibility of the interpretation of the test. It was clear from data presented in this table that tests interpreted as positive or diagnostic were not consistently obtained on the same individuals in the study population. Therefore, these data do not support reproducibility of numerical values or of positive or diagnostic test results.

DISCUSSION

The oral glucose tolerance test is useful as an aid in the diagnosis of early diabetes and in the selection of groups of patients for research. However, it has been established that the test is imperfect in many ways. For instance, it does not clearly distinguish the abnormal from the normal; no single interpretation or procedure has been universally accepted; and there are many unknown variables in the practical situation which influence test results.

The data presented in this report document the lack of individual reproducibility of results in a group of males twenty to sixty years of age who were not known to have diabetes. The data have shown that some individuals exhibited highly stable values for the same GTT reading in six tests administered over a one-year period. However, other individuals varied greatly on one or more of the readings. The variation was sufficiently large that values did, in some cases, range from normal to abnormal within the same individual.

Preliminary examination of the data has revealed a positive relationship between the individual's average glucose value and his variability. The relationship, however, does not indicate that an individual will show low variability if he exhibits low glucose values. Further study and definition of this relationship may reveal that variability tends to increase in persons who are approaching abnormality. At some point in the development of diabetes, glucose tolerance test results may be elevated consistently, but one should not assume that this is true in the early stages of the disease.

It is this point that has strong implications for public health detection programs and for private physicians who diagnose early cases. If the test is indeed variable in the early diabetic, one should not assume freedom from disease from a single test that is interpreted as normal. If there are other indications that an individual might have diabetes, such as an elevated screening test, etc., responsibility should be assumed for repeated testing. The patient should be informed that a single negative result is not conclusive and that further observation and testing are needed.

The data presented document the variability in a specific group of males without apparent diabetes. Further examination of variability in a comparable female population and in a group of individuals thought to be susceptible to diabetes is desirable.

It was hoped that the known characteristics of the men might permit identification of those who would have stable or highly variable results. Further examination of the data is under way in this regard. However, preliminary results are not encouraging.

It is not recommended that use of the oral glucose tolerance test be curtailed as a result of these data—at least not until a test proved more definitive, more reproducible, and more practical, is available to the clinician. Rather, it is hoped that these results will provide greater insight into the meaning of individual test results, and will also increase the responsibility which public health workers and clinicians assume for the continued observation of suspects.

A specific recommendation to public diabetes detection programs is that those persons classified as suspect on the basis of a screening test or other selected characteristics be retested periodically when the initial retest does not indicate immediate referral to a physician. Values selected for referral should be determined at the community level with the cooperation of local physicians, official agencies, and appropriate voluntary agencies. The screening agency should assume the responsibility for continued observation of all suspects not referred.

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New Adverse Drug Reaction Program

The U.S. medical profession, the pharmaceutical industry and the Food and Drug Administration of the U.S. Department of Health, Education, and Welfare are cooperating to establish a major addition to existing adverse drug reaction reporting programs.

A Registry of Tissue Reactions to Drugs will be established within the Armed Forces Institute of Pathology (AFIP) in Washington. Joint sponsors are the American Medical Association, FDA and the Pharmaceutical Manufacturers Association. The AFIP has the world's largest repository of pathological material for research and education.

The purpose of the Registry will be to obtain autopsy or biopsy tissue specimens from suspected adverse drug reaction cases. The material will be thoroughly studied by all methods available to a full-time pathologist, including consultation with other authorities in pathology and toxicology. Results of the studies will be reported to local pathologists who furnished the study material, and monthly summary reports will be made to each of the three sponsoring organizations. Important information obtained will then be disseminated to the medical community. The pathological material will remain on file at the Registry for future reference and study.

The Tissue Registry will augment the existing drug reaction reporting programs maintained by the AMA and FDA. The FDA at present receives reports of suspected adverse drug reactions from about 500 cooperating Federal and military hospitals, and from 110 civilian hospitals under contract.

The AMA receives such reports from physicians in private practice, a number of hospitals not reporting to FDA, and other sources.

Information is exchanged by the FDA and AMA, catalogued by data-processing technics, and filed by data-processing machines. The data are then available for use in identifying drugs possibly associated with adverse reactions; in assisting physicians to diagnose possible adverse drug reactions; and in scientific investigations.

The AFIP serves as a central laboratory of pathology for the Department of Defense and has become a center of research, teaching and consultation not only for the military but for civilian groups. AFIP offices and laboratories are in an eight-story building at Walter Reed Army Medical Center.

The cost of the Tissue Registry is to be borne equally by each of the three sponsors. In its first full calendar year of operation, which will be 1966, the cost of operation and administration is expected to be about $100,000. The fund will be administered by the Universities Associated for Research and Education in Pathology, Inc.