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Diurnal Patterns of Blood Glucose, Serum Free Fatty Acids, Insulin, Glucagon and Growth Hormone in Normals and Juvenile Diabetics

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Summary. Blood glucose, serum free fatty acids, -insulin, -glucagon and -growth hormone have been measured half-hourly in five newly diagnosed, untreated, male patients with classic juvenile diabetes and in five healthy male subjects during a 24-h period of daily life. — Blood glucose, serum insulin and -free fatty acids followed, on the whole, the expected pattern. Serum glucagon showed a fairly constant level during day and night in both groups. — In the *non-diabetic* subjects, serum growth hormone was low during most of the day. Only two peaks were observed before 10 p.m. Four of the subjects showed peaks at precisely the same time, namely at 10.30 p.m. and 1.30 a.m. Two showed peaks at 5.00—5.30 p.m. The mean serum growth hormone concentration during the 24-h period was 1.98 ng/ml. — In the *juvenile diabetics*, the growth hormone was higher and the level fluctuated much more, showing more frequent and higher peaks than in the non-diabetics. The mean serum growth hormone concentration during the 24-h period was 7.26 ng/ml, i.e. three to four times higher than in the non-diabetics.

Schéma d'évolution de la glycémie, des acides gras libres, de l'insuline, du glucagon et de l'hormone de croissance dans le sérum, chez des sujets normaux et des diabétiques juvéniles

Résumé. La glycémie, les acides gras libres, l'insuline, le glucagon et l'hormone de croissance sériques ont été mesurés toutes les demi-heures chez cinq patients de sexe masculin, atteints de diabète juvénile classique, récemment diagnostiqué et non traité, et chez cinq sujets de sexe masculin en bonne santé pendant une période de 24 h. — La glycémie, l'insuline et les acides gras libres du sérum suivaient dans l'ensemble le schéma attendu. Le taux de glucagon sérique était assez constant pendant le jour et la nuit dans les deux groupes. — Chez les *sujets non-diabétiques*, l'hormone de croissance du sérum était basse pendant la plus grande partie du jour. Deux pics seulement ont été observés avant 10 h du soir. Quatre des sujets ont eu des valeurs élevées exactement au même moment, c'est-à-dire à 10.30 h du soir et à 1.30 h du matin. Deux ont eu des valeurs élevées à 5 h — 5.30 h de l'après-midi. La concentration moyenne d'hormone de croissance du sérum pendant la période de 24 h était de 1.98 ng/ml. — Chez les *diabétiques juvéniles*, l'hormone de croissance était plus élevée et le taux variait beaucoup plus, montrant des pics plus fréquents et plus élevés que chez les non-diabétiques. La concentration moyenne d'hormone de croissance du sérum pendant la période de 24 h était de 7.26 ng/ml, c'est-à-dire une concentration trois à quatre fois plus élevée que chez les non-diabétiques.

Tagesrhythmen des Blutzuckers und der Serumspiegel der freien Fettsäuren, des Insulins, des Glucagons und des Wachstumshormons bei Normalpersonen und jugendlichen Diabetikern

Zusammenfassung. Bei gesunden Männern und 5 männlichen Patienten mit dem klassischen Bild eines frisch entdeckten, unbehandelten, jugendlichen Diabetes wurden in halbstündigen Abständen der Blutzucker und die Spiegel der freien Fettsäuren, des Insulins, des Glucagons und des Wachstumshormons im Serum während einer 24 Std-Periode des Tagesablaufs bestimmt. — Die Tageskurven für Blutzucker, freie Fettsäuren und Seruminsulin zeigten dabei im ganzen den erwarteten Verlauf. Das Serumglucagon wies in beiden Gruppen bei Tag und Nacht recht konstante Werte auf. — Bei den *Normalpersonen* fanden sich den größten Teil des Tages niedrige Wachstumshormon-Spiegel. Nur 2 Gipfel wurden vor 22 Uhr beobachtet. 4% der Kontrollpersonen zeigten solche Maxima genau gleichzeitig, nämlich um 22.30 und um 1.30 Uhr. Bei 2 ließen sich Gipfel um 17 Uhr und 17.30 nachweisen. Die durchschnittliche Wachstumshormon-Konzentration während der 24 Std-Periode betrug 1.9.— Bei den *jugendlichen Diabetikern* lagen die Werte für das Wachstumshormon höher, schwankten stärker und zeigten mehr und höhere Gipfel als bei den nichtdiabetischen Vergleichspersonen. Der mittlere Wachstumshormon-Spiegel betrug während der 24 Std-Periode 7.26 ng/ml, lag also 3—4 × höher als beim Kontrollkollektiv.

Key-words: Serum growth hormone, serum insulin, serum glucagon, serum free fatty acids, blood glucose, juvenile diabetes, diurnal patterns.

Current knowledge of endocrine factors concerning glucose homeostasis and its disturbance in diabetics is derived mainly from studies employing loading with glucose, amino acids or other compounds, or after the administration of various hormones. A few reports have also appeared discussing blood glucose homeostasis on the basis of experiments with "isolated" tissue, especially in forearm studies [4]. It is, however, often difficult to interpret results obtained in loading studies, particularly in studies of "isolated" tissue, in terms of overall homeostasis.

It seemed of interest, therefore, to endeavour to elucidate the blood glucose regulation as it actually occurs during daily life, by following a series of relevant parameters at short intervals during a 24-hour period.

The present report describes the 24-h pattern of blood glucose, serum free fatty acids, -insulin, -glucagon and -growth hormone in young patients with untreated, classic juvenile diabetes.

Methods

Five newly-diagnosed, untreated, male patients with classic juvenile diabetes were examined. Their mean age was 17 years (range 10—22). Five healthy, male students served as control subjects. Their mean age was 26 years (range 25—28). None of the subjects

were obese. The five healthy controls came to the hospital in the morning half an hour before the start of the experiments. The five diabetics were examined during admission to the hospital. Only one of the diabetics (No. 2 from above in Fig. 4) was ketotic during the experiment, with plasma total CO_2 between 16 and 12 mEq/l. All the subjects had been fasting 10 to 12 h before the beginning of the experiment at 8.30 a.m. An indwelling catheter was inserted into an antecubital

Table 1. *Time-table for the 24-h period of "daily life"*

a.m.				
8.30— 9.00	Breakfast containing	protein	g	6
		carbohydrate	g	65
		lipid	g	17
		calories		453
9.00— 9.10	One cigarette			
10.30—11.00	One cigarette, and one beer containing	carbohydrate	g	9
		alcohol	g	12
		calories		130
p.m.				
12.15—12.30	Lunch containing	protein	g	24
		carbohydrate	g	44
		lipid	g	28
		calories		538
12.30—12.45	One cigarette			
1.00— 1.30	One beer			
3.00— 4.00	Two cups of coffee without sugar, cream or milk. One cigarette.			
5.30— 6.00	Dinner containing	protein	g	16
		carbohydrate	g	123
		lipid	g	28
		calories		830
6.00— 6.30	One cigarette and one beer			
8.30— 9.30	Gentle walk			
10.30—11.00	One cigarette and one beer			
12.00—	Sleep period.			

vein, and blood samples were drawn every half hour during a 24-h period of "daily life" (Table 1). The subjects were ambulant during the day-time. They stayed in a room, reading, talking or listening to the radio, except for short walks on the same floor. 3 meals were served: at 8.30 a.m., 12.15 p.m. and 5.30 p.m. No other food or sweets was allowed except a drink of beer as indicated in Table 1. From 8.30—9.30 p.m. the subjects went for a gentle walk in the hospital grounds before retiring to sleep at 12 midnight.

The blood samples were centrifuged and stored at — 20° C until analysis. Blood glucose was measured by a glucose oxidase method [3], and serum free fatty acids were determined by a colorimetric method [13]. Serum insulin was measured by a double-antibody radioimmunoassay [7] with EDTA addition. Serum growth hormone was measured by a single-antibody radioimmunoassay [15], using a Wilhelmi preparation as standard. Serum glucagon was determined by a single-antibody radioimmunoassay [15] in three of the controls and two of the diabetics. With this method it is not possible to distinguish between gut and pancreatic glucagon.

Results

Non-diabetics

The results in the five control subjects are seen in Table 2, 3 and Fig. 1.

Blood glucose and serum insulin levels rose after eating and fell shortly thereafter. Serum free fatty acids fell after eating, rose in the late noon and during the evening, and remained high during the night. Serum glucagon showed a constant level during day

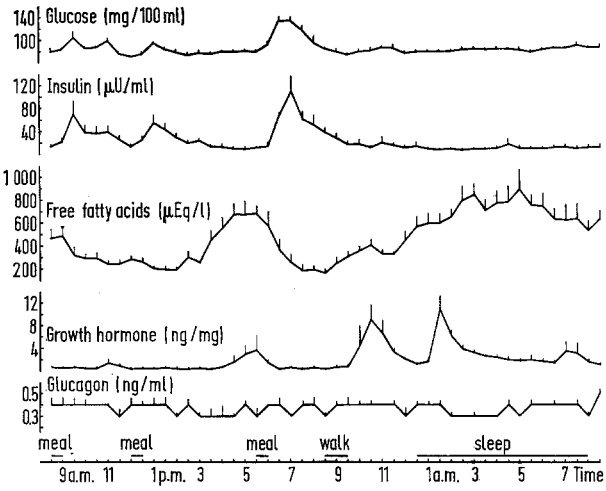

Fig. 1. Average curves of blood glucose, serum insulin, -free fatty acids, -growth hormone and -glucagon in five healthy males. Mean values + S.E.M.

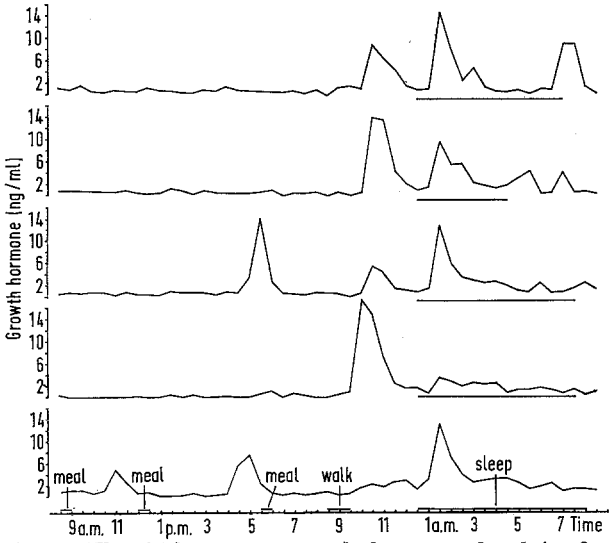

Fig. 2. The 24-h serum growth hormone level in five healthy males

and night. Serum growth hormone was low during most of the day. Only two growth hormone peaks (> 5 ng/ml) were observed before 10 p.m. (Fig. 2). Four of the subjects showed peaks at precisely the same time, namely at 10.30 p.m. and 1.30 a.m., and two showed peaks at 5—5.30 p.m. Together the five control subjects exhibited 11 growth hormone peaks.

Diabetics

The results from the five juvenile diabetics are seen in Table 3, 4 and Fig. 3.

Blood glucose rose after the meals, but to a much higher level than in the normal subjects and it fell more slowly. The fasting level was not reached during the day-time but only at 3—4 a.m. Serum insulin remained constantly low throughout the day and night in three of the patients. In the other two a significant rise was seen at 9.30—10.00 p.m. Serum free fatty acid levels fluctuated much more, and the mean serum free fatty acid level during the 24-h period was twice as high as in the controls, and the meal-related falls and rises seen in the controls were hardly discernable. The serum glucagon level was fairly constant during the day, and fell to a lower level during the night. The growth hormone values throughout the 24-h period were higher in the diabetics than in the non-diabetics (Fig. 4). Moreover, the growth hormone pattern in the diabetics was characterized by more frequent and higher peaks. The fasting serum growth hormone was 9.0 ± 2.94 ng/ml (mean ± SEM) in the juvenile dia-

Table 2. *The 24-h level of blood glucose, serum insulin, -glucagon and -free fatty acids in five normal subjects. (Mean ± S.E.M.)*

Time	Glucose mg/100 ml		Insulin μU/ml		Glucagon ng/ml		Free fatty acids μEq/l	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
	81	5.5	15	4.3	0.4	0.06	470	80
9 a.m.	85	3.2	23	5.5	0.4	0.06	490	93
	105	11.1	70	24.0	0.4	0.06	320	77
10	87	3.1	39	10.7	0.4	0.07	290	38
	88	4.1	37	10.7	0.4	0.03	290	51
11	99	6.3	39	11.5	0.4	0.03	240	34
	76	5.1	26	5.9	0.3	0.03	240	29
12	71	2.5	13	4.5	0.4	0.06	280	31
	76	2.8	25	7.1	0.4	0.03	260	31
1 p.m.	94	4.0	54	13.8	0.4	0.06	200	15
	83	4.5	43	10.8	0.4	0.06	190	26
2	78	5.2	29	7.3	0.3	0.03	190	17
	74	5.8	19	4.7	0.4	0.05	300	51
3	77	4.5	23	3.5	0.3	0.03	250	80
	75	4.3	13	2.9	0.3	0.06	440	87
4	79	2.0	12	4.7	0.3	0.09	550	85
	79	3.1	9	2.7	0.3	0.03	670	91
5	80	3.4	8	3.3	0.4	0.03	670	110
	78	2.3	10	3.2	0.3	0.07	680	62
6	91	4.0	13	4.7	0.4	0.00	570	118
	132	7.3	67	3.7	0.4	0.06	360	87
7	133	6.0	109	26.0	0.3	0.00	250	68
	116	8.0	60	12.9	0.4	0.03	180	50
8	94	9.8	50	15.7	0.4	0.06	190	25
	84	2.4	36	9.3	0.3	0.03	160	25
9	78	4.5	27	7.1	0.4	0.03	240	47
	74	2.2	16	5.6	0.4	0.06	300	39
10	79	4.0	16	7.2	0.4	0.03	350	38
	80	4.6	10	3.3	0.4	0.03	400	48
11	85	3.4	18	9.4	0.4	0.00	320	39
	85	5.2	14	4.1	0.4	0.03	320	21
12	76	3.9	9	5.0	0.3	0.07	440	81
	78	2.8	12	6.6	0.4	0.03	560	76
1 a.m.	78	3.9	7	3.4	0.4	0.03	590	88
	78	3.4	6	2.2	0.4	0.03	590	83
2	78	3.3	7	2.2	0.3	0.03	640	75
	81	4.0	5	2.9	0.3	0.00	790	125
3	83	3.3	7	3.0	0.3	0.03	830	105
	81	2.5	7	2.6	0.3	0.00	700	88
4	82	2.7	8	3.5	0.3	0.00	760	113
	82	2.1	15	7.9	0.4	0.03	770	136
5	80	4.9	10	4.2	0.3	0.00	880	174
	76	3.6	7	2.6	0.4	0.03	740	88
6	80	2.9	7	3.0	0.4	0.00	730	106
	83	2.8	9	3.3	0.4	0.03	620	92
7	82	3.3	10	4.2	0.4	0.00	610	133
	87	4.7	7	3.2	0.4	0.03	620	126
8	83	2.6	9	3.4	0.3	0.03	520	76
	83	4.1	9	4.8	0.5	0.03	620	72

betics, and 0.7 ± 0.15 ng/ml (mean ± SEM) in the non-diabetics. The mean serum growth hormone level during the 24 h (Fig. 5) was 7.26 ng/ml in the juvenile diabetics and 1.98 ng/ml in the non-diabetics, i.e. the diurnal growth hormone level was 3—4 times higher in the diabetics.

The serum insulin also varied as could be anticipated from earlier loading studies and 24-h studies. It rose immediately in relation to the rises in the blood glucose in the non-diabetic subjects, and the rise was proportional to the blood glucose elevations.

In the juvenile-diabetic subjects, the serum insulin values showed little fluctuation with one puzzling exception. In two of the four juvenile diabetics a significant elevation of serum insulin was observed during and after the walk in the evening. The meaning of this phenomenon cannot be explained at the present time. However, recently one of us has found a statistically significant rise in serum insulin immediately after ergometer exercise in untreated, juvenile diabetics [8].

Table 3. *The 24-h values of serum growth hormone (ng/ml) in five normal subjects and in five juvenile diabetics*

Time	Normals					Diabetics				
Patient no.	1	2	3	4	5	6	7	8	9	10
	1.1	0.8	0.3	0.4	0.8	5.9	0.3	12	18	9.0
9 a.m.	0.8	0.8	0.6	0	1.0	1.4	0	11	17	6.8
	1.6	0.7	0.4	0	1.0	0.2	5.1	5.6	17	9.0
10	0.6	0.7	0.7	0	0.4	0.3	3.6	18	7.6	8.0
	0.4	0.6	0.6	0	0.9	7.2	0	5.2	6.6	7.4
11	0.8	0.6	0.8	0	4.6	1.0	1.8	3.7	12	4.6
	0.6	0.9	0.7	0	2.3	1.4	4.8	3.0	18	7.2
12	0.6	0.4	0.3	0.2	0.5	2.3	0.2	3.2	19	20
	1.3	0.2	0.2	0	0.7	2.8	0.2	1.6	11	2.0
1 p.m.	0.8	0.4	0.8	0	0	1.0	0	2.0	7.2	3.0
	0.8	1.2	0.8	0.4	0	0.8		1.3	10	3.0
2	0.5	0.8	0.6	0	0.1	5.0	0.8	1.5	9.0	7.4
	0.4	0.2		0.4	0.5	8.0	0.5	1.8	5.8	4.8
3	1.0	0.8	0.6	0	0	1.4	0.1	3.1	5.6	8.6
	0.8	0.5	0.3	0	0.1	0.5	0	4.3	5.4	9.0
4	1.6	0.4	0.8	0.2	0.4	0.5	5.2	19	3.4	3.8
	1.0	0.4	0.6	0	5.6	0.5	2.0	4.0	6.6	7.0
5		0.4	3.2	0	7.4	0.6	0.1	2.7	13	19
	0.7	0.6	14	0.5	2.3	0.1		3.7	11	3.2
6		1.0	2.8	1.1	0.5		0	1.1	10	3.5
	0.6	0	0.6	0	0.2	1.4	0	1.6	11	5.6
7	0.9	0.4	0.5	0.7	0.6	4.9	0	1.1	24	10
	0.4	0.4	0.3	0.3	0.3	2.4	0	3.4	21	12
8	1.1	0.6	0.7	0	0.6	1.3	0	3.5	19	17
	0.2	0	0.6	0	0.8	0.8	6.6	12	14	2.2
9	1.5	0.6	0.5	0.5	0.3	0.5	5.0	6.0	12	4.5
	1.8	0	0	1.0	0.5	2.1	3.0	4.7	43	4.0
10	1.4	0.5	0.5	18	1.6	0.8	7.1	11	14	5.0
	9.2	14	5.4	15	2.2		15	7.3	13	6.2
11	6.6	14	4.3	7.3	1.8		3.8	3.2	19	6.2
	4.8	4.4	1.5	2.6	2.7		3.1	2.8	12	3.4
12	1.9	2.1	1.1	1.8	3.0		0.2	3.0	8.4	13
	1.1	0.9	0.8	1.9	1.5		0	12	14	7.4
1 a.m.	1.3	1.4	1.5	0.8	3.1		1.9	13	14	6.8
	15	9.5	13	3.6	13		10	19	34	5.4
2	8.4	5.5	6.0	3.1	7.2		29	11	24	10
	3.0	5.6	3.5	2.2	4.1		14	5.4	22	11
3	5.0	2.3	2.9	2.8	2.7		17	4.3	24	25
	1.8		2.4	2.6	3.0		12	4.0	15	12
4	1.1	1.3	2.7	2.8	3.4		1.6	2.8	14	12
	1.0	1.8	2.0	1.0	3.4		1.5	5.3	11	7.4
5	1.3		1.1	1.6	2.7		1.4	2.8	12	9.5
	0.8	4.3	0.8	1.6	1.6		0	2.9	6.5	7.0
6	1.5	0.1	2.4	2.0	2.0		0	3.6	3.6	16
	1.4	0.4	0.7	1.6	2.6		0	29	10	12
7	9.6	4.0	0.8	1.0	1.2		0	9.3	7.8	12
	9.6	0.6	1.5	1.7	1.6		0	4.3	9.2	8.6
8	2.0	0.6	2.5	0.7	1.6		0	3.2	9.6	6.8
	0.9	0.2	1.3	1.3	1.4		0.3	2.6	12	3.8

Discussion

This study has revealed the pattern of a series of parameters of importance in glucose homeostasis, as observed during a 24-h period in young normal subjects and in young patients with recently discovered juvenile diabetes mellitus.

The variations in blood glucose were found to be as expected, both in the normals and in the diabetics.

The 24-h pattern of serum glucagon has not been studied before. In the present study the concentration was found to be fairly constant during day and night in nondiabetics. No discernible rise could be seen in relation to food intake in either diabetics or non-diabetics. It is known [18] that large amounts of glucose (100—200 g) ingested orally can produce a rise in serum glucagon. Our meals contained 65, 44 and 123 g carbohydrate in a less readily absorbable form than a pure glucose solution. It thus seems that the alterations in serum pancreatic and gut glucagon which possibly occur during daily life are so small (or oppositely directed) that they cannot be recognized in peripheral venous blood.

In the non-diabetic subjects growth hormone peaks only occurred 3—4 h or more after meals, and only when blood glucose and serum insulin had returned to fasting level. Although no correlation can be seen in the 24-h pattern between the blood glucose level and the level of the serum growth hormone, a role for growth hormone in blood glucose homeostasis cannot be excluded. It is possible that growth hormone prevents blood glucose from falling to hypoglycaemic levels. Nine of the eleven growth hormone peaks

Table 4. *The 24-h level of blood glucose, serum insulin, -glucagon and -free fatty acids in five juvenile diabetics (Mean ± S.E.M.)*

Time	Glucose mg/100 ml		Insulin μU/ml		Glucagon ng/ml		Free fatty acids μEq/l	
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
	198	23.2	6	1.6	0.6	0.05	980	220
9 a.m.	192	15.8	6	1.7	0.6	0.10	610	138
	284	22.2	5	1.4	0.6	0.00	730	190
10	333	20.0	5	2.4	0.6	0.05	720	171
	343	16.2	6	1.7	0.5	0.00	800	190
11	365	27.2	7	2.4	0.5	0.00	760	205
	367	33.9	6	1.8	0.5	0.00	780	203
12	358	27.2	5	1.7	0.4	0.00	780	215
	359	34.2	9	1.3	0.7	0.00	770	185
1 p.m.	390	31.3	9	2.2	0.6	0.05	830	197
	383	37.3	9	1.6	0.4	0.00	690	188
2	385	44.7	8	1.2	0.4	0.10	660	184
	348	48.5	8	1.9	0.5	0.20	720	214
3	340	38.6	7	1.7	0.6	0.05	580	171
	312	34.9	8	2.2	0.5	0.00	660	194
4	295	24.7	6	0.5	0.3	0.13	990	276
	300	24.1	9	1.7	0.4	0.15	870	220
5	265	25.1	6	1.2	0.4	0.10	940	265
	278	31.9	9	0.9	0.4	0.00	1030	285
6	280	31.5	7	0.6	0.4	0.10	970	166
	336	30.4	5	1.5	0.3	0.05	820	130
7	373	43.4	6	1.3	0.3	0.15	790	160
	393	39.1	9	1.6	0.3	0.05	780	244
8	377	31.4	8	2.4	0.3	0.20	830	223
	349	30.7	7	1.7	0.3	0.00	820	192
9	353	26.8	6	2.3	0.1	0.05	1130	263
	340	27.6	13	6.1	0.1	0.03	1010	228
10	328	26.8	20	11.6	0.4	0.25	830	210
	303	21.0	9	5.3	0.1	0.10	650	145
11	303	30.2	7	2.5	0.2	0.15	680	204
	299	32.8	6	1.5	0.3	0.15	830	283
12	291	26.1	5	1.7	0.2	0.15	810	197
	279	21.0	4	2.4	0.1	0.00	820	258
1 a.m.	266	18.2	4	2.1	0.2	0.15	700	169
	259	15.0	5	2.0	0.2	0.10	610	108
2	250	11.3	5	2.3	0.1	0.10	650	156
	248	11.3	4	1.9	0.2	0.10	600	110
3	244	8.8	5	3.0	0.2	0.05	630	155
	239	9.0	4	1.6	0.1	0.05	650	196
4	236	9.3	4	1.6	0.1	0.05	820	294
	235	8.6	4	1.5	0.2	0.10	710	107
5	233	9.2	4	1.8	0.2	0.05	670	107
	233	11.1	4	1.9	0.2	0.05	640	125
6	232	10.9	4	2.2	0.1	0.00	630	113
	229	12.4	5	2.2	0.3	0.00	750	185
7	232	14.2	5	2.5	0.1	0.00	590	129
	232	15.1	3	1.9	0.2	0.05	770	145
8	231	13.0	4	1.9	0.2	0.05	920	280
	230	11.1	4	2.2	0.3	0.05	850	246

occurred during the evening and in the night in the non-diabetics.

Our results confirm the earlier reports [6, 9, 10, 11, 12, 17, 19] that serum growth hormone is depressed by food intake during the day, and also that during the night growth hormone is secreted in intermittent bursts.

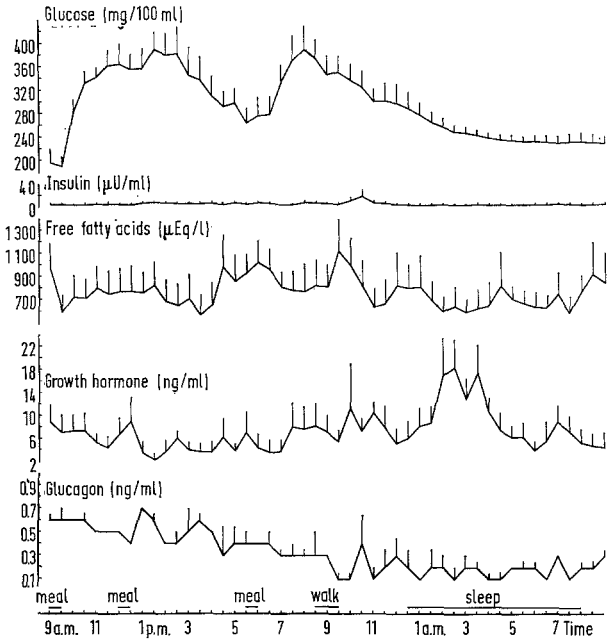

Fig. 3. Average curves of blood glucose, serum insulin, -free fatty acids, -growth hormone and -glucagon in five newly diagnosed, untreated male patients with classic juvenile diabetes. Mean values + S.E.M.

However, they do not contribute to the problem of a possible relationship between growth hormone peaks and the depth of sleep.

The well-known rebound of serum free fatty acids 4—6 h after oral ingestion of glucose has been attributed to the late rise in growth hormone secretion. Our findings in the non-diabetics are not compatible with this suggestion, because the rises in free fatty acid in the late noon and the evening were not preceeded by growth hormone peaks. However, growth hormone could play a role in maintaining the high free fatty acid level during the night. In other experiments [16], we have found that the late rise in free fatty acids and growth hormone after oral glucose in healthy males was related to the amount of glucose ingested, i.e. the greater the amount of glucose ingested the later the rise in growth hormone and free fatty acids will occur. In female subjects the same relationship between glucose ingestion and the free fatty acid rise was seen, but the growth hormone pattern was disrupted by sudden high growth hormone peaks, distributed throughout the six-hour period. These findings in the female subjects are also incompatible with the concept that a rise in growth hormone is responsible for the free fatty acid release. Quabbe *et al.* [17] also failed to find support for the idea of growth-hormone-induced release of free fatty acids during normal life. A connection between the high level of growth hormone and free fatty acids in the juvenile diabetics cannot, however, be ruled out.

The most interesting result obtained in the present study was the finding that the blood of male, non-obese

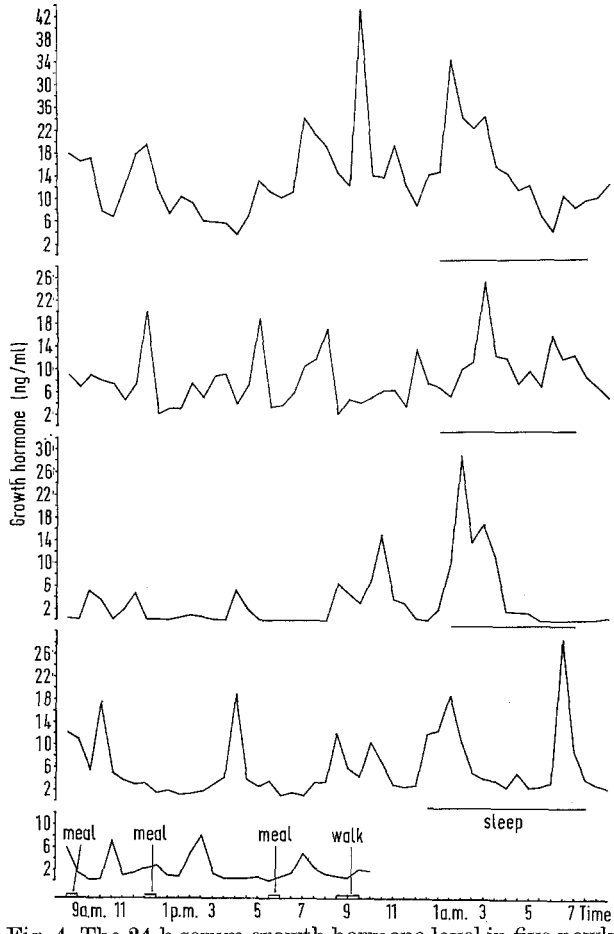

Fig. 4. The 24-h serum growth hormone level in five newly diagnosed, untreated male patients with classic juvenile diabetes

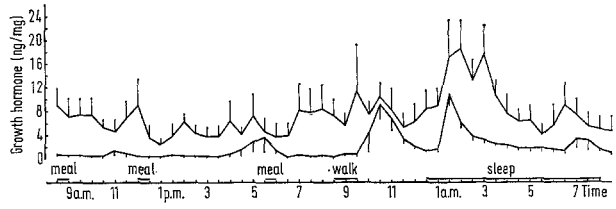

Fig. 5. Average curves of serum growth hormone in the five diabetics (upper curve) and in the five healthy subjects (lower curve). Mean values ± S.E.M.

patients with recently discovered, untreated, classic juvenile diabetes contains much more growth hormone than that of non-diabetics, and that the level fluctuates much more wildly.

The high level of growth hormone could be the result of a higher secretion rate or of a lower disappear-

ance rate. However, the diurnal growth hormone pattern, marked by numerous peaks makes the former alternative much more likely. The abnormal diurnal serum growth hormone pattern in untreated, juvenile diabetics could be an expression of high growth hormone secretion playing a role in the initiation of diabetes mellitus, as suggested by Young [23], or it could be a consequence of the metabolic derangement. Studies of the 24-h pattern in juvenile diabetes after normalization of the blood sugar and in pre-diabetics, are in progress to elucidate this problem.

Other abnormalities of serum growth hormone have been reported in pre-diabetics and diabetics. Pre-diabetics show a hyper-response to oral and intravenous glucose and to intravenous tolbutamide [1, 20]. An abnormal, early rise in plasma growth hormone 2½ hours after ingestion of 100 g of glucose has been found by Yde [22]. One of us [8] has found significantly elevated fasting growth hormone values, and an excessively high growth hormone response to exercise in male non-obese patients with recently discovered classic juvenile diabetes, *before as well as after* normalization of the blood glucose levels. Burday [2] observed a failure of hyperglycaemia to block arginine-induced growth hormone release in insulin-dependent diabetic patients.

The high and fluctuating values of growth hormone in normal women [5, 21, 16], and the steady hypersecretion of growth hormone in acromegaly is a stumbling block to any hypothesis postulating a role of growth hormone in the aetiology of diabetes mellitus.

However, a hypersecretion of growth hormone, if it occurs before the outbreak of diabetes mellitus, may well be an additional aetiological factor, the major prerequisite being an inherited insufficiency of the beta-cells, as stressed recently by Luft and Cerasi [14]. And even if the growth hormone is not of aetiological importance, the high diurnal level of this insulin-antagonistic hormone in established juvenile diabetes must in any case lay a further burden on the metabolism.

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Errata: The growth hormone values in Fig. 1 and Fig. 5 should be given in ng/ml, not in ng/mg.

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