MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

May 22, 1969

DIAGNOSIS OF DIABETES MELLITUS

Case #1. A 34 year old Air Force Command pilot was found on his annual exam to have the following oral glucose tolerance:

FBS - 105
1 hour - 190
2 hours - 130

A diagnosis of "early diabetes" ("chemical diabetes") was made and the patient was grounded.

Case #2. A 64-year old school teacher, convalescing from an acute myocardial infarction, was found to have this oral glucose tolerance:

FBS - 120
1 hour - 215
2 hours - 165

A diagnosis of diabetes was made and the patient was treated with Orinase and DBI.

INTRODUCTION

At a regional meeting of the American College of Physicians in Dallas, March 1969, about 30% of the internists diagnosed Case #1 as diabetic, while about 70% diagnosed Case #2 as diabetic. It is thus apparent that after more than a half century of use, and perhaps a million or more tests, internists in the United States disagree sharply on how to interpret the oral glucose tolerance test. In 1969, as in 1913, the diagnostic fate of a patient with respect to "chemical diabetes" depends as much upon the choice of the physician, who interprets the GTT, as upon any other single factor.

Since the diagnosis of diabetes carries an economic penalty in the form of unemployability and uninsurability, and imposes the psychological burden of having an incurable disease which shortens life and impairs health, the continuing diagnostic uncertainty constitutes an inexcusable lapse on the part of medical science.

The purpose of this presentation will be to examine the causes of the present diagnostic chaos and to consider means for its correction.

CAUSES OF DIAGNOSTIC CHAOS IN DIABETES

"All pigs are diabetic -- they all have abnormal glucose tolerances."

Anonymous Medical Scientist

I. Lack of a Proper and Uniform Diagnostic Nomenclature and Classification:

Definitions vary for terms like "diabetes mellitus" (to some this means a specific disseminated microangiopathic condition associated with disordered carbohydrate metabolism, to others it is synonymous with abnormal glucose tolerance), "normal controls" (to some this means "non-diabetic," to others it means young, healthy medical students), "abnormal glucose tolerance," etc.

II. Use of Glucose Tolerance Criteria of Unproven Validity:

A. Use of atypical population groups as controls from which to derive "normal" test standards.

B. Failure to prove the assumption that anyone above 2 S.D. of the mean of so-called "normal controls" has "diabetes," i.e., specificity of abnormalities.

III. Unrealistic Interpretation of Test Results: Failure to Take into Account:

A. Intrinsic variability of the test itself, i.e., reproducibility
B. Procedural variables
C. Demographic variables
D. Physiologic variables
E. Pathologic variables

EXAMINATION OF THE VALIDITY OF PRESENT GTT CRITERIA

I. Proper Procedure to Establish Valid Criteria for "Normal" and "Abnormal"

A. Selection of an Appropriate "Normal Control Population" - when criteria must be based upon tests in a "normal control group," the group must: 1) be of sufficient size, and 2) reflect the demographic characteristics of the general population.

NOTE: Past standards have been derived from "normal control groups" which either were too small (e.g., 50 patients of Mosenthal and Barry 1950), which formed basis of ADA criteria for many years), or too atypical (e.g., soldiers from Fort Sam-Moyer and Womack 1950), or from educated guessing (Marble: Over 150 at one hour; Wilkerson: Over 170-120; Fajans and Conn: 160 and 120)

B. Selection of the "Abnormal" Zone: Values more than 2 S.D.'s above the mean of a general population sample, as previously defined, matched for age, state of health, and other influential variables, can be regarded with 95% confidence as statistically "abnormal;" 3 S.D.'s = 99% confidence.

NOTE: There should be no prejudice as to the cause of the abnormality (i.e., no a priori equation with diabetes).

C. Examination of Validity of Present Criteria:

1. Use in Diabetes Surveys:

a. Dallas Survey: Twenty-six per cent of 152 Dallas food-handlers were "abnormal" by the Mosenthal standards; 22% were "abnormal" by the Fajans-Conn standards (Unger 1957). This group had been previously screened free of "abnormals" by fairly sensitive post-prandial blood sugar tests, and was, otherwise, as close to being a representative general population sample as any group previously studied; the high per cent of "abnormals" was attributed to criteria of abnormality set too low rather than to a prevalence of diabetes 10X as great as the general population. The mean GTT curve of this group of Dallas food-handlers using Somogyi-Nelson technique was:

F	1 hr.	2 hrs.
75.8 ± 9.5	138.5 ± 43.2	113.2 ± 39.2

b. Kristianstad Survey (Nilsson, S. E., et al, 1964) (Mean Capillary "True Glucose"):

Age	F	1 hr.	2 hrs.	3 hrs.
20-39	108	150	115	100
40-59	118	190	130	100
60-79	125	240	170	110

c. Cleveland Clinic Survey: Fifty-six per cent abnormality among 630 Cleveland Clinic patients (Keller, D. F., 1964); but the authors consider this a wonderful yield of "diabetics."

d. Sun Valley, California Survey: (Searcy, R. L., 1967); Thirty-five per cent of 456 suburbanites were > 140 mg% (glucose oxidase) two hours after 100g of glucose.

e. Tecumseh, Michigan Survey: (Hayner, N.S., et al, 1965) 2983 residents without known diabetes given 100g of glucose showed high per cent of abnormal one hour GTT (>170 mg%).

f. Streeten, D. H. P. (1965): Seventy-seven per cent of elderly were abnormal.

2. Tests for bimodality in GTT frequency distribution: (Hayner 1965, Klimt, 1964; West, 1966). No clearcut separation between "normal" and "abnormal" can be found in random groups.

3. Comparison with a parallel test of greater specificity (vide infra).

4. Longitudinal studies (vide infra).

NOTE: Reasons why present criteria could not possibly work: The following demographic variables known to influence glucose tolerance have been totally ignored:

a. Age: The most important variable of all. GTT clearly diminishes with age. Mean glucose of GTT rises from 99.7 mg% at 18-24 years to 166.3 mg% at 75-79 (Garst, C., National Health Survey, 1966). Everyone agrees (Hayner 1965; Fajans 1964; Andres 1967; Streeten 1965; Gottfried 1960; Balodimos, et al 1967; Shock N., 1960; Horvath 1947).

b. Race: Slight but probably trivial difference (National Health Survey 1966).

c. Socioeconomic: Men earning < $2,000 had 7.5 mg% higher mean GTT than men> $10,000 (National Health Survey, 1966).

d. Sex: Women about 10 mg% above men (National Health Survey, 1966).

CONCLUSIONS: The standards for "abnormal GTT" most often employed today are set far too low, because: 1) they are based on data from unacceptable "normal controls;" 2) they "over-abnormalize" random populations; 3) there is no bimodality; 4) they ignore relevant demographic variables, the most influential of which is age.

No single standard of abnormality which ignores age can be valid for all ages. Age-matched standards would be an improvement, and might even show bimodality (c.f. Pima Indian Survey).

EXAMINATION OF VALIDITY OF INTERPRETATION

OF AN INDIVIDUAL GTT

I. Reproducibility of Glucose Technique in a Clinical Laboratory: > ± 2%
(Reproducibility of glucose technique from one clinical laboratory to another. National Health Survey. Mean of 272 specimens in Brighton was 117 mg% in San Francisco the same specimens averaged 109 mg%.

II. Reproducibility of the OGTT:

1. Freeman, H., et al (1942): Striking spontaneous variability in duplicate OGTT's.

2 Unger (1957): Mean differences of 29 and 25 mg% at 1 and 2 hours, respectively, in duplicate GTT's performed two weeks apart in 41 Dallas food-handlers; 25% crossover from "normal" to "abnormal" or vice versa.

3. Horvath, S. M., et al (1947): Eleven tests in same individual yielded curves ranging from flat to diabetic-like.

4. Mirsky, I. A. (1944): Believes anyone can be labeled "diabetic" if enough OGTT's are performed.

5. McDonald, G. W., et al (1965): Best study of reproducibility; with six repeated GTT's finds high and low variability groups - they were similar with respect to age, race weight class, diabetic family history, but the high variability group in general had higher blood sugars, but not consistantly. Interpretation of OGTT results proved impossible in a high percentage of positive and negative tests.

CONCLUSIONS: In terms of both numerical reproducibility and interpretative reproducibility the OGTT rates poorly. A single negative test may, if repeated, be positive by current standards in as high as 25%, and vice versa.

III Effect of Variations in the GTT Procedure:

A. Antecedent diet:

1. Conn, J. W. (1940) found that on a diet of 20g CHO daily for three days glucose tolerance was less than on a 300g CHO diet. This led to the use of a "standard 300g" preparatory diet.

2 Wilkerson (1960) found that 150g/d was as effective as 300g in restoring normal tolerance after a 20g/d diet and concluded any adequately nourished individual is adequately prepared for a GTT. Even 50g diets do not cause false positives (Wilkerson, H. L. C. 1960)

3. Gwinup, et al (1963) suggested that "gorging" can cause "abnormal GTT" in persons who have a normal test if they "nibble."

CONCLUSION: Importance of antecedent CHO vastly overrated.

B. Time of day - not a factor (Hayner); others say tolerance is less in p.m.

C. Time of year - in the fall men, but not women, test 6-12 mg% higher at one hour.

D. Interval since previous meal - the 1-hour glucose level of tests conducted within four hours of a meal averages 25 mg% below that of tests conducted after a longer interval. (Hayner, N. S., et al, 1965).

E. Posture - cannot locate reference (by an Iranian author); there is a difference, but which way?

F. Vein - choice of a vein will influence the test since it reflects the impact of local metabolism upon the arterial blood. A superficial vein reflects skin and subcutaneous fat; a deep vein reflects muscle. Muscle can remove much more glucose than skin and will give lower values than a superficial hand vein which is closer to arterial. Even the glucose in same veins on opposite sides can differ significantly.

IV. Influence of Physiological Variables (other than beta cell function)

1. Gastric emptying - retarded by nausea and by pyloric or duodenal disease; high two hour values due to late influx of glucose.

2. Net intestinal glucose absorption (mg/minute): Depends on: a) rate of glucose delivery from stomach; b) surface area of gut exposed to glucose.

3. Hepatic glucose extraction: Depends on: a) blood flow; b) rate and timing of glucose presentation; c) anticipatory insulin augmentation (gut hormones) (?).

4. Glucose Utilization - a) prior physical activity (Ingle, D.J., 1948; Naughton, J.); b) levels by other counter-regulatory hormones, e.g. epinephrine if patient is very excited; c) other undetermined factors.

V. Influence of Pathologic Variables (See Page 6, III):

EXAMINATION OF THE SPECIFICITY FOR DIABETES OF "ABNORMAL" GTT

I. Longitudinal Studies:

A. Dallas 5-7 years follow-up study - of 87 normals (Mosenthal criteria - 100-150-100) 74% were normal 5-7 years later, 25% "abnormal," and 1% developed fasting hyperglycemia (equated with overt diabetes); of 74 "abnormals" 25% had become normal 5-7 years later, 55% were still "abnormal" and 20% developed fasting hyperglycemia. (Unger et al, 1957)

B. Fajans-Conn: Seventy-one percent of abnormal GTT's normal ten years later.

C. USPHS: Forty-five per cent of abnormal GTT's normal ten years later.

CONCLUSIONS: Based on Dallas Longitudinal Studies: 1) Mosenthal criteria are excellent (99%) for excluding persons who will develop fasting hyperglycemia within seven years; 2) the abnormal GTT group, though containing at least 20% true diabetics 20X as many as the normal GTT group, contains at least 25% normals; 3) there was no way on the basis of the initial test to differentiate an individual who was to revert to normal from one who developed fasting hyperglycemia (i.e., no biomodality): however, the greater the initial abnormality the greater the chance of subsequent overt diabetes.

NOTE: The crossover rate in both groups of the Dallas Longitudinal Study was 25%, the same as the crossover rate of the Dallas study of GTT reproducibility, in which two weeks, rather than seven years, separated the two tests: 4) the abnormal GTT test group contains many true "chemical diabetics" but even more non-diabetics.

II. Comparison of GTT with Quadriceps Muscle Capillary Basement Membrane (MCBM) Data:

Very preliminary data of Siperstein's shows abnormal MCBM in only about 30% of a small group of "abnormal GTT" patients (Fajans criteria), in contrast to 98% thickening in overt diabetics. This tool may ultimately provide a means of identifying truly specific GTT standards for diabetes, if they exist.

III. Diseases which can Cause "Abnormal" GTT (at least by Old Standards):

1. Pre-insular Diseases:
   a. Disorders of gastric emptying - gastric retention and rapid emptying (Robertson 1966).
   b. Rapid intestinal absorption (dumping, hyperthyroidism)
   c. Liver disease - most cirrhotics have an abnormal GTT
2. Insular Causes:
   a. Primary Hypoinsulinism
      1. Genetic diabetes mellitus
      2. Pancreatogenous diabetes - pancreas (acinar, alpha cell and delta cell tumors); miscellaneous (hemochromatosis, cystic fibrosis, mumps).
   b. Secondary Hypoinsulinism:
      1. Pheochromocytoma (Porte 1966) and hyperthyroidism (Woeber 1969).
      2. Hypokalemia - drug induced, aldosteronism, etc. (may have post-insular influences as well).
      3. Diazoxide therapy
      4. Starvation - <50g of CHO daily for three or more days (may be post-insular as well).

c. Primary Hyperglucagonism:

1. Glucagonoma (McGavran, et al, 1966)

d. 2°: 1) Diabetic hyperglucagonism (primary or secondary), (Parada, et al, 1969).

2) Hypercalcemic hyperglucagonism (Paloyan and Lawrence). Failure of α cell to suppress during glucose absorption could impair GTT, unless compensated for by increased insulin secretion.

3. Post-Insular Causes:

a. Obesity: Insulin insensitivity normally overcome by ↑ insulin secretion. May be due to increased tissue levels of FFA causing ↑ glucose uptake (theory), although Kipnis thinks it is due to ↑ dietary CHO consumed by most obese people.

b. Hypertriglyceridemia: Insulin insensitivity associated with ↑ insulin secretion. Insulin insensitivity may be due to ↑ fat and ↑ FFA in tissues of patients with CHO-induced hypertriglyceridemia; in fat-induced hypertriglyceridemia lack of lipoprotein lipase may account for normal GTT in that syndrome (theory) - no ↑ FFA.

c. Counter-regulatory hormone excess: HGH (Acromegaly), cortisol (Cushing's), epinephrine (pheo), ACTH (Cushing's) would reduce glucose utilization and impair GTT, especially, epinephrine, which prevents beta cell compensation by suppressing insulin secretion.

d. Other causes:

1. K^+ deficiency (?)
2. $Chromium^{+++}$ deficiency (?)
3. Azotemia (Perkoff, 1958; Sagild, 1962; Westervelt, 1962; Cohen, 1961).
4. Acidosis
5. Anemia
6. Carcinoma (Marks, et al, 1962)
7. Brain injury (unclassified)
8. Atherosclerotic disease: ↑ insulin (Tzagournis, 1967); ↓ insulin 12 hours after myocardial infarctions (Allison 1967); abnormal GTT lasts many years (Sowton 1962; Kingsbury 1966). Relation to lipid abnormalities (Albrink 1965; Ostranoler, 1965).
9. Rbc glucose-6-PD deficiency (Chanmugam 1964).
10. Amyotrophic lateral sclorosis (Steinke, 1964)
11. Drugs - most common are oral contraceptives
12. Neoplastic blood dyscrasia (Lisker, 1966)
13. Surgery (Engle)
14. Rheumatoid arthritis, gout
15. Acute porphyria
16. Infection
17. Hypertension

NOTE: Hecht (1961) found abnormal GTT's in almost all hospital patients, young as well as old, fully active as well as bedridden or wheelchair cases. His mean 1 and 2 hour values were 203 and 173 in ambulatory patients. Fajans states that his own diagnostic criteria apply only to healthy patients. (Proc. of Conference on Methodological Approached to Population Studies in Diabetes, P. 15); sick people cannot be judged by standards based on well subjects.

CONCLUSIONS: The logitudinal studies, the preliminary comparison with MCBM measurements, and the interminable list of extra-insular causes of abnormal glucose tolerance all suggest 1) that an abnormal GTT is not specific for chemical genetic diabetes and 2) that sick people cannot be judged by standards obtained from tests of healthy persons -- just about any important illness impairs glucose tolerance.

OTHER MORE SPECIFIC TESTS FOR DIABETES

A. FBS: Two or more FBS > 120 appears to be very specific for primary β-cell disease, i.e., genetic or pancreatogenous diabetes, with the following exceptions:

1. False positive FBS elevations:
   a. Failure to fast; b. excitement
2. Extra-insular Diseases Causing Fasting Hyperglycemia:
   a. Hypertriglyceridemia (CHO-induced only). Causes unknown -- insulin levels are high, suggesting insulin resistance; perhaps lipolysis of ↑ tissue TG causes ↑ tissue FFA.
   b. Uremia - cause unknown - some evidence that urea opposes insulin (Sagild 1964), but others find reduced insulin levels.
   c. Steroid diabetes: Can peripheral insulin resistance due to ↑ cortisol by itself cause fasting hyperglycemia in the presence of normal beta cells, or must the compensatory capacity of normal beta cells be limited for hyperglycemia to develop?
   d. Pheochromacytoma - here beta cell suppression by catechols prevents compensation for insulin-opposing effects of catechols on peripheral tissues.
   e. Acromegaly - probably cannot cause ↑ FBS if beta cells are normal; HGH causes hypertrophy of islets, which keeps pace with increased need for insulin. Siperstein found ↑ MCBM in acromegalics with ↑ FBS.

CONCLUSION: Since non-diabetic causes of fasting hyperglycemia are both rare and easily identified, fasting hyperglycemia is very strong evidence for primary hypoinsulinism. It is incapable of diagnosing chemical diabetes, obviously.

B Quadriceps Muscle Capillary Basement Membrane (MCBM)

1. 98% of overt diabetics >1325 Å
2. 50% of prediabetics > 1325 Å
3. 92% of non-diabetics < 1325 Å
4. 6 of 9 chronic pancreatitics < 1325 Å
5. Patients with pheochromocytoma, hypertriglyceridemia, steroid diabetes, lipodystrophic diabetes were < 1325 Å
6. Only lupus and rheumatoid arthritis are thought to cause false positives.

CONCLUSION: In patients without collagen disease a MCBM > 1325 Å probably is a marker for the genetic diabetic diathesis; in such people the GTT would serve to classify into prediabetic, subdiabetic, chemical diabetic, or overt diabetic categories.

PROPOSED SOLUTIONS

I. Redefinition of Terms:

A "Diabetes Mellitus" should be taken to mean genetic diabetes unless otherwise specified: An inherited disorder characterized 1) by thickening of capillary basement membranes (Siperstein, et al, 1968) 2) diminished glucose tolerance, and 3) reduced secretion of insulin in relation to the prevailing secretory stimulus (Seltzer 1959; Perley and Kipnis, 1967).

1. Subclassification of Diabetes Mellitus:

	Prediabetes	Subdiabetes	Minimal or Chemical Diabetes	Overt Diabetes
Fasting Blood Sugar	Normal	Normal	Normal	Elevated
GTT	Normal	Normal except in pregnancy, stress	Abnormal	Not necessary for diagnosis
Muscle capillary basement membrane	> 1500 Å in 50%	Probably the same (?)	Probably > 1500 Å in > 50% (?)	> 1500 Å in 98%

NOTE: Progression (or regression) from earliest stage(s) to next may:

a. never occur
b. proceed slowly over many years
c. be rapid or even explosive

2. In designating all other hyperglycemic states the word "diabetes" should be preceded by an identifying adjective: e.g., "pancreatogenous diabetes," "steroid" diabetes, etc.

B. "Normal Glucose Tolerance:" A curve within 2 S.D of the mean of a general population sample in the same age bracket.

C. "Abnormal Glucose Tolerance:" A curve more than 2 S.D. above the mean of a general population sample in the same age bracket; not necessarily synonymous with chemical diabetes mellitus.

II. New Standards for OGTT:

A. Revised Fajans-Conn (1969) Plasma Glucose

Age	1 hr.	2 hrs.
Under 50	184	140
50-60	196	149
60-70	207	161
70-80	218	172

B. The University of Texas Southwestern Medical School at Dallas:
Composite of Hayner (1966) one hour - Andres (1967) two hours. (Mean plus 2 S.D.)

Age	1 hr.	2 hrs.
20-29	222	170
30-39	241	170
40-49	267	201
50-59	286	217
60-69	276	235
70-79	-	248

C. Dallas Food-Handlers (1957) - S.D. plus the mean of the Dallas food-handler survey gives the following upper limit of "normal" for a 19-67 year age bracket (mean age 39.4) with a "true glucose" method.

	F	1 hr.	2 hrs.	
Whole Blood	95	225	192	2 S.D.
Plasma (Calculated)	109	263	226	2 S.D.

NOTE: The UTSWMS Standards would be very unlikely to embrace any normal subjects, although obviously they will miss individuals with minimal derangements in CHO metabolism, including some true chemical diabetics. However, until prophylaxis has been developed this is probably better than overdiagnosis.

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