I. IDENTIFICATION OF CHEMICAL DIABETES

The Definition of Chemical Diabetes

By Stefan S. Fajans

The natural history of diabetes mellitus can be arbitrarily divided into four stages based on the presence or absence of abnormal carbohydrate metabolism. Overt diabetes is the most advanced stage, characterized by elevated fasting blood glucose concentration and classical symptoms. This stage is divided into ketotic and nonketotic forms. Preceding overt diabetes is the latent or chemical diabetic stage, with no symptoms of diabetes but demonstrable abnormality of oral or intravenous glucose tolerance. Subclinical diabetes is an earlier stage when glucose tolerance is abnormal only with stress, such as pregnancy or the administration of cortisone. The earliest stage, prediabetes, extends from conception until the first demonstrable abnormality in glucose tolerance. In groups of presumed prediabetic individuals, delayed and/or decreased plasma insulin response to glucose has been noted. Progression of the diabetes may not occur, may occur very slowly or very rapidly, and regression to an earlier stage of abnormality may also occur.

BEFORE PROCEEDING WITH A DEFINITION of chemical diabetes, we need to review the stages in the natural history of the disease in order to put the stage of chemical diabetes in proper perspective. Any classification of genetic diabetes mellitus must be somewhat arbitrary, as is the classification that we have employed for a number of years.[1] Table 1 presents a scheme depicting the natural history of diabetes as divided into four stages.[1] This classification is based on the presence or absence of abnormalities of carbohydrate metabolism.

Overt or frank diabetes is the most advanced of these stages. Classical symptoms of the disease may be present: There is fasting hyperglycemia; a glucose tolerance test is not necessary for diagnosis. This stage of the disease has been subdivided into the nonketotic and ketotic forms of the disease.

The preceding stage is latent or chemical diabetes. A latent diabetic is an individual who has no symptoms referable to the disease but in whom a definite diagnosis of diabetes can be established by presently accepted laboratory procedures. The fasting blood glucose level may be elevated but is usually normal. However, the oral or intravenous glucose tolerance test is definitely abnormal, whatever the criteria for an abnormal glucose tolerance test may be.

An earlier stage is subclinical diabetes.[2] Here, not only the fasting blood sugar level but also the glucose tolerance test is normal under usual circum-

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Table 1. Natural History of Diabetes Mellitus

	Prediabetes	Subclinical Diabetes → Latent Diabetes → Overt Diabetes		
FBS	Normal	Normal	Normal or ▲	▲
GTT	Normal	Normal Abnormal during pregnancy, stress	Abnormal	Not necessary for diagnosis
Cortisone–GTT	Normal	Abnormal	Not Necessary	
Delayed and/or decreased insulin response to glucose	+	++	+++	++++
Vascular changes	+	+	++	++++

stances. However, diabetes may be suspected because of evidence of insufficient functional reserve of the islet cells. An example would be a woman who has a normal glucose tolerance test but who has a history of abnormality of standard glucose tolerance during pregnancy. The latter has been termed pregnancy or gestational diabetes. A high proportion of such women develop latent or overt diabetes in the years which follow. Another example of subclinical diabetes may be an individual with a normal standard glucose tolerance test but an abnormal cortisone–glucose tolerance test in the nonpregnant state.

The earliest stage is prediabetes.[2] The prediabetic state exists prior to the onset of identifiable diabetes mellitus, whether it be overt, latent, or subclinical. It identifies the interval of time from conception until the demonstration of impaired glucose tolerance in an individual predisposed to diabetes on genetic grounds. Prediabetes can be suspected to be present genetically in the nondiabetic identical twin of a diabetic patient and in the offspring of two conjugal diabetic parents. During the prediabetic period, glucose tolerance and cortisone–glucose tolerance tests are normal. A number of findings indicate that groups of prediabetic subjects can be differentiated from groups of normal control subjects although reliable diagnostic tests are not available for detection of prediabetes in the individual. A delayed and/or decreased plasma insulin response to the stimulus of glucose has been demonstrated in groups of genetic prediabetic individuals[3–6] and in other nondiabetic relatives of diabetic patients[7–9] by a number of investigators. This defect is similar to that demonstrated in patients with overt, latent, and subclinical diabetes. Vascular changes, reflected by thickening of the capillary basement

Table 2. Glucose Tolerance Test
Rapid Progression from "Prediabetes" to Overt Diabetes*

Date	Age	Test	F	½	1	1½	2	2½	3
						(mg/100 ml)			
12/2/54	16	GTT	82	106	88	85	74	85	79
12/3/54	16	Cortisone–GTT	81	121	91	84	90	98	67
11/55	17		350 — 7 wk of polyuria, polydipsia, 30-lb weight loss, fatigue						

*K.G., male; F.H., father, mother, 2 siblings with diabetes mellitus.

membrane of muscle obtained by biopsy, have been found by Siperstein et al.[10] in 52% of a group of "prediabetic" individuals; cortisone–glucose tolerance tests were not performed in these subjects.

In the natural history of diabetes, progression or regression from one stage to the next stage (1) may never occur, or (2) may occur very slowly over many years, or (3) may be rapid or even explosive.[1] The concept, supported by appropriate findings, that there may be fluctuations in the expression of the carbohydrate aspects of the disease in either direction is an important one. Such fluctuations are particularly common when carbohydrate intolerance is mild.[11,12] However, even the overt stage of the disease may regress. Extreme examples, such as regression from overt ketotic diabetes to prediabetes, have been reported in individuals who have been in diabetic coma and who subsequently exhibited normal standard and normal cortisone–glucose tolerance tests.[13] On the other hand, rapid progression from prediabetes to overt or symptomatic diabetes without recognition of the intermediary stage of latent diabetes can be documented as is illustrated by the following example (Table 2). K.G. was a 16-yr-old prediabetic boy, who was the offspring of two asymptomatic diabetic parents and the sibling of two ketotic-type diabetics, one of whom had died of diabetic nephropathy. K.G. had normal glucose tolerance and normal cortisone–glucose tolerance tests in December 1954, followed by symptomatic diabetes 10 mo later.

Table 3 gives an example of very slow progression to overt diabetes. This child was seen in our Department of Pediatrics at the age of 6 mo, and was referred because of furunculosis and glycosuria. In 1938, this glucose tolerance test (Benedict blood glucose method) was called normal and the mother was told to forget about any possible abnormality, which she did. The patient was readmitted at the age of 14 with a history of upper respiratory infection, followed in just a few days by symptoms of overt diabetes. He was in diabetic coma and died. It is entirely possible that more effective therapy might have saved this child's life. However, even if a diagnosis of diabetes

Table 3. Very Slow Progression From Chemical Diabetes to Overt Diabetes*

1938 — Age 6 mo					
Furunculosis for 6 wk					
Glycosuria (+–+++) for 2 wk					
GTT:	F	½	1	2	3
			(mg/100 ml)		
	84	172	153	129	105
Well until:					
1951 — Age 14 yr					
12/2 Sore throat, anorexia, restlessness					
12/6 Polyuria, polydipsia					
12/7 Air hunger, confusion					
12/8 Coma					
Urine: ++++ glucose and ketone bodies					
CO_2 comb. power: 5 meq/liter					
NPN: 92 mg/100 ml					

*F.P., male.

was not possible in 1938, close followup with periodic testing should have been advised. It is possible that this unfortunate death might have been prevented by recognition of the disease before complete decompensation of islet cell function occurred.

In Table 4, an example is given of a remission of overt diabetes complicated by diabetic coma to the prediabetic stage (on the basis of a normal glucose tolerance test). A year later abnormal glucose tolerance indicated latent or chemical diabetes.

A longer remission of overt diabetes is shown in Table 5. A 41-yr-old male was in profound diabetic coma. Insulin therapy was discontinued 6 wk later and shortly thereafter the glucose tolerance test was normal. Three yr later he had a normal glucose tolerance test and a normal cortisone–glucose

Table 4. Temporary Remission of Overt Diabetes*

Date	Wt. (kg)	Test:	F	½	1 (mg/100 ml)	1½	2
5/12/55	68.0		330 Urine: ++++ Acetone				
			Serum CO_2 content:			8.5 meq/liter	
			Serum pH:			7.18	
8/26/55	62.6		Insulin therapy discontinued				
12/55		GTT:	75		150		80
12/56		GTT:	97	186	200		260

*J.N., male, 24 yr.
By permission.[14]

Table 5. Remission of Overt Diabetes*

10/12/54	Profound diabetic coma, circulatory collapse
	B.S.: 1280 mg/100 ml; Urine: ++++ Acetone
	Plasma CO_2 C.P.: 3 meq/liter; BUN: 60 mg/100 ml
11/27/54	Insulin therapy discontinued

	Test:	F	½	1 (mg/100 ml)	1½	2	2½	3
12/17/54	GTT:	82		154		100		113
6/29/57	GTT:	82	104	76	90	131	104	110
6/30/57	Cortisone–GTT:	84	156	158	127	90	98	82

*R.W., male, 41 yr.
By permission.[13]

Table 6. Regression of Latent (Chemical) Diabetes to Prediabetes*

Date	Age	Wt (kg)	Test:	F	½	1	1½ (mg/100 ml)	2	2½	3
1/12/54	34	101	GTT:	102	175	260	247	236	128	99
5/15/43		79								
11/29/54		98	GTT:	89	150	160	132	104	89	66
11/30/54			Cortisone–GTT:	97	173	140	104	97	85	85
4/ 5/63	43	109	died of myocardial infarction							

*J.P., male; F.H., diabetes in father, mother, one bothers, and two sisters.

Table 7. "Maturity-onset-type" Diabetes in Childhood*

Date	Age	Glucose Tolerance Test (mg/100 ml) F	½	1	1½	2	2½	3	Height	Weight (lb)
1/12/54	10	94	146	214	207	161	160	135	4 ft 9 in. (1400-cal diet)	118
11/29/54	10	85	—	129	146	100	118	104		110
5/ 8/58	14	82	105	136	142	150	105	—	5 ft 2½ in.	177
5/19/59	15	92	144	185	157	156	164	133	5 ft 2¼ in. (1400-cal diet)	178
11/23/59	15	91	125	132	106	136	120	102		160
1/16/61	17	Delivery: M, 8 lb, 6 oz								
3/ 6/62	18	Delivery: F, 11 lb, 8 oz								
3/ 4/63	19	88	—	224	—	207	162	—	5 ft 3 in.	205
3/ 7/63	19	Oral Tolbutamide Test: Per cent of FBS: 20 min—97%, 30 min—85%, 40 min—80%								
7/ 4/66	22	Delivery: M, 10 lbs, 8 oz								
1/11/68	24	87	169	—	182	168			5 ft 3 in.	185
11/12/69	26	85	149	207	222	212	161	131		170
7/15/70										215
11/30/70	27	101	210	269	238	246	227	165		199

*A.P.S., female; F.H., diabetes: (1) Father—died of vascular disease; (2) Mother—died of vascular disease; (3) two brothers (one died of vascular disease) and one sister.

tolerance test (prediabetes). I would like to emphasize again that if one can have regression from the most advanced stage to the prediabetic stage, then one should not be surprised that, as reported by O'Sullivan and Hurwitz,[11] 27% of young women with grossly abnormal glucose tolerance tests reverted to normal glucose tolerance. Thus, variability in the results of the glucose tolerance test in any one individual may be due to biologic variations in the individual tested rather than due to variability ("lack of reproducibility") in the test procedure. Other examples are given in the next two tables.

Table 8. Glucose Tolerance Tests in 7 of 10 Asymptomatic Children of a Diabetic Father

Age	Sex	F	½	1	1½	2	2½	3
					(mg/100 ml)			
30	F	322 (4+ glucose and acetone)						
29	M	147* (tr)	264	337	357	355 (++++)	287	229
27	M	210 (++)						
25	M	113 (0)	236	274	267	259 (++++)	216	175
21	M	80 (0)	146	178	141	140 (0)	129	157
16	F	98 (0)	175	210	121	160 (0)	156	154
11	M	109 (0)	183	219	188	161 (0)	170	128

*Clinitest reaction noted below blood glucose values in parentheses.

J.P. (Table 6) was an offspring of conjugal diabetic parents. He was diabetic, as can be seen from the glucose tolerance test performed on January 12, 1954. He was grossly overweight, reduced 22 kg in body weight, but regained that weight. In spite of a similar degree of obesity, he exhibited normal glucose tolerance and normal cortisone–glucose tolerance tests. This demonstrates reversion of latent (chemical) diabetes to the prediabetic stage. He died of a myocardial infarction 9 yr later at the age of 43.

Data on this patient's sister are given in Table 7. A diagnosis of diabetes was made at the age of 10 yr. She was overweight. Normal glucose tolerance was recorded 10 mo later after modest weight reduction. Borderline glucose tolerance was noted at age 14, and definitely abnormal glucose tolerance at the age of 15. She gave birth to an infant weighing 11 lb 8 oz. Abnormal glucose tolerance was found between the ages of 19 and 27 yr. There has been only a minor degree of progression in her carbohydrate intolerance.

Routine glucose tolerance tests were performed in 10 offspring of a diabetic father (Table 8). Seven were found to be diabetic on the first glucose tolerance test. I am showing results obtained in this family to indicate that within one family with the same genetic endowment we have a broad range of abnormality in carbohydrate tolerance. With an age span of 20 yr among these siblings, one gets the impression that progression of latent or chemical diabetes need not be rapid even among young nonobese individuals.

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