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.

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 Johannsen 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	—	
			1974	—	—	— 0.05	
b		norm. Gl. tlrc. 15	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
b		norm. Gl. tlrc. 30	1967+	2.88	norm	— 3.70	
5a	13	D.m. (Ins) 9	1974	—	—	—	Grandmother
b		s.D.m.1 13	1974	0.75	norm	— 3.00	
6a	34	D.m. (Ins) 30	1970++	0.19	path	— 3.30	Cousin
b		s.D.m.1 40	1970++	1.26	norm	— 7.40	
7a	66	D.m. (Ins) 55	1970++	—	path	—	Cousin
b		D.m.(Diet) 62	1970++	—	path	—	
8a	14	D.m. (Ins) 8	1970++	—	path	— 0.30	Grandmother, Mother
			1974	—	path	+ 0.35	
b		norm. G. t.rc. 10	1970++	1.64	norm	— 3.35	
		s.D.m.1. 14	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	1970++	1.21	norm	— 4.80	
		D.m. (Ins) 26	1974	—	—	—	
10a	52	s.D.m.1 48	1970++	1.69	norm	— 1.50	none
		norm. G. tlrc. 52	1974	1.42	norm	— 5.05	
b		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.l. 39	1969+	1.15	norm	— 4.30	
		norm. Gl. tlrc. 41	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).

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

IVGTT

Pair No. / Year		0'	2,5'	5'	10'	20'	40'	60'	120'
1a	1969	126	361	339	319	275	244	219	-
	1971	96	-	-	237	212	192	169	-
b	1969	92	297	282	254	209	158	127	-
	1971	70	-	-	179	138	93	72	-
	1974	97	284	254	219	192	125	104	62
2a	1969	171	372	345	300	286	260	255	-
b	1966	68	-	-	208	171	125	92	-
	1969	80	278	257	222	173	103	77	-
	1974	95	300	296	224	158	78	66	98
3b	1971	86	-	-	179	160	114	99	-
	1974	84	205	186	137	125	92	81	77
4a	1967	92	219	205	185	164	127	101	-
b	1967	85	224	204	250	187	105	94	-
5b	1974	92	289	246	197	159	137	110	81
6a	1970	152	-	-	270	256	246	228	-
b	1970	72	-	-	185	152	119	93	-
8b	1970	84	-	-	341	286	206	138	-
	1974	71	335	290	205	215	165	122	64
9a	1970	68	-	289	205	178	176	156	-
b	1970	78	-	188	198	163	128	106	-
10a	1970	75	-	-	246	181	129	99	-
	1974	87	359	319	260	231	174	119	54
b	1974	79	369	244	243	201	134	88	69
11a	1969	83	239	244	230	205	164	136	-
	1971	68	-	-	175	157	127	103	-
b	1969	84	196	242	214	180	143	114	-
	1971	72	-	-	176	167	126	96	-

OGTT

Pair No. / Year		0'	15'	30'	60'	120'	150'
1a	1969	225	-	366	416	459	478
	1971	158	-	239	296	362	361
b	1969	92	-	168	168	155	121
	1971	67	-	94	108	96	68
	1974	83	121	142	137	110	92
2a	1966	157	-	242	320	364	384
	1969	85	-	179	241	280	306
2b	1964	84	-	141	115	103	100
	1965	65	-	97	76	91	72
	1966	80	-	139	112	112	86
	1969	74	-	142	109	111	104
	1974	94	169	121	82	79	83
3b	1971	78	-	132	133	120	90
	1974	86	177	142	135	154	88
4a	1967	85	-	115	130	101	114
b	1967	81	-	104	131	116	71
6a	1970	227	-	336	>400	>400	397
b	1970	75	-	142	158	130	69
7b	1970	318	-	-	-	-	-
b	1970	120	-	170	229	255	250
8a	1970	267	-	381	484	636	652
	1974	266	320	387	410	422	400
b	1970	80	-	175	152	127	117
	1974	58	96	82	82	65	77
9a	1970	144	-	200	291	372	290
b	1970	82	-	137	132	111	89
10a	1970	77	-	139	156	112	87
	1974	86	129	160	-	100	74
b	1970	80	-	152	158	100	72
	1974	83	-	154	121	-	100
11a	1969	84	-	194	246	150	63
	1971	69	-	136	182	155	122
b	1969	77	-	122	148	111	68
	1971	74	-	121	135	107	78

IVTT

Pair No / Year		0'	2,5'	5'	10'	20'	30'	45'	60'	120'
1a	1969	164	158	158	161	161	164	158	158	139
	1974	202	197	202	197	197	197	201	196	187
b	1969	91	88	87	78	63	54	66	72	78
	1974	86	88	85	78	64	55	48	53	65
2a	1969	48	48	49	50	51	50	52	53	53
b	1969	73	73	65	62	40	40	48	61	67
	1974	95	97	100	85	56	35	43	70	82
3a	1971	368	245	346	335	330	-	335	357	358
	1974	130	110	106	107	106	108	110	112	147
b	1971	87	74	74	69	56	-	55	59	66
	1974	99	97	96	94	81	70	54	64	68
4a	1967	85	-	85	80	65	57	-	84	71
b	1967	80	-	77	71	60	47	-	56	66
6a	1970	130	-	138	98	106	114	130	146	310
b	1970	75	-	67	55	39	31	40	48	64
8a	1970	308	288	291	287	292	300	294	288	272
	1974	248	250	245	-	-	270	265	280	270
b	1970	80	73	74	68	56	55	60	62	67
	1974	65	70	65	60	45	40	45	45	60
9a	1970	115	-	150	150	150	153	155	155	160
b	1970	80	-	56	58	49	48	56	56	63
10a	1970	70	-	73	73	69	54	51	58	66
	1974	80	76	76	73	58	37	47	54	73
b	1970	73	-	73	70	60	50	48	62	-
11a	1969	83	-	76	76	62	55	55	60	71
b	1969	76	-	79	66	60	47	57	67	68

Table 2 *b*. *Serum insuline (uU/ml) during tolerance tests*

IVGTT

Pair No / Year		0'	2,5'	5'	10'	20'	40'	60'	120'
1a	1969	50	39	45	46	44	52	55	-
	1971	36	-	-	27	27	34	40	-
b	1969	25	184	170	129	99	79	45	-
	1971	9	-	-	99	47	12	1	-
	1974	5	51	44	49	38	19	10	3
2a	1969	148	143	144	145	-	154	159	-
b	1969	10	88	80	69	47	31	60	-
	1974	14	70	60	-	35	18	14	14
3b	1971	30	-	-	100	62	54	38	-
	1974	21	105	110	76	66	40	27	20
4a	1967	63	58	82	153	160	155	90	-
b	1967	58	49	148	128	60	105	65	-
5b	1974	6	45	30	20	16	15	6	<2,5
6a	1970	26	-	-	25	21	19	15	-
b	1970	5	-	-	19	17	19	-	-
7b	1970	10	-	-	88	91	86	168	-
	1974	15	82	58	66	33	40	56	21
8a	1970	78	-	65	67	104	58	95	-
b	1970	8	-	27	24	23	19	23	-
9a	1970	5	-	-	17	16	12	13	-
	1974	4	56	50	31	26	24	26	10
b	1974	9	50	25	25	31	25	16	12
10a	1969	<6,25	40	30	<6,25	46	44	19	-
	1971	1	-	-	17	16	14	7	-
b	1969	75	136	74	50	57	120	71	-
	1971	1	-	-	12	9	9	9	-

OGTT

Pair No. / Year		0'	15'	30'	60'	120'	180'
1a	1969	32	-	39	32	31	30
	1971	56	-	24	39	35	45
b	1969	20	-	190	180	>200	160
	1971	<6,25	-	86	102	103	69
	1974	6	46	53	73	76	37
2b	1964	16	-	50	45	50	40
	1965	25	-	49	37	82	35
2a	1966	114	-	76	96	91	111
	1969	132	-	144	139	158	136
b	1966	24	-	48	32	80	62
	1969	10	-	105	57	44	40
	1974	15	26	66	26	38	28
3a	1971	32	-	80	80	76	66
	1974	17	130	110	100	210	58
4a	1967	38	-	38	134	178	146
b	1967	164	-	32	106	>200	160
6a	1970	17	-	16	17	16	-
b	1970	3	-	28	53	43	8
8a	1970	185	-	180	153	133	131
	1974	46	35	33	33	35	40
b	1970	19	-	125	112	120	68
	1974	11	62	120	66	35	9
9a	1970	437	-	118	175	77	135
b	1970	<6,25	-	45	67	43	41
10a	1970	8	-	22	40	6	25
	1974	6	130	230	230	135	90
b	1970	7	-	14	27	11	21
	1974	8	37	66	39	34	34
11a	1969	126	-	146	134	84	127
	1971	1	-	21	25	18	22
b	1969	66	-	131	51	119	65
	1971	2	-	22	23	13	9

IVTT

Pair No. / Year		0'	2,5'	5'	10'	20'	30'	45'	60'	120'
1a	1969	65	53	51	51	50	39	56	41	56
	1974	15	14	17	14	16	16	16	17	-
b	1969	32	>200	147	151	161	50	48	39	32
	1974	6	63	46	35	23	11	9	8	3
2a	1969	145	193	166	150	153	153	-	140	160
b	1969	<6,25	59	47	35	17	-	<6,25	<6,25	<6,25
	1974	95	97	100	85	56	35	43	70	82
3a	1971	28	25	26	26	29	-	27	25	28
	1974	56	56	35	43	43	43	35	43	31
b	1971	20	130	100	56	38	-	27	16	11
	1974	28	250	190	150	80	50	29	38	17
6a	1970	21	-	25	28	22	20	20	21	10
b	1970	6	-	106	78	37	17	10	7	18
8a	1970	124	154	133	158	124	128	151	127	135
b	1970	9	55	49	59	34	36	19	19	19
	1974	13	52	56	52	42	28	23	23	15
9a	1970	131	-	166	124	150	163	140	178	169
b	1970	1	-	10	37	<6,25	20	2	<6,25	<6,25
10a	1970	<6,25	-	-	29	-	18	<6,25	<6,25	<6,25
	1974	2,5	20	15	17	17	6	<2,5	2,5	2,5
b	1970	6,25	6,25	6,25	6,25	<6,25	<6,25	6,25	6,25	6,25
11a	1969	9	63	61	41	35	26	7	7	7
b	1969	7	62	62	36	16	9	<6,25	<6,25	<5,25

Table 2 *c*. *Fatty acids (uMol/l) during tolerance tests*

IVGTT

Pair No. / Year		0'	2,5'	5'	10'	20	40'	60'	120'
1a	1969	722	-	633	585	540	484	442	-
	1971	586	-	-	512	581	502	536	-
b	1969	508	-	497	415	404	362	309	-
	1971	803	-	-	726	565	560	428	-
	1974	326	311	303	298	241	214	230	225
2a	1969	533	-	472	444	452	392	327	-
b	1966	820	-	-	775	882	726	687	-
	1969	548	-	466	428	377	335	297	-
	1974	769	689	643	-	430	312	294	374
3b	1971	592	-	-	443	377	362	304	-
	1974	546	510	503	452	388	402	490	519
4a	1967	629	-	590	517	502	493	490	-
b	1967	613	-	602	597	582	474	544	-
6a	1970	566	-	-	495	468	433	386	-
b	1970	489	-	-	391	357	305	-	-
8b	1970	528	-	-	464	373	303	-	-
	1974	964	827	824	789	586	435	395	580
9a	1970	284	-	310	332	284	278	268	-
b	1970	294	-	458	363	308	337	297	-
10a	1970	597	-	497	407	579	481	-	-
	1974	473	492	556	427	325	273	252	299
b	1974	365	401	453	406	291	403	263	497
11a	1969	497	-	413	415	393	235	316	-
	1971	476	-	-	442	426	362	359	-
b	1969	435	-	387	327	263	213	142	-
	1971	644	-	-	678	580	458	437	-

IVTT

Pair No. / Year		0'	2,5'	5'	10'	20'	30'	45'	60'	120'
1a	1969	790	-	779	713	553	609	657	558	604
	1974	376	389	391	362	370	338	225	267	370
b	1969	598	-	463	517	327	407	512	670	558
	1974	286	303	300	308	274	247	348	252	241
2a	1969	527	-	480	466	423	418	394	-	335
b	1969	488	-	464	454	445	-	384	378	375
	1974	598	563	555	518	443	395	379	342	427
3a	1971	464	-	-	433	388	-	417	457	-
	1974	404	346	346	311	300	298	279	290	442
b	1971	525	-	-	407	354	-	351	378	-
	1974	795	795	787	790	776	718	641	606	641
4a	1967	602	-	578	554	532	438	-	490	545
b	1967	656	-	593	567	-	551	-	588	598
6a	1970	441	-	424	418	443	534	604	621	696
b	1970	510	-	488	462	389	379	392	505	553
8a	1970	649	-	573	517	453	416	512	525	483
b	1970	482	-	405	370	327	322	311	302	302
9a	1970	140	-	312	291	260	250	244	241	129
b	1970	436	-	-	298	348	197	238	200	505
10a	1974	374	400	413	418	359	302	291	361	567
11a	1969	458	-	450	348	188	347	317	332	412
b	1969	458	-	406	373	312	296	323	289	365

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	53.0		45.1		
		0.78	0.73		0.71		
	b	66.0	61.4		50.8		
		0.86	0.81		0.75		
MM	2a				66.5		62.9
					0.88		0.80
	b	66.7			65.0		58.6
		0.90			0.88		0.78
MM	3a	82.3	76.9				
		0.94	0.89				
	b	107.5	103.5				
		1.18	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		29.6			
		0.65		0.72			
	b	47.6		30.6			
		0.71		0.71			
MM	9a	61.0		60.4			
		0.79		0.79			
	b	63.0		61.0			
		0.82		0.81			
FF	10a	56.3		56.9			
		1.08		1.11			
	b	61.6		58.3			
		1.14		1.08			
MM	11a		71.4		72.7		
			1.08		1.06		
	b		79.2		77.1		
			1.14		1.11		

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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 secretionbut 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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