MEDICAL GRAND ROUNDS

February 22, 1979

THE POST PRANDIAL HYPOGLYCEMIAS

AN UPDATE ON THE EPIDEMIC OF IDIOPATHIC REACTIVE HYPOGLYCEMIA

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SIGNS AND SYMPTOMS OF HYPOGLYCEMIA

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      3. FOLLOWING EXERCISE.

   B. REPETITIVE NATURE OF ATTACKS:

      USUALLY THE SAME PATTERN IN THE SAME PATIENT BUT DIFFERS FROM PATIENT TO PATIENT.

TABLE 2 CONT'D

SIGNS AND SYMPTOMS OF HYPOGLYCEMIA

II. SPECIFIC CHARACTERISTICS

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B. HYPOTHERMIA

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RESTLESSNESS	PALPITATIONS	TACHYCARDIA
ANXIETY	SWEATING	TREMULOUSNESS

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1. MENTAL DISTURBANCES - PERSONALITY CHANGES

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NIGHTMARES	RESTLESSNESS	DISORDERS OF SPEECH &
LETHARGY	BIZZARE BEHAVIOR	GAIT

2. SOMNOLENT - AGITATED STATES

MONOPLEGIA	BLINDNESS
HEMIPLEGIA	INCOORDINATION OF EYE MUSCLES
WRITHING	POSITIVE BABINSKI

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FLACCIDTY	DECEREBRATE RIGIDITY	TRISMUS

SECTION II

CRITERIA* FOR THE DIAGNOSIS OF IDIOPATHIC REACTIVE HYPOGLYCEMIA DURING THE ORAL GLUCOSE TOLERANCE TEST

INTRODUCTION

In a Medical Grand Rounds presented April 15, 1971, it was pointed out that the criteria for the diagnosis of idiopathic reactive hypoglycemia varied widely amongst clinical investigators and in all instances were selected arbitrarily and were not based on any substantial scientific data.

Despite the paucity of scientific data defining the responses of a large number of healthy asymptomatic people to the 5 hour oral glucose tolerance test, what data were available at that time indicated that decreases in blood glucose to levels to or below 45 and even 40 mg/dl were too common for the oral glucose tolerance test to be of any use in the diagnosis of idiopathic reactive hypoglycemia.

The fact that a nervous, tense, depressed or apprehensive patient with recurrent post-prandial "spells" even those that seem typically adrenergic, develops a low blood glucose during a 5 hour oral glucose tolerance test does not establish a causal nexus between the "hypoglycemia" and the symptoms occurring in everyday life.

Recent data on the response of normal asymptomatic subjects to a prolonged oral glucose tolerance test support these conclusions.

NOTE: ALL GLUCOSE LEVELS MENTIONED IN THIS PROTOCOL ARE WHOLE BLOOD GLUCOSE VALUES. MOST AUTOANALYZER MEASURE PLASMA OR SERUM GLUCOSE. THE VALUES FOR SERUM OR PLASMA AVERAGE 10-15% HIGHER THAN BLOOD GLUCOSE

PREVIOUSLY PROPOSED CRITERIA FOR THE DIAGNOSIS OF IDIOPATHIC REACTIVE HYPOGLYCEMIA

TABLE 3

ZEALOT'S CRITERIA FOR DIAGNOSIS OF FUNCTIONAL HYPOGLYCEMIA DURING THE GLUCOSE TOLERANCE TEST

1. Fall in blood sugar below fasting.
2. Fall in blood sugar more than 10 mg% below fasting (Abrahamson and Pezet).
3. Fall in blood sugar more than 20 mg% below fasting (Fredericks and Goodman).
4. Fall in blood sugar more than 30 mg% below fasting (Roberts).

TABLE 4

"SCIENTIFIC" CRITERIA FOR THE DIAGNOSIS OF REACTIVE HYPOGLYCEMIA DURING THE ORAL GLUCOSE TOLERANCE TEST – TO 1970

FALL IN BLOOD GLUCOSE TO OR BELOW		
60 mg/dl	Mostow, Hamwi & Skillman – 1962 Berson & Yalow – 1965 Fabrykant – 1950	Zieve – 1966 Smelo – 1966 Portis – 1950
50 mg/dl	Seltzer, Fajans & Conn – 1956 Faludi, Bendersky & Gerber – 1969 Williams – 1968 Bondy – 1969	Marble – 1959 Goldner – 1954 Boshell – 1966 Shipp – 1966
45 mg/dl	Sussman – 1966 Horton & Bressler – 1968	
40 mg/dl	Conn – 1947 Conn & Seltzer – 1955	Marks & Rose – 1965

TABLE 5

"SCIENTIFIC" CRITERIA FOR THE DIAGNOSIS OF REACTIVE HYPOGLYCEMIA DURING THE ORAL GLUCOSE TOLERANCE TEST – SINCE 1970 TO PRESENT

FALL IN BLOOD GLUCOSE TO OR BELOW		
60 mg/dl	None	
50 mg/dl	None	
45 mg/dl	Seltzer – 1971 Drash, Ellenberg, & Seltzer – 1971 Ensinck & Williams – 1974	Crofford – 1973 Field – 1975 Permutt – 1976
40 mg/dl	Conn – 1947 Seltzer & Conn – 1955 Seltzer – 1974 Luycks & Lefebrve – 1971 (41 mg/dl)	Marks – 1975 Hofeldt & Forsham – 1972 Vinicor – 1975

All of the investigators listed in Tables four and five (except for Marks, 1975 and Lefebrve, et al, 1976), have continued to recommend use of the five hour oral glucose tolerance test in the diagnosis of reactive (postprandial) hypoglycemia. Examples of such recommendations follow:

Ensinck and Williams in Williams Textbook of Endocrinology 5th edition, 1974.

> "The oral glucose tolerance test is indispensible in the differentiation of the causes of the post-absorptive or "reactive" hypoglycemia"

Fajans and Floyd, J.C., Jr. 1973

> "The three major types of functional hypoglycemia (idiopathic reactive, chemical diabetic, alimentary) cannot be diagnosed without using the oral glucose tolerance test and establishing a history of hypoglycemic symptoms that occur during the appropriate interval after the patients customary meals."

Seltzer, H., 1974

> "Ordinary functional (reactive) hypoglcyemia is easily differentiated from the other two main clinical types of postprandial hypoglycemia (mild or chemical diabetic and alimentary) because each of them has characteristic clinical manifestations and a pathognomonic oral glucose tolerance test."

SECTION III

RESPONSE OF NORMAL CONTROL SUBJECTS TO THE ORAL GLUCOSE TOLERANCE TEST - INCIDENCE OF HYPOGLYCEMIA

TABLE 6

HYPOGLYCEMIA IN NORMAL CONTROLS DURING THE OGTT

Author	Duration OGTT Hours	Number Tested	Percent of Normals Falling to or Below Blood Glucose			
			60mg/dl	50mg/dl	45mg/dl	40mg/dl
Wilkerson, et al 1960	3	18	61	50	38.8	27.7
Sisk, et al 1970	3	100	37	17	11.0	4.0
Luyckx and Lefebvre 1971	4	663				(7.1)*
Williamson, et al 1969	4	20	65	40	25.0	15.0
Klachko and Burns 1978	5	44	70	34	20.5	13.6
Hofeldt, et al 1975	5	25		48		
Park, et al 1972	5	123		23		

*G.O. = 41mg/dl

TABLE 7

HYPOGLYCEMIA IN NORMAL CONTROLS DURING OGTT

	Number Tested	Percent of Normals Falling to or Below Blood Glucose				
		60mg/dl	50mg/dl	45mg/dl	40mg/dl	35mg/dl
Williamson, et al 4 Hr – GTT	20	65%	40%	25%	15%	15%
Sisk, et al 3 Hr – GTT 4 Tests	100	67%	33%	23%	8%	2%
Burns, et al 5 Hr – GTT Cont. Monitoring	44	70%	34%	20.5%	13.6%	5%

PERCENT OF NORMAL SUBJECTS WHO WOULD BE DIAGNOSED AS "HYPOGLYCEMIC" ACCORDING TO THE ZEALOTS CRITERIA

FIGURE 1

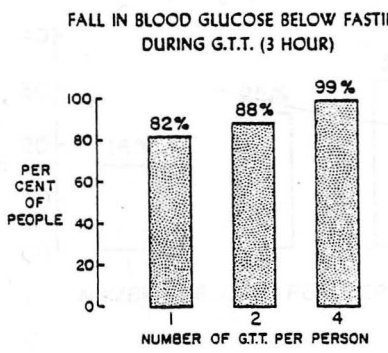


FIGURE 2

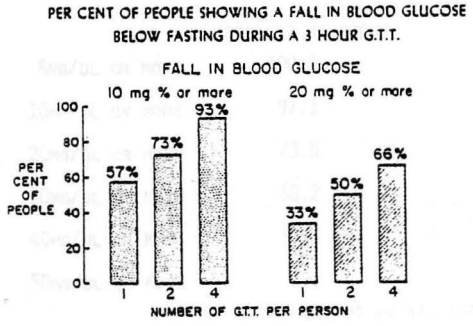


FIGURE 3

PER CENT OF PEOPLE SHOWING A FALL IN BLOOD GLUCOSE BELOW FASTING DURING A 3 HOUR G.T.T.

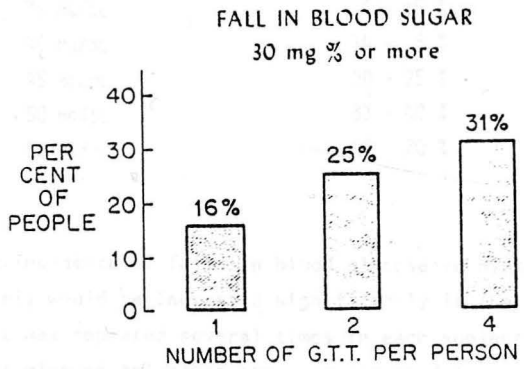


TABLE 8

MAXIMUM FALL IN BLOOD GLUCOSE BELOW FASTING DURING 5 HOUR OGTT IN 34 NORMAL SUBJECTS.

	PERCENT OF GROUP
8MG/DL OR MORE	100.0
10MG/DL OR MORE	97.1
20MG/DL OR MORE	73.5
30MG/DL OR MORE	38.2
40MG/DL OR MORE	11.6
50MG/DL OR MORE	5.9

(BURNS et al, 1965)

TABLE 9

OVERALL INCIDENCE OF BIOCHEMICAL HYPOGLYCEMIA
IN NORMAL, ASYMPTOMATIC, HEALTHY SUBJECTS
DURING A SINGLE 4 TO 5 HOUR OGTT

FALL IN BLOOD GLUCOSE TO OR BELOW	PERCENT OF SUBJECTS
35 MG/DL	5 - 15 %
40 MG/DL	14 - 15 %
45 MG/DL	20 - 25 %
50 MG/DL	33 - 40 %
60 MG/DL	65 - 70 %

The incidence of falls in blood glucose to hypoglycemic levels very likely would be increased significantly if the oral glucose tolerance test was repeated several times in each subject. When a three hour oral glucose tolerance test was repeated four times in each 100 normal subjects the incidence of falls in blood glucose to hypoglycemic levels doubled.

FIGURE 4

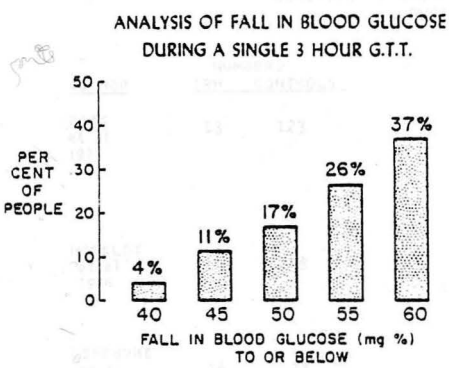
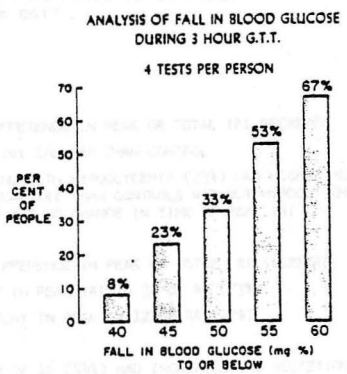


FIGURE 5



SECTION IV

POSTULATED PATHOGENESIS OF IDIOPATHIC REACTIVE HYPOGLYCEMIA

A. ABNORMALITY OF INSULIN SECRETION

Conn (1947) and later Conn and Seltzer (1955) postulated that functional hypoglycemia was the consequence of a hypersensitization of the beta cells resulting in an excessive insulin secretion in response to a normal postprandial rise in blood glucose. For this reason they classified this condition as "functional hyperinsulinism".

Three recent studies (Park et al, 1972, Hofeldt et al, 1974, and Lefebvre et al, 1976) which compared the insulin response during a 5 hour oral glucose tolerance test in patients with idiopathic reactive hypoglycemia to age and weight matched controls failed to disclose any consistent abnormality in total insulin secreted, in the time of peak insulin secretion or in the magnitude of the peak insulin secretion.

TABLE 10

COMPARISON OF INSULIN DYNAMICS IN IDIOPATHIC REACTIVE HYPOGLYCEMIA (IRH) COMPARED TO CONTROLS DURING 5 HOUR OGTT

AUTHOR	NUMBERS IRH	NUMBERS CONTROLS	
PARK et al 1972	13	123	1. NO DIFFERENCE IN PEAK OR TOTAL IRI SECRETED 2. PEAK IRI EARLIER THAN CONTROL 3. CONTROL WITH HYPOGLYCEMIA (23%) HAD HIGHER MEAN AND PEAK IRI THAN CONTROLS WITHOUT HYPOGLYCEMIA (77%) BUT NO CHANGE IN TIME OF PEAK IRI
HOFELDT et al 1974	44	28	1. NO DIFFERENCE IN PEAK OR TOTAL IRI SECRETED 2. DELAY IN PEAK IRI IN 32 OF 44 (73%) 3. NO DELAY IN PEAK IN 12 OF 44 (27%)
LEFEBVRE et al 1976	16	23	1. SEVEN OF 16 (44%) HAD INCREASED IRI SECRETION 2. NINE OF 16 (56%) - NO ABNORMALITY OF IRI SECRETION

TABLE 11

COMPARISON OF INSULIN DYNAMICS IN IDIOPATHIC REACTIVE HYPOGLYCEMIA (IRH) COMPARED TO CONTROLS DURING 5 HOUR OGTT

	TOTAL IRI SECRETED		MAGNITUDE OF IRI PEAK		TIME OF IRI PEAK		
	NO DIFF	INCREASED	NO DIFF	INCREASED	EARLIER	SAME	LATER
PARK ET AL 1972	13	28*	13	28*	13	28*	
HOFELDT ET AL 1974	44		44			12	32
LEFEBVRE ET AL 1976	9	7	9	7		9	7
	66	35	66	35	13	49	39
	65%	35%	65%	35%	13%	48%	39%

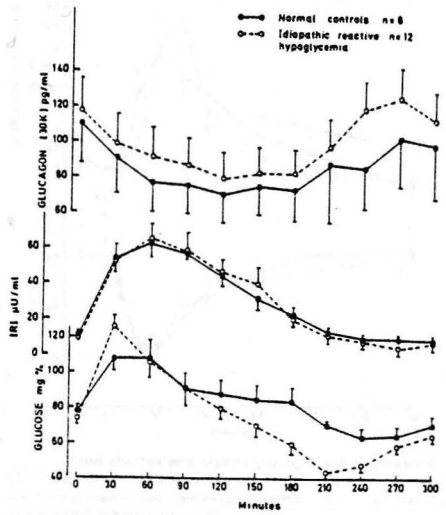
*CONTROLS WITH HYPOGLYCEMIA

B. HYPOGLUCAGONEMIA

The failure to find a consistent association of idiopathic reactive hypoglycemia with excessive or deranged insulin secretion led Unger, in 1968, and Lefebvre et al in 1971 to suggest hypoglucagonemia as a possible cause of this disorder. However, studies by Lefebvre, Luyckx, and Lecompte in 1976 revealed no abnormalities in basal glucagon levels, glucagon suppressibility during an oral glucose tolerance test or glucagon response to hypoglycemia in 12 subjects with normoinsulinemic idiopathic reactive hypoglycemia when compared to age and weight matched controls.

FIGURE 6

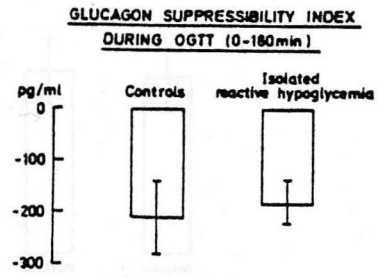
COMPARISON OF CHANGES IN PLASMA GLUCAGON DURING AN ORAL GLUCOSE TOLERANCE TEST



Blood glucose, plasma IRI and glucagon values (mean ± SEM) during OGTT performed in patients with "isolated normoinsulinemic reactive hypoglycemia" (o - - - o) and normal control subjects (●——●).

FIGURE 7

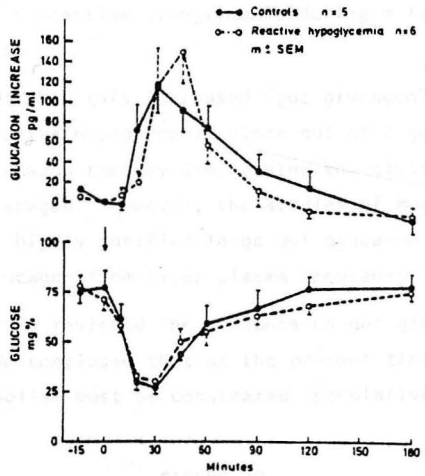
GLUCAGON SUPPRESSIBILITY



"Glucagon suppressibility indices" and "glucagon stimulation indices" in normal controls and in patients with "isolated normoinsulinemic reactive hypoglycemia"

FIGURE 8

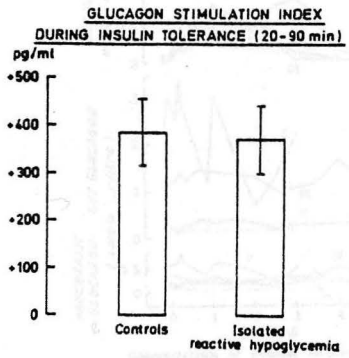
COMPARISON OF CHANGES IN PLASMA GLUCAGON DURING AN INSULIN TOLERANCE TEST



Blood glucose and plasma glucagon values (mean ± SEM) during insulin tolerance test in patients with "isolated normoinsulinemic reactive hypoglycemia" (o - - - o) and normal control subjects (●——●).

FIGURE 9

GLUCAGON STIMULATION INDEX



"Glucagon suppressibility indices" and "glucagon stimulation indices" in normal controls and in patients with "isolated normoinsulinemic reactive hypoglycemia"

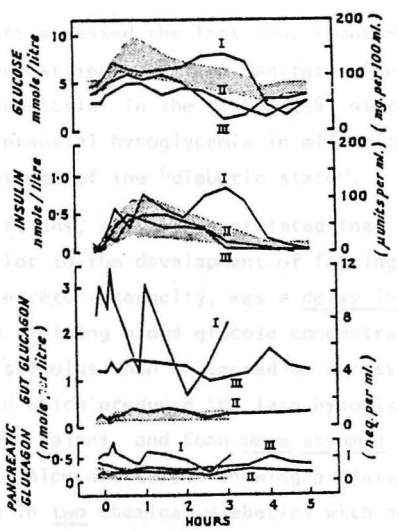
C. INCREASED "GUT GLUCAGON" RELEASE

Rehfeld, Heding, and Holst in 1973 also failed to find any evidence of hypoglucagonemia in 6 subjects with reactive hypoglycemia. However, their studies disclosed increased basal levels and an increased secretion of gut-glucagon-like immunoreactivity in 2 of 3 patients with idiopathic reactive hypoglycemia during a five hour oral glucose tolerance test.

They suggested that this increased "gut glucagon" may be a pathogenic factor in reactive hypoglycemia since gut glucagon may compete with pancreatic glucagon thereby diminishing the glycogenolytic effect of pancreatic glucagon. However, the studies of Murphy et al (1973) revealed that highly purified large gut glucagon did not displace pancreatic glucagon from liver plasma membranes.

Buchanan in 1976 reviewed the evidence on gut glucagon-like immunoreactivity and concluded that at the present time its role in carbohydrate metabolism must be considered speculative.

FIGURE 10



Concentrations of glucose, immunoreactive insulin, gut-glucagon-like immunoreactivity, and pancreas-glucagon-like immunoreactivity in plasma in three patients (I-III) with essential reactive hypoglycaemia during an O.G.T.T.

The shaded area indicates mean concentrations ±2 S.D. in sixteen controls.

SECTION V

REACTIVE HYPOGLYCEMIA AS AN EARLY MANIFESTATION OF DIABETES MELLITUS

A. BIRTH OF THE SYNDROME

Although the concept of postprandial hypoglycemia as an early manifestation of mild or chemical diabetes had been gestating since the early reports of Seale Harris (1924) and Allen (1953), the syndrome had a healthy birth in 1956 when Seltzer, Fajans, and Conn reported 110 cases of " mild diabetes with secondary late hypoglycemia" during a prolonged oral glucose tolerance test.

These subjects were said to have glucose tolerance test "clearly diagnostic of diabetes mellitus" and which also exhibited a steep secondary late hypoglycemic phase. Ninety-three percent had normal fasting blood glucose levels. Patients with overt diabetes, i.e., with fasting blood glucose values of 130 mg/dl or greater did not exhibit secondary hypoglycemia.

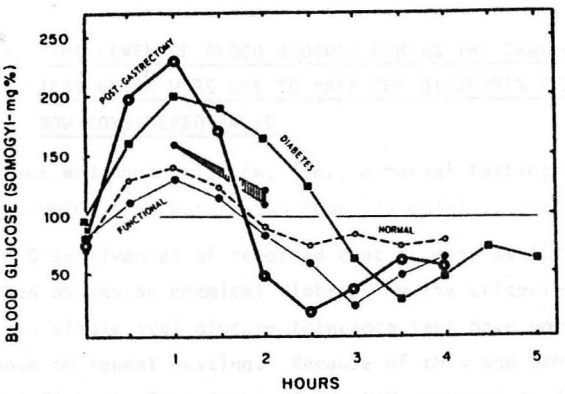
The authors stressed the fact that symptomatic reactive hypoglycemia may be the earliest chemical manifestation of diabetes. Six years later an editorial in the NEJM (1956) stated that the occurrence of late postprandial hypoglycemia in mild diabetes represented yet another aspect of the "diabetic state".

Seltzer, Fajans, and Conn postulated that the early defect in diabetes, prior to the development of fasting hyperglycemia and reduced insulin secretory capacity, was a delay in insulin release in response to a rising blood glucose concentration. The resulting hyperglycemic stimulus then triggered an excessive and late secretion of insulin which produced the late hypoglycemia. In 1965 the predictions of Seltzer, Fajans, and Conn were assumed to be confirmed by the report of Yalow and Berson showing a "late and excessive" insulin secretion in two chemical diabetics with normal fasting blood glucose

who showed initial hyperglycemia and late hypoglycemia during the oral glucose tolerance test.

The syndrome was said to be distinct from idiopathic reactive hypoglycemia since the oral glucose tolerance test was "overtly diabetic" during the first two hours in the former and within normal limits in the latter. Moreover, the hypoglycemic dip occurred late during the last 3 to 5 hours in the former and early during the first 2 to 4 hours in idiopathic reactive hypoglycemia.

FIGURE 11 (From Seltzer 1974)



"THE ORAL GTT IS PATHOGNOMIC FOR EACH OF THE THREE MAIN TYPES OF POSTPRANDIAL HYPOGLYCEMIA IN ADULTS. THE SHADED TRIANGLE REPRESENTS THE FAJANS-CONN CRITERIA FOR DIABETES MELLITUS"

TABLE 12

SELTZER, FAJANS, AND CONN'S CRITERIA FOR MILD DIABETES WITH SECONDARY HYPOGLYCEMIA (1956)

1. ONE HOUR BLOOD GLUCOSE LEVEL OF 160 MG/DL OR ABOVE
2. TWO HOUR BLOOD GLUCOSE LEVEL OF 120 MG/DL OR ABOVE
3. LATER FALL IN BLOOD GLUCOSE TO OR BELOW 50 MG/DL

B. DEATH OF THE SYNDROME

Although the syndrome of "early diabetes" with late reactive hypoglycemia was embraced widely, dissenting voices from Smelo (1956) and Fabrykant (1957) were soon heard. Both pointed out that repeat glucose tolerance tests in such patients often returned to or toward normal. Moreover, Smelo followed many such patients for over a period of 12 or more years and found that there was no increase in the incidence of overt diabetes mellitus in subjects demonstrating the type of glucose tolerance test considered pathognomonic of diabetes by Seltzer, Fajans and Conn (1956).

IN LIGHT OF MORE RECENT DATA THERE IS SERIOUS DOUBT ABOUT THE VERY EXISTENCE OF THE SYNDROME OF EARLY CHEMICAL DIABETES WITH LATE HYPOGLYCEMIA DIAGNOSED BY THE ORAL GLUCOSE TOLERANCE TEST.

1. THE LEVEL OF BLOOD GLUCOSE DURING THE ORAL GLUCOSE TOLERANCE TEST WHICH WERE USE TO MAKE THE DIAGNOSIS OF DIABETES ARE NOT NOW CONSIDERED VALID

The Fajans and Conn criteria, i.e., a normal fasting blood glucose, 1 hour 160 mg/dl or greater, two hour 120 mg/dl or greater, were used.

In 1968 O'Sullivan et al reported that as many as 66% of patients diagnosed as having chemical diabetes by the criteria of Fajans and Conn on a single oral glucose tolerance test have normal glucose tolerance on repeat testing. Because of this and other data the National Diabetes Data Group of the NIH convened an International Workshop in April, 1978 to establish more valid and realistic criteria for the diagnosis of diabetes by means of the oral glucose tolerance test (Fajans was a member of the study group).

Seltzer, 1979 - "I seldom use GTT. Its often misused and misread. You tend to be overdiagnosing with it."

TABLE 13.

CRITERIA OF SELTZER, FAJANS, AND CONN - 1956
FOR THE DIAGNOSIS OF DIABETES

1. ONE-HOUR BLOOD GLUCOSE LEVEL OF 160 MG/DL OR ABOVE
(PLASMA = 185 MG/DL)

2. TWO-HOUR BLOOD GLUCOSE LEVEL OF 120 MG/DL OR ABOVE
(PLASMA = 140 MG/DL)

TABLE 14

RECOMMENDED CRITERIA OF INTERNATIONAL
STUDY GROUP - 1978 - FOR THE DIAGNOSIS OF DIABETES

1. AT LEAST ONE PLASMA GLUCOSE VALUE BETWEEN ZERO TIME AND TWO HOURS $\geq$ 200 MG/DL

2. TWO HOUR PLASMA GLUCOSE CONCENTRATION $\geq$ 200 MG/DL

2. THE LEVEL OF BLOOD GLUCOSE, I.E., 50 MG/DL OR LESS USED TO MAKE THE DIAGNOSIS OF HYPOGLYCEMIA IS NOT NOW ACCEPTABLE EVEN BY SELTZER (1974) AND FAJANS AND FLOYD (1973) WHO NOW REQUIRE A FALL IN BLOOD GLUCOSE TO OR BELOW 40 MG/DL

Moreover, different studies have shown (see Tables 7, 8, and 9) that during an oral glucose tolerance test in normal asymptomatic subjects blood glucose may fall to or below 50 mg/dl in from 33 to 40 percent of tests.

3. LATE HYPOGLYCEMIA, I.E., DURING THE FOURTH TO FIFTH HOURS OF THE ORAL GLUCOSE TOLERANCE TEST ALSO OCCURS IN NON-DIABETICS

Fabrykant (1955) reported that both peaks and nadirs of blood glucose and the time of their occurrence during an oral glucose tolerance test vary during repeated testing in subjects with postprandial hypoglycemia. In 1969, Freinkel and Metzger and in 1976 Permutt reported that on studying subjects by repeated tolerance tests the patterns varied in the same subject from early diabetes with late hypoglycemia to idiopathic reactive hypoglycemia.

FIGURE 12

TIME OF NADIR OF BLOOD GLUCOSE DURING AN ORAL GLUCOSE TOLERANCE TEST IN NON-DIABETIC SUBJECTS (Marks and Guilford, 1976)

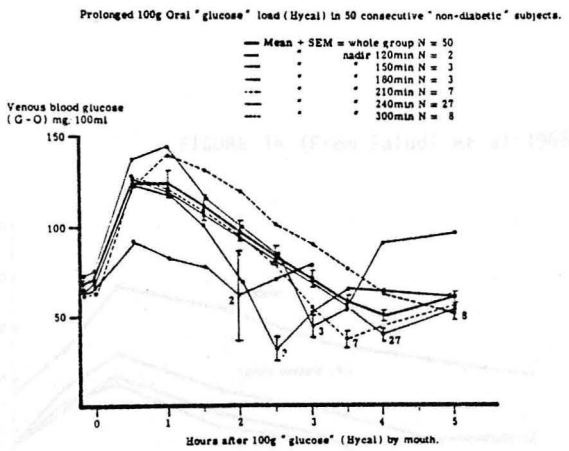
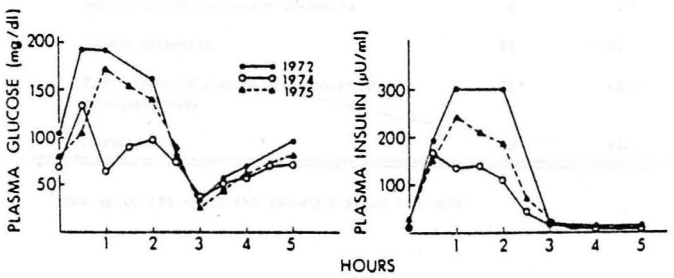


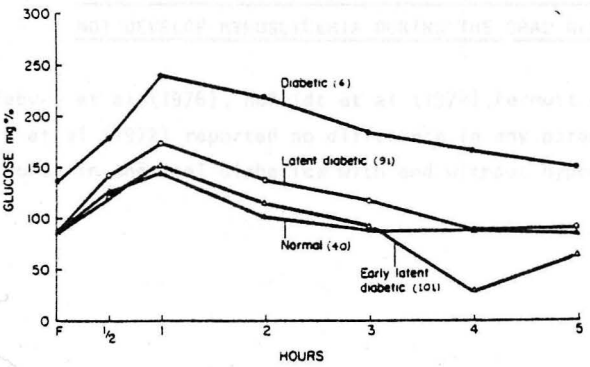
FIGURE 13

VARIABILITY OF PLASMA GLUCOSE AND INSULIN PATTERN ON REPEATED ORAL GLUCOSE TOLERANCE TEST (Permutt, 1967)



Serial five-hour oral GTTs in a patient with postprandial hypoglycemia indicating the variability of plasma glucose and insulin patterns with repeated tests.

FIGURE 14 (From Faludi et al 1968)



Mean blood sugar values during five-hour glucose tolerance test in 238 obese subjects.

TABLE 15 (From Faludi et al 1968)

ABNORMAL GLUCOSE TOLERANCE IN OBESITY

Type	Number	Percent
Obese subjects (known diabetics excluded)	238	100
Newly discovered overt diabetics	6	2.5
Latent diabetics	91	38
Early latent diabetics (with functional hypoglycemia)	101*	42.5
Normals	40	17

*PEAK BELOW 150 mg/dl AND TWO-HOUR BELOW 110 mg/dl

4. THE ABNORMALITIES IN INSULIN SECRETION (INITIAL DELAY FOLLOWED BY A LATE PEAK) IS NOT SPECIFIC FOR EARLY DIABETES MELLITUS SINCE IT ALSO HAS BEEN REPORTED IN SUBJECTS WITH IDIOPATHIC REACTIVE HYPOGLYCEMIA

see Tables 10 and 11

5. THE DELAYED PEAK IN INSULIN SECRETION CANNOT BE CAUSALLY LINKED TO THE LATE HYPOGLYCEMIA SINCE A SIMILAR DELAYED PEAK WAS FOUND IN SUBJECTS WITH CHEMICAL DIABETES WHO DID NOT DEVELOP HYPOGLYCEMIA DURING THE ORAL GLUCOSE TOLERANCE TEST

Lefebvre et al (1976), Hofeldt et al (1974), Permutt et al (1976) and Park et al (1972) reported no difference in any parameter of insulin response in chemical diabetics with and without hypoglycemia.

TABLE 16

COMPARISON OF INSULIN DYNAMICS IN EARLY (CHEMICAL) DIABETES WITH AND WITHOUT "REACTIVE HYPOGLYCEMIA"

AUTHOR	NUMBER REACT. HYPO	NUMBER NO HYPO	INSULIN (IRI) DYNAMICS DURING 5 HOUR OGTT
PARK, et al 1972	6 (21)*	52 (64)*	NO DIFFERENCE IN ANY IRI PARAMETERS (MEAN IRI, TOTAL IRI, PEAK IRI, TIME OF PEAK)
HOFELDT et al 1974	16	15	A) NO DELAY OR INCREASE IN IRI COMPARED TO MATCHED CONTROLS B) DELAY IN INSULIN SECRETION WHEN COMPARED TO 28 NORMAL CONTROLS C) NON-DIABETIC SUBJECTS (44) WITH REACTIVE HYPOGLYCEMIA ALSO HAD DELAYED INSULIN SECRETION COMPARED TO NORMAL CONTROLS.
LEFEBVRE, et al 1976	9	11	A) NO DIFFERENCE IN ANY PARAMETER OF INSULIN RESPONSE IN OBESE DIABETICS WITH AND WITHOUT HYPOGLYCEMIA

*"Genetic Prediabetics"

6. THE INCIDENCE OF HYPOGLYCEMIA (FALL IN BLOOD GLUCOSE TO 50 MG/DL OR LESS) WAS LESS IN CHEMICAL DIABETICS THAN IN NORMAL ASYMPTOMATIC CONTROLS OR IN GENETIC PREDIABETICS WITH NO EVIDENCE OF DIABETES

TABLE 17

INCIDENCE OF LATE HYPOGLYCEMIA IN SUBJECTS WITH CHEMICAL DIABETES MELLITUS ON THE BASIS OF THE ORAL GLUCOSE TOLERANCE TEST (5 HOURS)

	NUMBER TESTED	HYPOGLYCEMIC NO.	HYPOGLYCEMIC PERCENT
PARK ET AL 1972	58	6	10%
FALUDI ET AL 1968	91	0	0%
TOTAL	149	6	4%

TABLE 18

INCIDENCE OF BIOCHEMICAL HYPOGLYCEMIA IN NORMAL CONTROLS, CHEMICAL DIABETES, AND GENETIC PREDIABETICS DURING 5 HOUR ORAL GLUCOSE TOLERANCE TEST

GROUP	NUMBER	PERCENT FALLING BELOW BLOOD GLUCOSE OF 50 mg/dl
NORMALS	123	23 %
CHEMICAL DIABETICS	58	10 %
PRE-DIABETICS	85	25 %

(PARK, et al 1972)

T. J. MERIMEE 1977

There are recent findings suggesting that two overdiagnosed varieties of hypoglycemia have no established validity, i.e., idiopathic reactive hypoglycemia and hypoglycemia in early or chemical diabetes.

"FALSE STANDARDS CREATE FALSE DISEASE"

TABLE 19

THE ORAL GLUCOSE TOLERANCE TEST
AND CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS, IMPAIRED GLUCOSE TOLERANCE, GESTATIONAL DIABETES, AND NORMAL TOLERANCE IN ADULTS

A. THE ORAL GLUCOSE TOLERANCE TEST

The standard oral glucose tolerance test is often unnecessary for the diagnosis of diabetes, as for example when the fasting blood glucose concentration is elevated on more than one occasion. When it is used, however, it should be performed in the morning following at least three days of unrestricted diet and physical activity. The subject should have fasted for at least 10 hours but no more than 16 hours; water is permitted during this period. The subject should remain seated and not smoke throughout the test.

The dose of glucose administered should be 1.75 g per kg body weight, up to a maximum of 75 g of glucose. A carbohydrate load equivalent to the glucose dose is also acceptable. Commercially prepared solutions of glucose, maltose, and low molecular weight dextrins with flavoring provide a very palatable carbohydrate load, which is rapidly hydrolyzed to glucose in the stomach. In order to use the criteria for Gestational Diabetes below, a dose of 100 g is required.

A fasting blood sample should be collected, after which the glucose dose in a concentration no greater than 25 g/100 ml of flavored water should be drunk in approximately 5 minutes. Zero time is the beginning of the drink, and blood samples should be collected at 30 minute intervals for two hours. For pregnant subjects, the criteria below for Gestational Diabetes require sampling at fasting, one, two, and three hours. If possible, venous blood samples should be collected, and unless glucose concentrations can be determined immediately using a rapid glucose analyzer, blood should be collected in a tube containing sodium fluoride (5 ml whole blood to 30 mg NaF). The sample should be centrifuged and separated within 4 hours of collection, and the plasma frozen unless glucose levels are to be determined immediately.

Plasma glucose is the preferred measurement by any of the following methods, which have been shown to be comparable when performed with adequate quality control procedures: glucose oxidase, hexokinase, o-toluidine, Somogi-Nelson, AutoAnalyzer ferricyanide, or AutoAnalyzer neocuproine. See G.R. Cooper, "Methods for Determining the Amount of Glucose in Blood", C.R.C Crit. Rev. Lab. Sci., August, 1973, p. 101-145.

See "Standardization of the Oral Glucose Tolerance Test", Diabetes, vol. 18, 1969, p. 299-307, for discussion of factors other than diabetes which influence glucose tolerance.

B. CRITERIA FOR DIAGNOSIS

The values below refer to venous plasma samples. Values for venous whole blood glucose concentration should be 15% lower. Values for capillary samples (plasma or whole blood) should be 10% higher than the respective venous values.

Criteria for Diagnosis of Diabetes Based on Fasting Plasma Glucose Concentration:

Fasting plasma glucose concentration $\geq$ 140 mg/dl on more than one occasion

Criteria for Diagnosis Based on the Oral Glucose Tolerance Test (not required if the fasting plasma glucose concentration is $\geq$ 140 mg/dl on more than one occasion):

Diabetes Mellitus:

Two-hour plasma glucose concentration $\geq$ 200 mg/dl
and
At least one value between zero time and two hours $\geq$ 200 mg/dl

Impaired Glucose Tolerance:

Two-hour plasma glucose concentration $\geq$ 140 mg/dl and < 200 mg/dl
and
At least one value between zero time and two hours $\geq$ 200 mg/dl

Gestational Diabetes:

Gestational diabetes is diagnosed when two or more of the following plasma glucose values are met or exceeded (after 100 g glucose dose):

fasting - 105 mg/dl
one-hour - 190 mg/dl
two-hour - 165 mg/dl*
three-hour - 145 mg/dl

C. CRITERIA FOR NORMAL GLUCOSE TOLERANCE

Fasting plasma glucose concentration < 140 mg/dl
and
Two-hour plasma glucose concentration < 140 mg/dl

*Several members of the workgroup recommended that a category "Impaired Gestational Glucose Tolerance" be defined by a two-hour plasma glucose level between 120 mg/dl and 164 mg/dl.

SECTION VI

RESPONSE TO A LOW CARBOHYDRATE, HIGH PROTEIN DIET AS ONE OF THE CRITERIA FOR THE DIAGNOSIS OF IDIOPATHIC REACTIVE HYPOGLYCEMIA

Carbohydrate restriction for several days prior to an oral glucose tolerance test results in increased hyperglycemia - the so-called "diabetes" of starvation or carbohydrate deprivation (Sweeney 1927, Conn 1940). This phenomenon led Sweeney and later Conn to promulgate the use of a high carbohydrate diet prior to the performance of an oral glucose tolerance test for the diagnosis of diabetes. It also resulted in Conn's promoting the use of a low carbohydrate (75-100 gms), high protein (120-140 gms) diet in the treatment of reactive hypoglycemia. The rationale was that the low carbohydrate diet would decrease the insulin response to such meals and thereby alleviate the hypoglycemia.

The beneficial response to such a diet has been said to be so characteristic that it has been included in the criteria for the diagnosis of idiopathic reactive hypoglycemia by several investigators (Conn, 1947, Conn and Seltzer, 1955, Fajans and Floyd, 1973, and Seltzer, 1974).

TABLE 20 (Seltzer, 1974)

CRITERIA FOR DIAGNOSIS OF ORDINARY FUNCTIONAL HYPOGLYCEMIA*

AUTHOR(S)	DEFINITE	PROBABLE (PRESUMPTIVE)	POSSIBLE (SUGGESTIVE)	UNLIKELY
CONN	BLOOD GLUCOSE (BG) NADIR BELOW 40 MG/100 ML	BG NADIR 40-49 MG/100 ML	BG NADIR 50-59 MG/100 ML	BG NADIR 50 MG/100 ML OR MORE
ANTHONY, DIPPE, HOFELDT, et al	BG NADIR 40 MG/100 ML OR LESS;	BG NADIR 40 MG/100 ML OR LESS WITHOUT 11-OHCS RESPONSE; OR	BG NADIR 50-60 MG/100 ML WITH 11-OHCS RESPONSE AND TYPICAL SYMPTOMS IN DAILY LIFE; OR	NO STRONG LABORATORY EVIDENCE OF HYPOGLYCEMIA
	POSITIVE PLASMA 11-OHCS RESPONSE**	BG NADIR 40-50 MG/100 ML, WITH 11-OHCS RESPONSE;	PREVIOUSLY DOCUMENTED (OUTSIDE) BG BELOW 40 MG/100 ML, WITH TYPICAL SYMPTOMS IN DAILY LIFE; OR	SYMPTOMS IN DAILY LIFE ARE ILL-DEFINED
	TYPICAL SYMPTOMS IN DAILY LIFE	TYPICAL SYMPTOMS IN DAILY LIFE;		
	TYPICAL SYMPTOMS AT TIME OF BG NADIR	TYPICAL SYMPTOMS AT TIME OF BG NADIR	TYPICAL SYMPTOMS IN DAILY LIFE BG NADIR 40-60 MG/100 ML, WITHOUT 11-OHCS RESPONSE	
SELTZER	BG NADIR 40 MG/100 OR LESS;	BG NADIR 45 MG/100 ML OR LESS;	BG NADIR 46-59 MG/100 ML;	BG NADIR ABOVE 45 MG/100 ML;
	TYPICAL SYMPTOMS AT TIME OF BG NADIR;	WITH OR WITHOUT SYMPTOMS AT TIME OF BG NADIR;	NO SYMPTOMS DURING THE ORAL GTT;	ATYPICAL SYMPTOMS (CHRONIC FATIGUE, ETC.) IN DAILY LIFE;
	TYPICAL SYMPTOMS IN DAILY LIFE;	TYPICAL SYMPTOMS IN DAILY LIFE;	TYPICAL SYMPTOMS IN DAILY LIFE;	TRANSIENT OR NO RESPONSE TO DIET
	PROMPT, SUSTAINED RESPONSE TO HIGH-PROTEIN LOW-CARBOHYDRATE DIET.	PROMPT, SUSTAINED RESPONSE TO DIET	PROMPT, SUSTAINED RESPONSE TO DIET	

*ALL ORAL GTTs ARE NORMAL FOR THE FIRST TWO HOURS, THEN FALL TO THE BLOOD GLUCOSE (BG) NADIRS INDICATED. "TRUE BLOOD SUGAR" VALUES ARE SHOWN (SOMOGYI-NELSON OR GLUCOSE-OXIDASE METHODS)

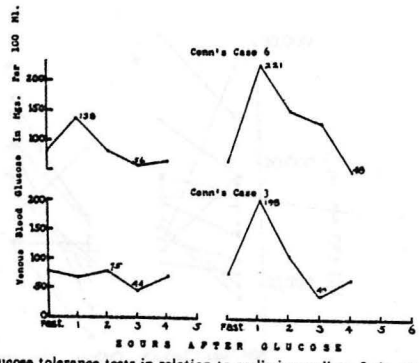
**A POSITIVE PLASMA 11-OHCS RESPONSE IS DEFINED AS AN INCREASE GREATER THAN 5 μG/100 ML, OCCURING 30 TO 60 MINUTES AFTER THE BG NADIR

However, many other investigators have reported failures in the treatment of idiopathic reactive hypoglycemia with the low carbohydrate, high protein diet (Fabrykant, 1955, Anderson and Herman, 1967 and 1975, Stambaugh et al, 1974, Sekso et al, 1957, Permutt et al 1976 and 1977).

Indeed a worsening of the reactive hypoglycemia has been documented by Anderson and Herman (1967 and 1975).

In 1955 Fabrykant pointed out that emphasis on the effect of a low carbohydrate diet on subsequent glucose tolerance was confined to the first two to three hours of the glucose tolerance test. Careful studies on the fourth to fifth hours were not done. Fabrykant noted that following carbohydrate restriction although there was initial hyperglycemia during the glucose tolerance test this not infrequently was followed by a more pronounced hypoglycemic dip. He noted that this effect was overlooked by Conn but present in his data.

FIGURE 15 (From Fabrykant, 1955)



Glucose tolerance tests in relation to preliminary diets. Left, after high carbohydrate diets (300 Gm. carbohydrate, 2500 to 3000 calories); right, after low carbohydrate, high protein diets (25 Gm. carbohydrate, 120 to 140 Gm. protein and enough fat to cover caloric needs).

Permutt et al (1976) recently studied the effect of carbohydrate restriction on the hypoglycemic phase of the oral glucose tolerance test in 10 normal subjects and has confirmed Fabrykant's earlier findings.

FIGURE 16

CHANGES IN BLOOD GLUCOSE RESPONSE TO ORAL GLUCOSE AFTER CARBOHYDRATE RESTRICTION

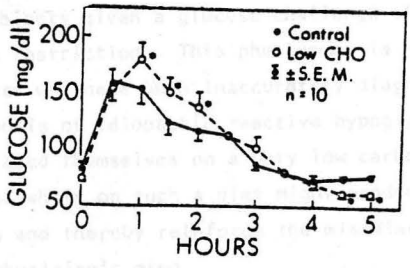
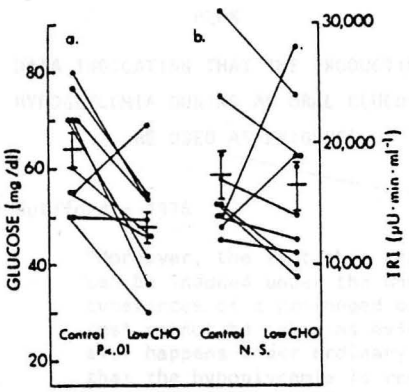


FIGURE 17

CHANGES IN BLOOD GLUCOSE RESPONSE TO ORAL GLUCOSE AFTER CARBOHYDRATE RESTRICTION (Permutt 1976)



Nadir plasma glucose (a), and total insulin secreted (b), for each normal subject in the control test and following three days of a low CHO diet.

The mean nadir of plasma glucose on the usual preparatory diet was 64 ± 4 mg/dl, whereas after carbohydrate restriction the mean nadir was 48 ± 4 mg/dl.

Six of the ten normal subjects had a plasma glucose nadir less than 50 mg/dl after carbohydrate restriction and five of these developed typical adrenergic symptoms of perspiration, tremulousness, palpitations, and anxiety.

These results demonstrate that reactive hypoglycemia may be provoked in normal subjects given a glucose challenge after several days of carbohydrate restriction. This phenonomen is especially important in those subjects who have been inaccurately diagnosed or who have made a self-diagnosis of idiopathic reactive hypoglycemia. If they were placed or placed themselves on a very low carbohydrate diet, a carbohydrate binge while on such a diet might produce symptomatic reactive hypoglycemia and thereby reinforce the mis-diagnosis in the person's and in the physician's mind.

SECTION VII

A. THE ORAL GLUCOSE TOLERANCE TEST VS THE MEAL TEST IN THE DIAGNOSIS OF IDIOPATHIC REACTIVE HYPOGLYCEMIA

PLUS

B. DATA INDICATING THAT THE PRODUCTION OF TYPICAL SYMPTOMS OF HYPOGLYCEMIA DURING AN ORAL GLUCOSE TOLERANCE TEST CANNOT BE USED AS EVIDENCE OF THIS DISORDER

Marks and Guilford - 1976

> "Moreover, the fact that reactive hypoglycemia can be induced under the wholly artificial circumstances of a prolonged oral glucose tolerance test cannot be taken as evidence that this ever happens under ordinary, every-day conditions nor that the hypoglycemia is responsible for the patients spontaneous symptoms"

A. COMPARISON OF THE ORAL GLUCOSE TOLERANCE TEST AND A MEAL TEST IN THE DIAGNOSIS OF IDIOPATHIC REACTIVE HYPOGLYCEMIA

FIGURE 18

EFFECT OF MEALS ON BLOOD GLUCOSE AND PLASMA INSULIN (Genuth 1973)

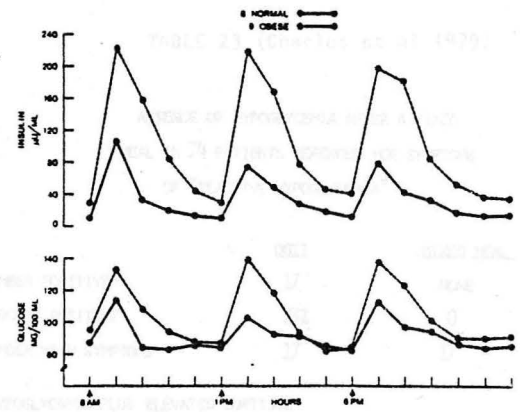


TABLE 21 (Kansal et al 1977)

COMPARISON OF THE 5 HOUR OGTT AND A MEAL TEST IN 11 SUBJECTS REFERRED FOR SYMPTOMS OF "REACTIVE HYPOGLYCEMIA"

	OGTT	MEAL TEST
NUMBER FALLING TO OR BELOW GLUCOSE OF 50 MG/DL	6	NONE
PERCENT POSITIVE	54%	0%
PLASMA GLUCOSE		
MEAN NADIR	45.8 MG/DL	76.8 MG/DL
RANGE	30-50 MG/DL	62-86 MG/DL

TABLE 22 (Hofeldt et al 1978)

ABSENCE OF HYPOGLYCEMIA AFTER A TEST MEAL IN PATIENTS (11) WITH "IDIOPATHIC" REACTIVE HYPOGLYCEMIA

	OGTT	TEST MEAL
PLASMA GLUCOSE NADIR (MG/DL)	47 ± 3 (29-60)	79 ± 3 (61-95)
PLASMA CORTISOL RISE (UG/DL)	11 ± 1.3	-0.6 ± 0.7
PEAK	21 ± 1.5	8.5 ± 1.
TOTAL INSULIN ABOVE BASELINE NG/300 MIN.	664 ± 116	169 ± 28
SYMPTOMS OF "HYPOGLYCEMIA"	100%	82%

TABLE 23 (Charles et al 1979)

ABSENCE OF HYPOGLYCEMIA AFTER A MIXED MEAL IN 74 PATIENTS REFERRED FOR SYMPTOMS OF "REACTIVE HYPOGLYCEMIA"

	OGTT	MIXED MEAL
NUMBER POSITIVE*	17	NONE
PERCENT POSITIVE	23%	0
NUMBER WITH SYMPTOMS	17	17

*=HYPOGLYCEMIA PLUS ELEVATED CORTISOL

B. NON-SPECIFICITY OF SYMPTOMS OF HYPOGLYCEMIA DURING THE ORAL GLUCOSE TOLERANCE TEST

TABLE 24

HYPOGLYCEMIC SYMPTOMS IN 44 NORMAL SUBJECTS DURING OGTT

SYMPTOMS	NONE	HUNGER, TIREDNESS HEADACHE	ADRENERGIC
NUMBER	15	14	15
NADIR GLUCOSE MG/DL	58.3	58.6	46.9
RANGE	30-85	40-78	34-64
FALL FROM FASTING	20.4	24.4	34.9
TIME OF NADIR MINUTES	258	251	252

(KLACHKO AND BURNS, 1978)

TABLE 25

LACK OF CORRELATION BETWEEN SYMPTOMS AND HYPOGLYCEMIA DURING 5 HOUR OGTT IN 51 PATIENTS

NON-HYPOGLYCEMIC 29 SUBJECTS		HYPOGLYCEMIC* 22 SUBJECTS	
SYMPTOMS	NO SYMPTOMS	SYMPTOMS	NO SYMPTOMS
6 (21%)	23 (79%)	5 (23%)	17 (77%)

*BLOOD GLUCOSE BELOW 40 MG/DL

MARKS AND GUILDFORD, 1976

TABLE 26

PROBANTHELINE TREATMENT IN "IDIOPATHIC REACTIVE HYPOGLYCEMIA".

	OGTT	OGTT + PROBAN.
GLUCOSE PEAK TIME - MIN.	30	81
INSULIN PEAK TIME - MIN.	77 ± 34	124 ± 44
NADIR GLUCOSE MG/DL	45 ± 4.6	76 ± 7
PREVENTION OF HYPOGLYCEMIA		7 OF 7
PERSISTENCE OF SYMPTOMS		6 OF 7

(ABBASI, ET AL, 1975)

1976 - Lefebvre and Luyckx - The Breakfast Tolerance Test: A Return to Physiology

> "It is suggested to the clinician to use this breakfast tolerance test as a simple means to reconsider, on physiologic grounds, widely accepted pathophysiologic concepts (i.e., glucose intolerance, reactive hypoglycemia, sluggish or delayed insulin responses, etc.) derived from highly unphysiologic procedures such as the oral glucose tolerance test."

1977 - Kansal et al

> "These data question the validity of the oral glucose tolerance test as a diagnostic test for reactive hypoglycemia, since chemical hypoglycemia was not elicited when investigated by a more natural stimulus such as a meal test."

1971 - Madison

> "Idiopathic reactive hypoglycemia should not be diagnosed unless the subject develops chemical hypoglycemia following his regular meal. The oral glucose tolerance test should never be used to make this diagnosis."

SECTION VIII

TABLE 27

CRITERIA FOR THE DIAGNOSIS OF IDIOPATHIC REACTIVE HYPOGLYCEMIA

1. EPISODES MUST BE ONLY POSTPRANDIAL*
2. MUST DOCUMENT A LOW BLOOD SUGAR
   A. DURING A SPONTANEOUS ATTACK INDUCED BY PATIENT'S DIET.
   B. DURING A SPONTANEOUS ATTACK INDUCED BY A MIXED MEAL.
3. OTHER CAUSES OF POSTPRANDIAL HYPOGLYCEMIA MUST BE RULED OUT.
4. THE PATIENT SHOULD IMPROVE
   A. DURING A 24 HOUR FAST
   B. ON A REDUCED CHO INTAKE (120-150 GMS/DAY)
5. THE 5 HOUR ORAL GLUCOSE TOLERANCE TEST SHOULD NEVER BE USED.

*On the basis of presently available data from 162 meals in 65 subjects, hypoglycemia after meals can be defined as a fall in blood glucose below 50 mg/dl or in plasma glucose below 57 mg/dl.(ref. 79-82, 86) These criteria may have to be altered in the future as the changes in blood glucose after meals are reported in a large number of healthy asymptomatic persons.

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SECTION VII - The Oral Glucose Tolerance Test Vs The Meal Test In The Diagnosis of Idiopathic Reactive Hypoglycemia - Plus - Data Indicating That The Production of Typical Symptoms of Hypoglycemia During An Oral Glucose Tolerance Test Cannot Be Used As Evidence of This Disorder

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