Diurnal Serum Growth Hormone Levels in Poorly and Well-controlled Juvenile Diabetics

K. Johansen, M.D., and Aa. P. Hansen, M.D., Aarhus, Denmark

SUMMARY

Serum growth hormone, free fatty acids and blood glucose have been measured half-hourly for twenty-four hours in seven male patients with juvenile diabetes. Three of the patients had newly diagnosed diabetes and the four other patients had had diabetes for six to nine years. In five of the patients the studies were made during good as well as poor control.

The serum growth hormone level was high and fluctuating in the newly diagnosed diabetics as well as in the diabetics with diabetes of some years duration when compared with the growth hormone level of nondiabetics. The three newly diagnosed diabetics had significantly lower diurnal serum growth hormone concentration during good control compared with poor control. In the two patients with diabetes for some years the diurnal serum growth hormone concentration was unaltered in one and higher in the other in good compared with poor control. DIABETES *20*: 239-45, April, 1971.

In a previous report it was shown that the serum of newly diagnosed untreated male patients with juvenile type diabetes contained more growth hormone than that of nondiabetics and that the level fluctuated more.[1] The present study was undertaken to determine whether this growth hormone abnormality was present not only at the clinical onset of diabetes mellitus, but also after some years duration of diabetes. In addition, the relation of the degree of control of diabetes to the concentration of serum growth hormone in the circulation was investigated.

In order to answer these questions we have studied the twenty-four-hour pattern of serum growth hormone in patients with newly diagnosed juvenile type diabetes and in patients with juvenile diabetes of some years duration. Observations were made during a period of strict control of diabetes as well as during a period of poor control.

From the Second Clinic of Internal Medicine, Aarhus University School of Medicine, Aarhus, Denmark.

MATERIALS AND METHODS

Seven young nonobese male patients with juvenile type diabetes were examined (table 1). Patients Nos. 1-3 were newly diagnosed. Patients Nos. 4-7 had had their disease known for six to nine years. No patients had signs or symptoms of angiopathy. Patients Nos. 1-5 were examined during good as well as poor control. Patients Nos. 6 and 7 were examined only during poor control. In patients Nos. 1-3 observations during poor control were performed before institution of insulin treatment. The period of time between the study in poor and good control was nine to ten months in patients Nos. 1-3, one week in patient No. 4 and three months in patient No. 5. Four of the five patients were clinically well-controlled at least for two days prior to the experiment in good control. One patient, No. 5 was, however, only in good control during the experimental day. The points of time of injection as well as the type and dose of insulin given during the day of the experiment are seen in table 1.

Patients Nos. 1-3, who were examined before institution of insulin treatment were maintained in poor control three to ten days before the study. In the four other patients poor control was allowed only on one day of experimentation. The plasma CO_2 content during this regime fell to acidotic levels in four of the patients, and in two of them the investigation could not be carried out throughout the twenty-four hours.

The findings were compared with those of five healthy male students with a mean age of twenty-six years (range 25-28). None of them was obese. They followed the same "daily life" as the diabetic subject. The results from these control subjects have been published in detail elsewhere.[1]

The experimental procedure was identical to that followed in the earlier study.[1] The patients had been fast-

TABLE 1

Clinical data on patients studied

Patient No.	1	2	3	4	5	6	7
Age in years	22	17	18	25	30	10	17
Height/weight (cm./kg.)	177/65	176/59	174/70	182/68	175/74	134/30	146/45
Diabetes duration in years	0	0	0	9	7	6	6
Insulin dose (IL) during good control							
8:30 a.m.	8 NPH, 4 Reg.	24 Reg.	8 NPH, 4 Reg.	60 NPH, 16 Reg.	36 NPH, 24 Reg.		
5:00 p.m.	8 Reg.	8 Reg.	8 Reg.	8 NPH, 8 Reg. (9 p.m.)	16 NPH		
Changes in total CO_2 in plasma during experiments in poor control mEq./L.)	16 → 12	24 → 29	21 → 24	23 → 8		18 → 13	25 → 7

ing ten to twelve hours when the investigations were started at 8:30 a.m. An indwelling catheter (15 cm. length) was inserted into an antecubital vein and blood samples drawn every half hour during a twenty-four-hour period. The first one to two milliliters of blood were sucked out by a syringe and discarded, and it was not necessary to prevent occlusion of the catheter by either saline or heparin. During the investigation the patients were at their leisure, sitting, talking, listening to the radio and moving quietly around in their room

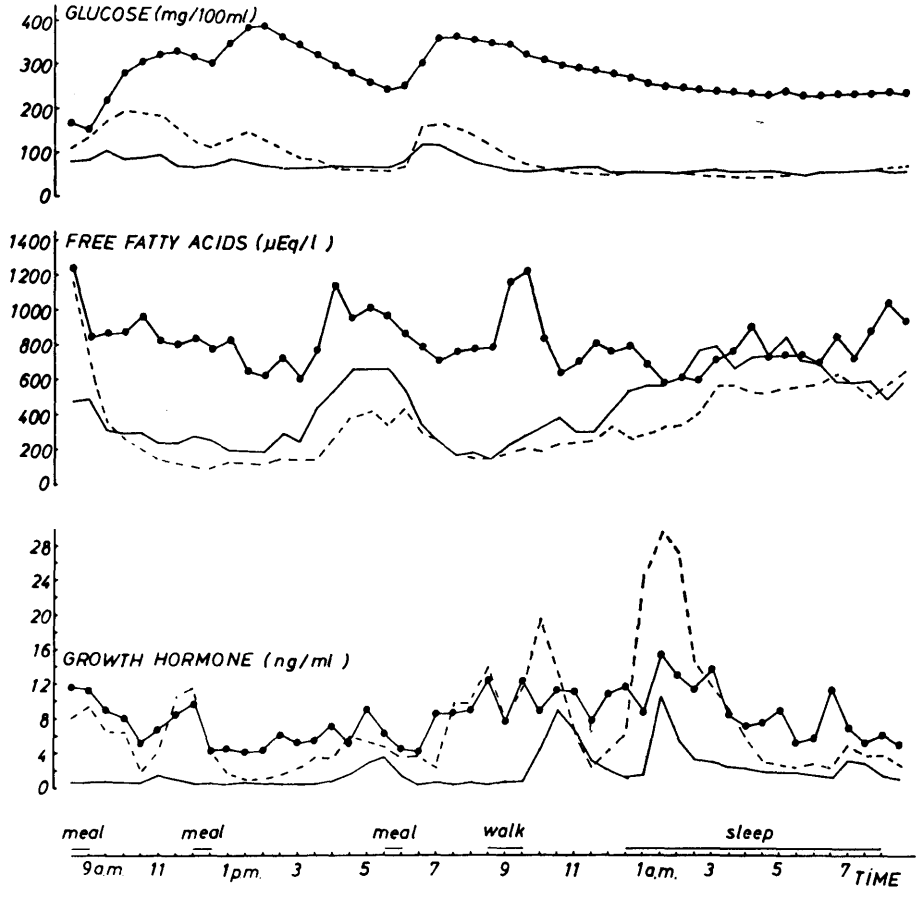

FIG. 1.

Average curves of blood glucose, serum free fatty acids and growth hormone in the nondiabetics and in the five patients with juvenile diabetes during poor control and during good control.
Nondiabetics: ————
Poor control: ●————●
Good control: — — — —

TABLE 2

Timetable for the twenty-four-hour period of "daily life"

a.m.		
8:30- 9:00	Breakfast containing:	
	protein	gm. 6
	carbohydrate	gm. 65
	lipid	gm. 17
	calories	453
9:00- 9:10	One cigaret	
10:30-11:00	One cigaret and one beer containing:	
	carbohydrate	gm. 9
	alcohol	gm. 12
	calories	130
p.m.		
12:15-12:30	Lunch containing:	
	protein	gm. 24
	carbohydrate	gm. 44
	lipid	gm. 28
	calories	538
12:30-12:45	One cigaret	
1:00- 1:30	One beer	
3:00- 4:00	Two cups of coffee, without sugar, cream or milk. One cigaret	
5:30- 6:00	Dinner containing:	
	protein	gm. 16
	carbohydrate	gm. 123
	lipid	gm. 28
	calories	830
6:00- 6:30	One cigaret and one beer	
8:30- 9:30	Gentle walk	
10:30-11:00	One cigaret and one beer	
12:00-	Sleep period	

when necessary. They all followed the program of "daily life" outlined in table 2 with the only exception that patient No. 6 did not smoke cigarettes and was given juice instead of beer. They all consumed the same number of calories.

The blood samples were centrifuged and stored at 20° C. until analysis. Blood glucose was measured by a glucose oxidase method.[2] Serum free fatty acids were determined by a colorimetric method.[3] Serum growth hormone was measured by a single antibody radioimmunoassay employing wick-chromatography.[4] In each assay it was possible to demonstrate at least 0.005 ng growth hormone. A Wilhelmi preparation HS 968 C was used for growth hormone standards.

RESULTS

The *blood glucose* values are seen in table 3 and figure 1. The mean blood glucose level of the diabetics while they were in good control was higher than that of the nondiabetics during most of the day while a nearly normal blood glucose was obtained at night. In the period of poor control, however, the mean values were considerably higher.

The diurnal *serum free fatty acid* levels were much higher during the experiments in poor control than during the experiments in good control (table 3 and figure

TABLE 3

The twenty-four-hour level of blood glucose and serum free fatty acids in patient 1-5 examined during good and poor control

	Good control				Poor control			
	Glucose mg./100 ml.		Free fatty acids μEq./L.		Glucose mg./100 ml.		Free fatty acids μEq./L.	
Time	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.
	114	6	1160	306	166	38	1240	185
a.m.								
9	139	7	700	145	156	29	850	118
	174	14	360	53	220	32	870	178
10	199	10	270	13	281	33	870	137
	193	10	200	20	309	30	960	171
11	190	9	150	20	326	40	820	247
	161	9	120	13	333	39	810	232
12	129	10	100	9	322	34	840	251
	118	8	100	13	305	33	780	238
p.m.								
1	139	7	140	30	353	41	830	279
	155	10	120	34	389	39	660	262
2	136	10	120	18	396	47	620	257
	115	13	160	29	369	46	740	264
3	96	15	150	26	351	43	610	213
	94	14	150	23	329	38	780	185
4	77	13	280	77	304	31	1,150	267
	71	10	380	99	289	34	960	248
5	72	7	430	154	268	36	1,030	325
	70	5	350	137	253	32	980	321
6	80	9	450	158	262	36	880	245
	170	16	310	63	315	46	810	171
7	180	25	270	40	372	51	720	210
	169	35	200	25	379	51	780	310
8	154	34	160	27	370	44	800	273
	129	29	160	23	361	40	810	226
9	104	25	200	60	362	34	1,180	326
	89	20	230	92	337	32	1,250	108
10	81	13	210	96	326	32	860	261
	78	9	250	86	315	28	670	129
11	70	7	260	85	309	29	730	163
	74	11	280	76	305	28	840	273
12	68	11	350	71	296	25	780	219
	78	8	290	82	287	23	820	255
a.m.								
1	80	6	300	78	277	24	720	158
	79	10	350	93	272	25	610	110
2	76	9	360	79	270	24	640	160
	74	10	430	136	265	26	630	88
3	74	11	600	137	262	26	750	105
	75	12	600	124	262	25	800	157
4	76	13	560	120	254	28	940	255
	75	13	560	122	252	24	770	72
5	77	13	580	113	263	23	780	82
	69	18	590	204	250	24	780	78
6	81	13	620	170	251	22	730	90
	81	12	670	213	258	26	880	163
7	84	11	620	135	258	26	760	125
	91	9	540	90	259	27	920	72
8	98	10	610	140	261	27	1,070	204
	100	12	680	142	260	26	980	179

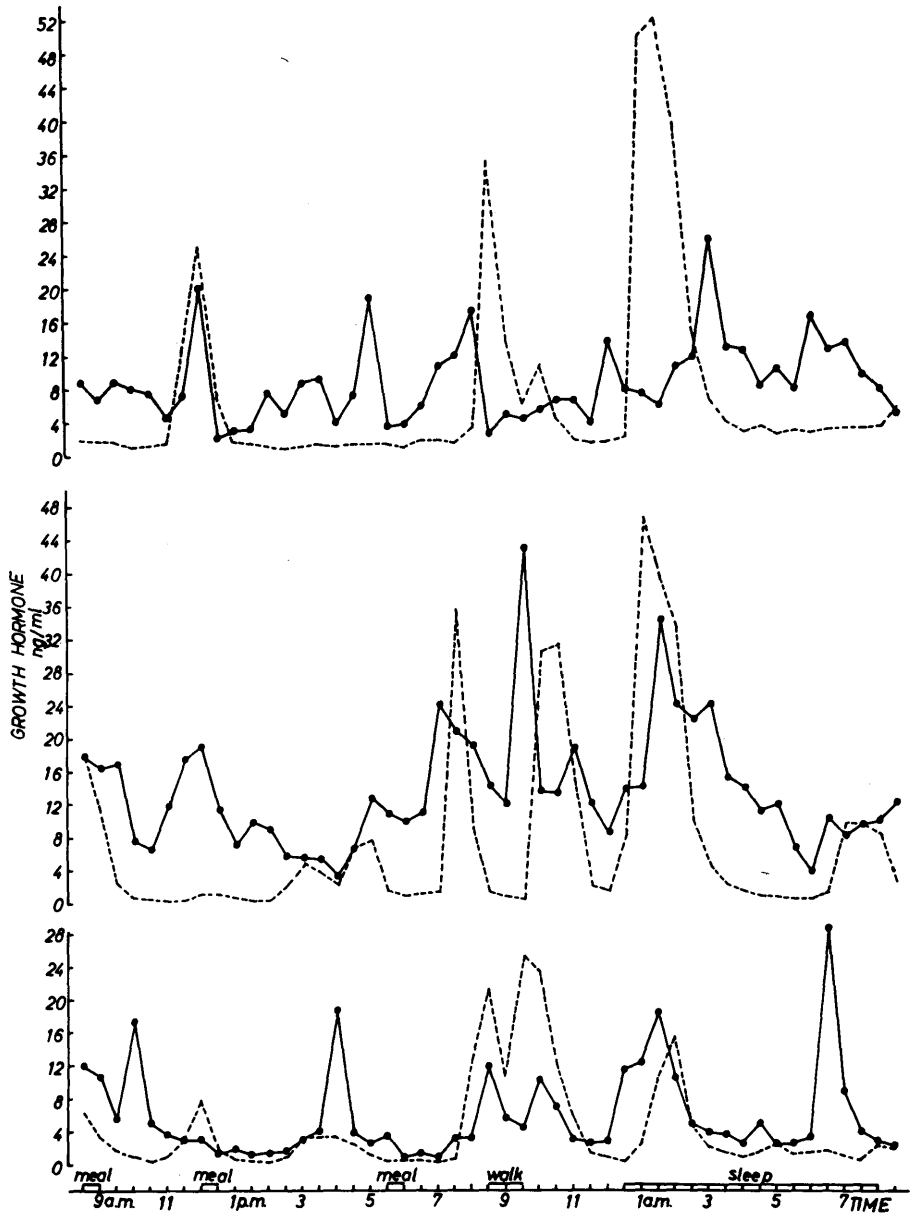

FIG. 2.

The twenty-four-hour serum growth hormone level in the three newly diagnosed diabetics.
Poor control: ●————●
Good control: — — — —

1). The fasting values were, however, not significantly different. The meal-related falls and rises were hardly discernible in the experiments in poor control. The diurnal free fatty acid level in the experiments in good control were not different from that in the five nondiabetics. However, the mean fasting values in the diabetics were significantly higher ($p < 0.01$) than in the controls.

The average *serum growth hormone* values are seen in figure 1, and the growth hormone determinations in the individual patients are seen in table 4 and figures 2 and 3. The value fluctuated from low to high throughout the twenty-four-hour periods in all patients, in good control as well as in poor control, without the distinct sleep- or meal-related peaks found in the control group.[1] There was no difference between the levels or patterns of the twenty-four-hour growth hormone in patients with newly diagnosed diabetes and in patients with diabetes for some years.

The five experiments in which the influence of the metabolic state was studied, i.e., the effects of good as well as poor control, gave results which appeared to be somewhat conflicting. The three patients with newly diagnosed diabetes had lower twenty-four-hour growth

TABLE 4

The twenty-four hour values of serum growth hormone (ng/ml.) in patients 1 through 5 examined during good and poor control, and patients 6 and 7 examined only during poor control

	Good control					Poor control						
Pt. No.	1	2	3	4	5	1	2	3	4	5	6	7
Time												
	2.2	18	6.5	2.9	10	9.0	18	12		8.0	17	0.0
9 a.m.	1.9	12	3.8	25	4.8	6.8	17	11	18	4.1	15	1.7
	1.8	2.6	1.9	24	2.6	9.0	17	5.6	9.6	4.0	8.4	5.3
10	1.1	0.8	1.2	17	12	8.0	7.6	18	4.4	2.3	7.2	3.8
	1.2	0.6	0.6	6.2	1.0	7.4	6.6	5.2	7.0	0.1	0.0	1.6
11	1.6	0.4	1.2	4.3	14	4.6	12	3.7	13	1.0	8.6	2.1
	13	0.6	3.4	14	22	7.2	18	3.0	7.0	7.6	12	11
12	25	1.2	8.0	8.0	15	20	19	3.2	3.6	3.2	11	53
	7.0	1.2	2.1	3.6	5.9	2.0	11	1.6	3.2	3.9	6.4	
1 p.m.	1.8	0.7	0.8	2.6	2.8	3.0	7.2	2.0	2.2	8.6	11	4.9
	1.5	0.3	0.6	1.8	1.0	3.0	10	1.3	2.7	3.6	13	3.2
2	1.0	0.3	0.5	2.1	0.4	7.4	9.0	1.5	3.3	0.1	16	0.9
	0.7	2.1	1.0	1.0	2.0	4.8	5.8	1.8	18	0.6	23	1.8
3	1.1	4.9	3.6	1.5	0.0	8.6	5.6	3.1	7.0	2.3	20	28
	1.3	3.8	3.6	8.6	0.0	9.0	5.4	4.3	5.5	3.5	11	17
4	1.0	2.4	3.6	10	0.0	3.8	3.4	19	1.1	8.9	6.2	2.2
	1.2	6.8	2.8	19	0.0	7.0	6.6	4.0	1.9	6.4	18	2.0
5	1.2	7.8	1.4	17	0.0	19	13	2.7	9.6	1.9	39	0.0
	1.2	1.6	0.7	20	0.0	3.2	11	3.7	13	0.7	18	2.2
6	0.8	1.0	0.8	15	0.0	3.5	10	1.1	7.0	1.0	18	6.0
	1.6	1.2	0.8	15	0.0	5.6	11	1.6	2.9	0.1	21	5.6
7	1.7	1.5	0.5	7.6	0.4	10	24	1.1	6.4	0.6	24	0.0
	1.3	36	1.0	3.7	7.0	12	21	3.4	5.5	1.9	22	8.2
8	3.3	8.9	13	1.9	21	17	19	3.5	2.8	3.3	23	16
	35	1.5	22	1.6	9.6	2.2	14	12	3.0	31	14	4.8
9	14	0.8	11	3.4	12	4.5	12	6.0	2.8	13	20	9.0
	5.9	0.6	26	13	13	4.0	43	4.7	3.1	7.0	13	10
10	11	30	24	19	14	5.0	14	11	12	3.7	9.2	8.1
	4.0	31	13	13	8.0	6.2	13	7.3	29	1.7		4.8
11	1.5	15	6.3	5.6	6.2	6.2	19	3.2	26	2.5		3.4
	1.1	2.1	1.8	3.6	4.2	3.4	12	2.8	21	0.5		3.6
12	1.1	1.4	1.3		1.6	13	8.4	3.0	30	0.2		4.5
	1.8	8.3	0.7	20	0.2	7.4	14	12	25	1.0		1.9
1 a.m.	50	47	2.8	22	1.4	6.8	14	13	10	0.7		0.3
	52	39	11	42	5.6	5.4	34	19	6.4	13		4.9
2	39	33	16	37	15	10	24	11	5.0	16		2.2
	14	10	5.4	24	21	11	22	5.4	6.6	13		2.0
3	6.3	4.6	2.7	32	16	25	24	4.3	10	6.0		4.9
	3.4	2.1	1.8	25	16	12	15	4.0	8.3	3.2		3.4
4	2.0	1.3	1.2	14	12	12	14	2.8	5.8	1.6		3.6
	2.7	0.7	1.9	8.2	2.6	7.4	11	5.3	12	2.9		2.7
5	1.7	0.6	3.0	7.5	1.0	9.5	12	2.8	19	2.5		3.7
	2.0	0.3	1.6	8.8	0.0	7.0	6.5	2.9	7.5	1.9		6.7
6	1.8	0.5	2.0	10	0.0	16	3.6	3.6	5.7	1.6		
	2.2	1.1	2.2	5.2	1.2	12	10	29	5.9	0.3		
7	2.2	9.4	1.6	8.3	3.4	12	7.8	9.3	4.7	0.9		
	2.2	9.5	1.0	6.2	0.8	8.6	9.2	4.3	3.6	1.2		
8	2.3	8.1	2.8	4.0	2.2	6.8	9.6	3.2	9.8	1.7		
	4.7	2.2	2.3	1.9	2.8	3.8	12	3.6	5.7	1.9		

hormone levels during good control than during poor control. With use of the median chi-square test the significant difference was: patient No. 1 ($p < 0.0005$), No. 2 ($p < 0.0005$) and No. 3 (< 0.005). In the two patients with few years known duration of diabetes the twenty-four-hour growth hormone level was the same during good and poor control in one patient, No. 5 ($p > 0.5$), but in the other patient, No. 4, the level was significantly higher during good control ($p < 0.05$). Comparing the values in good and poor control during the period only from 4 a.m. to 9 p.m., and thereby excluding the period where high and fluctuating

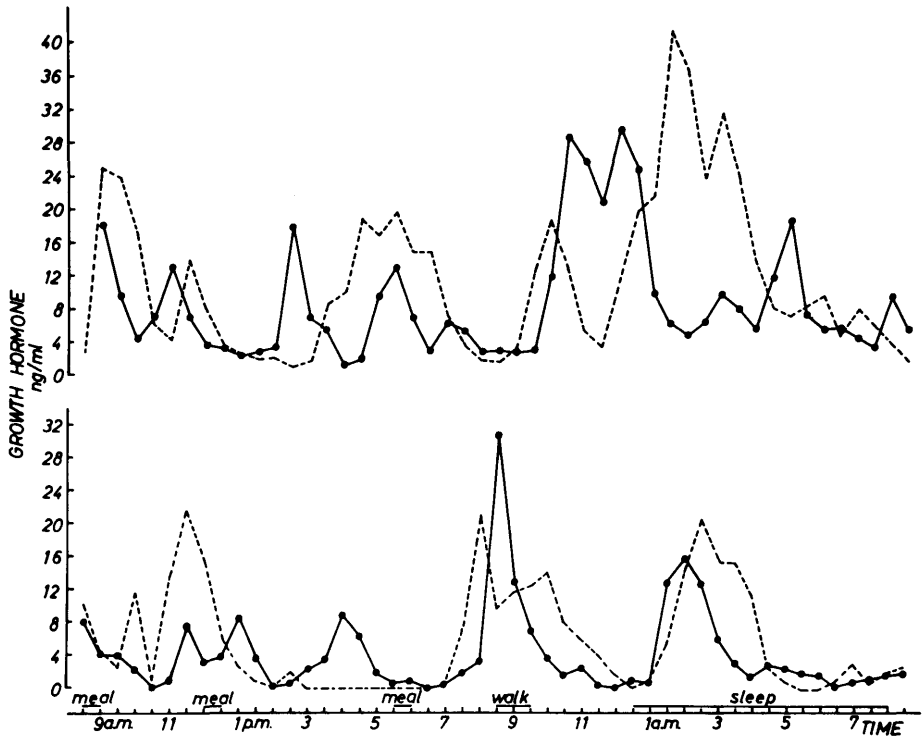

FIG. 3.

The twenty-four-hour serum growth hormone level in the two patients with diabetes of some years duration.
Poor control: ●————●
Good control: — — — —

serum growth hormone values are observed also in nondiabetics, the analysis gives similar results for patients Nos. 1, 2, 3 and 5 ($p < 0.0005$), ($p < 0.0005$), ($p < 0.001$) and ($p > 0.5$). However, in patient No. 4, in whom the very high values during good control were confined to the period 9 p.m. to 4 a.m. the difference now becomes nonsignificant ($p > 0.3$).

The mean twenty-four-hour growth hormone concentration in the diabetics during good control as well as during poor control were higher and the level fluctuated more than of the five comparable nondiabetics. The mean twenty-four-hour concentrations were 7.41 ng/ml. (range 4.67-11.79) in good control, 8.26 ng/ml. (range 4.29-13.57) in poor control and 1.98 ng/ml. (range 1.68-2.35) in the nondiabetics.

DISCUSSION

We have found that blood of male nonobese patients with newly diagnosed juvenile type diabetes and patients with juvenile diabetes of some years duration contains more growth hormone than that of nondiabetics. Furthermore the high growth hormone level is present whether these patients are clinically well regulated with nearly normal diurnal blood glucose level or they are less well regulated with high blood glucose values and, in four of the patients, in slight to moderate acidosis. In the three patients with newly diagnosed diabetes (patients Nos. 1-3) the twenty-four values were lower and less fluctuating in the well regulated condition than in the poorly regulated condition. This finding indicates that the high growth hormone level observed in these diabetics may be at least partly of metabolic origin. But the study does not resolve the problem whether or not the level in juvenile diabetics will be completely normalized with complete *normalization* of the diurnal blood glucose level. Our patients have only been *normalized in the clinical sense of the word,* and then only for a comparatively short period. In the two other patients (Nos. 4 and 5) the twenty-four-hour growth hormone level was the same or even higher during the experiments in good control compared to the experiments in poor control. These conflicting results could be due to the longer duration of diabetes in these two patients. However, one of us has shown[5] that fasting serum growth hormone and the response to exercise show the same degree of abnormality in recently diagnosed juvenile diabetics, in short-term diabetics and in long-term diabetics.

We believe that the difference in the results in the three newly diagnosed diabetics and the two short-term diabetics are due to the fact that our newly diagnosed diabetics had been more well regulated with insulin than our short-term diabetics, when attending our outpatient diabetic clinic at monthly intervals. Some of our pa-

tients had short periods with hypo- and hyperglycemic levels during the investigations in good control though painstaking efforts were made in order to establish normal blood glucose concentrations during the whole twenty-four-hour period. Therefore, the possibility exists that some of the growth hormone peaks observed during the experiments in good control could be attributed to downward fluctuations in blood glucose levels.[6]

Abnormalities in serum growth hormone in juvenile diabetes mellitus are described by several authors.[1,7-12] However, in diabetic children Parker et al.[13] and Baker et al.[14] have found a normal growth hormone response to oral and intravenous glucose as well as to intravenous tolbutamide. One of us[5] observed an abnormally early and high serum growth hormone rise during exercise in juvenile diabetics. A significant diminution in this growth hormone hyperresponse could be demonstrated only after exceedingly strict diabetes control with fasting blood glucose values between 60 and 100 mg./100 ml. With fasting blood glucose values between 100 and 140 mg./100 ml. which in clinical terms may indicate a very good diabetic control no such diminution was observed. A metabolic component in the growth hormone abnormality in diabetes mellitus is also supported by the findings of Unger[15] and Jacobs et al.[16] that the elevated serum growth hormone values in ketoacidotic diabetics decreased to normal values after insulin treatment.

The long-term effect(s) of this high diurnal serum growth hormone level in juvenile diabetics is at the present time unknown. Some findings seem, however, to show indirectly that diabetic angiopathy is influenced by measures which reduce growth hormone secretion.[17]

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by measure which reduce growth hormone secretion.[17]
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