

# METABOLIC RESEARCH IN MONOZYGOTIC TWINS WITH DIABETES MELLITUS

## Progress Report\*

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*An intravenous and oral glucose tolerance test and an intravenous tolbutamide test have been performed in 11 MZ twin pairs, discordant for diabetes mellitus. Blood sugar, immunoreactive insulin, and free fatty acids were determined. The research aimed at finding out whether prediabetic subjects may show any characteristic parameter which could be suggestive of the hereditary disposition. Three MZ twins of juvenile diabetics showed a normal blood glucose, immunoreactive insulin, and free fatty acids during the glucose and tolbutamide loads within a maximum of 10 years observation.*

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### INTRODUCTION

For some years methodically selected series of twins with diabetes have been investigated in order to answer the question whether characteristic parameters for the so-called prediabetic state exist which can be regarded as a hint of hereditary disposition (Daweke et al. 1970). The prediabetic state is considered the phase before manifestation of diabetes mellitus where abnormalities in glucose tolerance cannot be proven. Long-term observations made with 11 MZ sets of twins, behaving discordantly concerning diabetes mellitus, are reported.

### METHOD

The sets of twins have been chosen from our systematically selected series. Monozygosity was assessed by anthropological (Siemens 1924, v. Verschuer 1933) and serological characteristics. The twins were submitted to the following tests:

1. Intravenous glucose tolerance test (IVGTT) with 25 g glucose;
2. Oral 100 g glucose tolerance test (OGTT);
3. Intravenous tolbutamide-test with 1.0 g tolbutamide (IVTT).

The assimilation coefficient  $k$  for glucose was calculated according to Conard et al. (1953).  $K$ -values under 1.0 were considered as pathologic, above 1.4 as normal, and those in between as pathologic in the sense of subclinical diabetes mellitus (Schilling et al. 1965). The OGTT was regarded as normal if the blood glucose (BG) did not rise above 100, 160, 135 and 105 mg/100 ml when measured on fasting, one, two and three hours after glucose load respectively. BG above 130, 225, 150 and 120 mg/100 ml, respectively, were considered manifest diabetes mellitus. Subclinical diabetes was stated if BG were within these limits. The tolbutamide test was evaluated with the  $T_3$ -value by Lange and Knick (1965). The test was pathologic at  $T_3$ -values above -1.5; below -1.5 it was normal.

Glucose was determined in venous blood by the o-toluidin method (Dubowski 1962) in the Technicon Autoanalyzer.

Immunoreactive insulin (IRI) was measured firstly according to Hales and Randle (1960), since 1974 by a solid phase radioimmunoassay (Wide and Porath 1966, Wide et al. 1967, Wide 1969).

The determination of free fatty acids (FFA) was carried out titrimetrically in a modification of Dole's (1956) method.

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## RESULTS

The first four sets of twins comprised in Table 1 were absolutely discordant after loads of glucose and tolbutamide. Three index twins out of four were juvenile diabetics, the fourth found to be a subclinical diabetic. The period of discordance of the first three sets of twins was 9, 14 and 21 years. The manifestation age of the diabetics is below 20. The fourth index twin was discovered to have subclinical diabetes mellitus at 30 years. Only in the third and fourth set of twins there is a family history of diabetes. Both parents of the fourth pair were known diabetics. During the IVGTT, OGTT and IVTT the first three sets of twins behaved discordantly with regard to BG, IRI and FFA. In nondiabetic partners BG, IRI and FFA was normal.

The insulin response of the unaffected twin of pair number 2 was delayed and diminished in the OGTT in 1964, 1965 and 1966 but, nevertheless, found to be normal in 1969 and 1974. The nondiabetic partner of the first set of twins showed normal FFA in 1969 and pathologically high values in 1971. In 1974 FFA were within normal limits.

After an oral glucose load, pair number 4 behaved concordantly concerning BG and IRI. Both twins had a normal increase in BG during OGTT. The insulin response, however, was delayed but greater than among normal subjects.

The index twins of pair number 5 and 6 were insulin-requiring diabetics. Their partners had only a decreased k-value. Pair number 7 had clinical diabetes but differed in the treatment: The index twin was insulin-requiring, whereas the partner was treated with diet only. The index twins were 9, 20 and 55 years of age when clinical diabetes was discovered. All three families have a positive history of diabetes. Both twins of pair number 6 showed a diminished insulin response during the IVGTT. The cotwin, however, showed lower BG-values than his diabetic partner. The FFA are more declining in the nondiabetic. A normal insulin response was found in the unaffected twin after oral glucose. Distinct changes in the behaviour after glucose and tolbutamide load could be noticed during long-term observations of the sets of twins numbers 8 to 11.

In 1974 the unaffected partner of pair number 8 showed a subnormal IVGTT in the sense of a subclinical diabetes mellitus. The insulin response was found increased in 1970 and within normal limits in 1974. The decrease of FFA was normal at both times. Neither in 1970 nor in 1974 an abnormal insulin response could be stated after oral glucose.

In 1970 the insulin response of the partner of pair number 9 was decreased in all three tests. In the IVGTT the FFA initially ascended. There was a marked decrease of FFA in the IVTT. In 1973 this twin exhibited an insulin-requiring diabetes mellitus.

In 1970 the index twin of pair number 10 had a pathologic  $T_3$ -value in the IVTT. In 1974 it was normal. Glucose tolerance tests in her partner were as well normal in 1970 as in 1974 despite a 3 kg increase in body weight.

The partner of the twin number 11 showed in 1971 an improved IVGTT as compared with the previous examination. The index twin showed unchanged results.

## DISCUSSION

Three MZ twins of juvenile diabetics showed normal blood glucose, immunoreactive insulin and free fatty acids during glucose tolerance and tolbutamide tests within a maximum of 10 years observation. A diminished or delayed insulin response, described by Cerasi and Luft (1967), to be typical for the prediabetic state could only be temporarily stated in one case.

Tattersall and Pyke (1972) and Johansen et al. (1974) also report long-term discordances of MZ twins with an insulin-requiring partner. Therefore, it can be assumed as a hypothesis that exogenous factors are of substantial importance for the manifestation of juvenile-onset diabetes mellitus. Interaction of predisposing genes and environmental factors can induce the manifestation of diabetes mellitus. In some cases juvenile diabetes mellitus may be caused by external factors alone (f. i. Coxsackie-B viruses; Gamble and Taylor 1969, Gamble et al. 1969). It may be questioned whether the

Table 1. Behaviour of blood glucose during IVGTT, OGTT, and IVTT

Pair no.	Age	Age at diagnosis	Year at test	IVGTT	OGTT	IVTT	Other members of family with diabetes
1a	20	D.m. (Ins) 11	1969+	0.60	path	+ 0.05	Grandmother
			1971++	0.49	path	—	
b	norm. Gl. tlrc. 15		1974	—	—	— 0.05	
			1969+	1.40	norm	— 4.70	
			1971++	1.97	norm	—	
			1974	2.15	norm	— 2.90	
2a	33	D.m. (Ins) 19	1966+	—	path	—	none
			1969+	0.48	path	+ 1.90	
b	norm. Gl. tlrc. 23		1964+	—	norm	—	
			1965+	—	norm	—	
			1966+	2.72	norm	—	
			1969+	2.59	norm	— 6.75	
			1974	3.51	norm	— 9.10	
3a	36	D.m. (Ins) 15	1971++	—	—	— 1.35	none
			1974	—	—	— 2.00	
b	norm. G. tlrc. 33		1971++	1.69	norm	— 4.30	
			1974	1.53	norm	— 2.50	
4a	37	s.D.m.1 30	1967+	1.23	norm	— 1.75	Father, Mother
			1967+	2.88	norm	— 3.70	
b	norm. Gl. tlrc. 30						
5a	13	D.m. (Ins) 9	1974	—	—	—	Grandmother
			1974	0.75	norm	— 3.00	
b	s.D.m.1 13						
6a	34	D.m. (Ins) 30	1970++	0.19	path	— 3.30	Cousin
			1970++	1.26	norm	— 7.40	
b	s.D.m.1 40						
7a	66	D.m. (Ins) 55	1970++	—	path	—	Cousin
			1970++	—	path	—	
b	D.m.(Diet) 62						
8a	14	D.m. (Ins) 8	1970++	—	path	— 0.30	Grandmother, Mother
			1974	—	path	+ 0.35	
b	norm. G. t.rc. 10	s.D.m.1. 14	1970++	1.64	norm	— 3.35	
			1974	1.33	norm	— 3.30	
9a	27	D.m. (Ins) 17	1970++	0.05	path	+ 2.15	none
			1974	—	—	—	
b	s.D.m.1 23	D.m. (Ins) 26	1970++	1.21	norm	— 4.80	
			1974	—	—	—	
10a	52	s.D.m.1 48	1970++	1.69	norm	— 1.50	none
			1974	1.42	norm	— 5.05	
b	norm. G. tlrc. 52	norm. G. tlrc. 48	1970++	—	norm	— 3.90	
			1974	2.03	norm	—	
11a	44	s.D.m.2 39	1969+	1.12	path	— 2.55	none
			1971++	1.05	path	—	
b	s.D.m.1. 39	norm. Gl. tlrc. 41	1969+	1.15	norm	— 4.30	
			1971++	1.40	norm	—	

D.m. (Ins) = insulin requiring diabetes mellitus  
 s.D.m.1 = subclinical diabetes with one abnormal glucose tolerance test  
 s.D.m.2 = subclinical diabetes with two abnormal glucose tolerance tests  
 norm. Gl.tlrc. = normal glucose tolerance  
 + Data from Daweke et al. (1970)  
 ++ Data from Grote et al. (1971).

Table 2 a. *Blood glucose (mg/100 ml) during tolerance tests*

IVGTT	OGTT												IVTT													
	Pair No.	Year	0'	7.5'	5'	10'	20'	30'	40'	60'	90'	120'	150'	180'	Pair No.	Year	0'	7.5'	5'	10'	20'	30'	45'	60'	75'	90'
1a	1948	176	341	335	316	315	276	319	-	-	-	-	-	1a	1949	184	158	150	181	181	161	184	158	158	139	
b	1971	96	-	237	212	192	180	-	246	416	489	478	-	b	1974	202	197	202	197	197	197	197	197	201	196	187
b	1949	92	297	262	254	299	160	127	-	239	294	262	261	b	1949	91	80	87	78	63	54	64	64	72	78	
b	1971	70	-	179	138	93	72	-	160	100	105	121	-	b	1974	86	88	85	78	84	55	48	53	53	65	
b	1974	97	204	214	219	192	175	180	62	-	94	100	96	2a	1949	40	48	49	50	51	50	52	53	53	53	
2a	1949	171	372	345	300	284	260	255	-	142	137	118	92	b	1949	73	73	65	62	40	40	40	40	48	61	
b	1946	44	-	-	208	171	185	92	-	242	320	264	384	b	1974	95	97	100	85	56	35	43	43	70	82	
b	1949	60	278	257	222	173	183	77	-	179	241	200	386	3a	1971	368	245	346	335	330	-	325	357	358		
b	1974	94	300	296	274	160	78	64	94	-	161	115	103	100	b	1974	130	110	106	107	106	108	110	112	107	
3a	1971	64	-	179	160	114	99	-	-	97	76	81	72	b	1971	87	74	74	69	56	-	55	59	64		
b	1974	86	205	184	127	125	92	61	77	-	129	112	112	86	b	1974	99	97	96	94	81	70	54	64	68	
b	1949	72	178	205	165	164	127	101	-	163	109	111	104	6a	1947	85	-	85	80	65	47	-	84	71		
b	1974	95	248	244	199	195	170	87	-	132	159	121	93	6a	1947	80	-	77	71	60	57	-	56	64		
6a	1970	132	-	-	279	264	246	224	-	132	133	120	90	6a	1970	130	-	138	98	106	114	130	146	310		
b	1970	72	-	-	165	152	119	91	-	162	135	154	88	b	1970	75	-	67	55	39	31	40	48	64		
6b	1970	84	-	-	261	266	206	136	-	177	162	154	88	6a	1970	280	280	280	293	287	282	300	294	288	272	
6a	1970	71	315	290	295	278	165	122	65	-	115	130	101	114	b	1974	248	230	245	-	-	270	245	280	270	
b	1970	68	-	-	209	198	163	128	104	-	104	131	116	71	b	1970	80	73	74	68	56	55	60	62	67	
10a	1970	78	-	-	100	190	162	128	104	-	236	200	207	287	b	1974	65	70	65	60	45	40	45	45	40	
b	1970	78	-	-	246	181	179	99	-	142	158	130	69	9a	1970	115	-	150	150	150	153	155	155	160		
b	1974	87	359	319	240	231	174	119	14	-	170	229	255	260	b	1970	80	-	54	38	49	48	54	56	63	
b	1974	79	269	244	243	281	134	80	69	-	281	404	638	652	10a	1970	70	-	73	73	69	34	51	58	64	
11a	1949	83	239	244	230	204	164	136	-	-	320	387	410	422	b	1974	80	76	76	73	58	37	47	54	73	
b	1949	64	196	247	214	180	163	114	-	-	175	185	127	117	b	1970	73	-	73	70	60	50	46	62	-	
b	1971	72	-	-	174	167	126	96	-	-	175	152	117	77	11a	1949	81	-	76	76	62	55	55	60	71	
															b	1949	76	-	76	66	60	47	57	67	80	
															b	1970	164	-	200	201	372	290	-	-	-	
															b	1970	82	-	137	132	111	89	-	-	-	
															10a	1970	77	-	139	156	112	87	100	74	74	
															b	1974	86	129	160	-	100	74	-	-	-	
															b	1970	80	-	152	158	100	72	-	-	-	
															b	1974	83	-	154	121	-	160	-	-	-	
															11a	1949	84	-	194	246	150	63	-	-	-	
															b	1971	69	-	124	182	185	122	-	-	-	
															b	1949	74	-	122	148	111	68	-	-	-	
															b	1971	74	-	121	135	107	78	-	-	-	

Table 2 b. Serum insulinine ( $\mu$ U/ml) during tolerance tests

Year	IVGTT										OGTT										IVTT									
	0'	2.5'	5'	10'	15'	20'	30'	45'	60'	120'	180'	0'	15'	30'	60'	120'	180'	0'	2.5'	5'	10'	20'	30'	45'	60'	120'				
1a 1969	50	38	45	46	44	44	44	44	44	44	44	32	39	32	31	30	30	65	53	51	51	50	39	56	41	56				
1b 1971	34	-	-	27	27	24	40	-	-	-	-	56	24	39	35	45	45	15	14	17	14	16	16	16	16	17	-			
2a 1969	23	104	170	129	99	79	45	-	-	-	-	20	190	180	>200	160	160	32	>200	107	151	161	50	48	39	32	-			
2b 1974	5	5	5	44	49	36	19	10	3	3	3	-	-	-	-	-	-	6	63	46	35	23	11	9	8	3	-			
3a 1969	145	143	144	145	-	154	109	-	-	-	-	6	46	53	73	76	37	145	193	166	150	153	153	-	-	160	160			
3b 1974	10	81	80	49	47	31	60	-	-	-	-	16	50	45	50	40	40	6	25	97	100	85	56	35	43	70	82			
4a 1969	20	-	-	190	62	54	38	-	-	-	-	25	49	37	82	35	35	26	25	26	26	26	29	-	27	25	28			
4b 1974	21	108	110	70	66	40	27	20	-	-	-	114	76	94	91	111	111	20	130	100	56	38	-	27	16	11	-			
5a 1969	158	49	106	126	80	105	65	-	-	-	-	132	144	139	158	126	126	28	250	190	150	80	50	29	38	17	-			
5b 1974	6	45	20	20	16	15	6	<2.5	-	-	-	24	48	32	80	62	62	21	-	-	25	22	20	20	21	10	7			
6a 1970	10	-	-	48	48	48	48	-	-	-	-	10	105	57	44	40	40	6	-	-	106	78	37	17	10	7	18			
6b 1974	15	62	56	66	52	40	46	-	-	-	-	15	26	66	26	38	28	28	28	124	154	133	158	124	128	151	127			
7a 1970	8	-	-	45	47	44	46	21	-	-	-	32	80	80	76	66	66	55	49	59	34	36	19	19	19	19	15			
7b 1974	4	54	50	31	28	24	24	10	-	-	-	38	134	178	166	166	166	1	-	-	166	124	150	163	143	170				
8a 1969	43.25	40	40	4.25	44	44	19	12	-	-	-	3	28	53	43	43	43	32	106	>200	160	-	-	10	37	<6.25	20			
8b 1971	1	-	-	17	16	14	7	-	-	-	-	16	17	16	16	16	16	2.5	20	15	17	17	6	-	18	<6.25	<6.25			
9a 1969	75	116	74	60	57	160	71	-	-	-	-	185	46	35	33	35	40	9	63	63	61	41	35	28	7	7				
9b 1971	1	-	-	12	9	9	9	-	-	-	-	11	62	120	66	35	9	7	62	62	62	62	36	16	9	<6.25	<6.25			
10a 1970	437	-	-	118	175	77	135	-	-	-	-	437	-	45	67	43	41	-	-	-	-	-	-	-	-	-	-			
10b 1974	8	-	-	22	40	6	25	6	25	6	25	8	130	230	230	135	131	131	131	131	131	131	131	131	131	131	131			
11a 1969	7	-	-	14	27	11	21	21	21	21	21	7	14	27	11	21	21	21	21	21	21	21	21	21	21	21	21	21		
11b 1974	8	37	66	39	34	34	34	34	34	34	34	8	37	66	39	34	34	34	34	34	34	34	34	34	34	34	34	34		
12a 1971	1	-	-	21	25	18	22	22	22	22	22	1	21	25	18	22	22	22	22	22	22	22	22	22	22	22	22	22		
12b 1971	2	-	-	22	23	13	13	13	13	13	13	2	22	23	13	13	13	13	13	13	13	13	13	13	13	13	13	13		

Table 2 c. Fatty acids ( $\mu\text{Mol/l}$ ) during tolerance tests

IVGTT		IVITT																		
Pair No.	Year	0'	2.5'	5'	10'	20'	40'	60'	120'	Pair No.	Year	0'	2.5'	5'	10'	20'	30'	45'	60'	120'
1a	1969	722	633	585	540	484	442	-	-	1a	1969	790	-	779	713	553	609	657	558	604
	1971	586	-	512	581	502	536	-	-		1974	376	389	391	362	370	338	225	267	370
b	1969	508	-	497	415	404	362	309	-	b	1969	598	-	463	517	327	407	512	670	558
	1974	326	311	303	298	241	230	225	-		1974	286	303	300	308	274	247	348	252	241
2a	1969	533	-	472	444	452	392	327	-	2a	1969	527	-	480	466	423	418	394	-	335
b	1966	820	-	775	882	726	687	-	-	b	1969	488	-	464	454	445	-	384	378	375
	1969	548	-	466	428	377	335	297	-		1974	598	563	555	518	443	395	379	342	427
	1974	769	689	643	-	430	312	294	374	3a	1971	464	-	-	433	388	-	417	457	-
3b	1971	592	-	443	377	362	304	-	-		1974	404	346	346	311	300	298	279	290	442
	1974	546	510	503	452	388	402	490	519	b	1971	525	-	-	407	354	-	351	378	-
4a	1967	829	-	590	517	502	493	490	-		1974	795	795	787	790	776	718	641	606	641
b	1967	613	-	602	597	582	474	544	-	4a	1967	602	-	578	554	532	438	-	490	545
6a	1970	566	-	495	468	433	386	-	-	b	1967	656	-	593	567	-	551	-	588	598
b	1970	489	-	391	357	305	-	-	-	6a	1970	441	-	424	418	443	534	604	621	696
	1974	964	827	824	789	586	435	395	580	b	1970	510	-	488	462	389	379	392	505	553
9a	1970	284	-	310	332	284	278	288	-	8a	1970	649	-	573	517	453	416	512	525	483
b	1970	284	-	458	363	308	337	297	-	b	1970	482	-	405	370	327	322	311	302	302
10a	1970	597	-	497	407	579	481	-	-	9a	1970	140	-	312	291	260	250	244	241	129
	1974	473	492	556	427	325	273	252	299	b	1970	436	-	-	298	348	197	238	200	505
b	1974	365	401	453	406	291	403	263	497	10a	1974	374	400	413	418	359	302	291	361	567
11a	1969	497	-	413	415	393	235	316	-	11a	1969	458	-	450	348	188	347	317	332	412
b	1971	476	-	442	426	362	359	-	-	b	1969	458	-	406	373	312	296	323	289	365
	1969	435	-	387	327	263	213	142	-		1971	644	-	-	678	580	458	437	-	-

Table 3. *Body-weight (first line) and Broca-index (second line) at test*

Sex	Pair no.	Year					
		1974	1971	1970	1969	1967	1966
MM	1a	57.9 0.78	53.0 0.73		45.1 0.71		
	b	66.0 0.86	61.4 0.81		50.8 0.75		
MM	2a				66.5 0.88		62.9 0.80
	b	66.7 0.90			65.0 0.88		58.6 0.78
MM	3a	82.3 0.94	76.9 0.89				
	b	107.5 1.18	103.5 1.14				
MM	4a					94.0 1.14	
	b					91.0 1.11	
FF	5a	38.0 0.85					
	b	47.9 0.86					
MM	6a			67.5 0.69			
	b			69.2 0.99			
FF	7a			63.5 1.22			
	b			73.5 1.55			
FF	8a	38.5 0.65		29.6 0.72			
	b	47.6 0.71		30.6 0.71			
MM	9a	61.0 0.79		60.4 0.79			
	b	63.0 0.82		61.0 0.81			
FF	10a	56.3 1.08		56.9 1.11			
	b	61.6 1.14		58.3 1.08			
MM	11a		71.4 1.08		72.7 1.06		
	b		79.2 1.14		77.1 1.11		

development of diabetes progresses in every case from prediabetes via the latent to a manifest diabetes. The diminished k-value in MZ twins of insulin-requiring diabetics was not always due to an abnormal insulin secretion. The cotwin who developed an insulin-requiring diabetes mellitus during our investigation was found to have an impaired glucose tolerance with markedly reduced insulin release prior to manifestation of the disease.

However, other identical twins were found to have normal blood glucose values in spite of an insignificantly diminished insulin response. Two partners showed a slightly reduced decline of blood glucose together with normal insulin release. It is to be expected that not only the insulin secretion but also other mechanisms — unknown up to now — play a part during the development of diabetes mellitus. Further observations will have to show whether only these MZ twins of insulin-requiring diabetics develop a manifest diabetes mellitus in whom a reduced insulin response is correlated with reduced glucose assimilation.

These results no longer justify our former assumption (Grote et al. 1971) that increased fasting values of free fatty acids could be a first sign of the manifestation of diabetes mellitus.

Toeller and Knussmann (1973) report dissimilar blood glucose levels after repeated oral glucose loads under similar conditions. A phenomenon alike can be suggested concerning the insulin response. With these reservations it will have to be decided whether transitional abnormalities of insulin secretion are a hint for the genetic disposition of diabetes mellitus (Daweke et al. 1970).

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