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Research Article

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In 10 normal subjects and 10 patients with primary type IV hyperlipoproteinemia, plasma triglyceride, free fatty acid, blood sugar, and insulin levels were followed in short intervals for 24 h while a 2,400 cal, 80% carbohydrate, fat-free formula diet was given in six equal portions during the day (control experiments). This procedure was repeated in the same subjects, 10 of whom (5 normal subjects and 5 patients) received additional feedings of glucose between 2000 and 0600 h while the other 10 persons (5 normal subjects and 5 patients) were given nicotinic acid by intravenous infusion during the same time interval. Both procedures resulted in maintained lowering of free fatty acid levels over 24 h. Mitigation of carbohydrate-induced hypertriglyceridemia appeared to result from the additional glucose in normals and in patients. Nicotinic acid abolished the nocturnal rise of plasma triglyceride levels which in the control studies [...]

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Diurnal Patterns of Triglycerides, Free Fatty Acids, Blood Sugar, and Insulin during Carbohydrate-Induction in Man and Their Modification by Nocturnal Suppression of Lipolysis

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ABSTRACT Previous studies have shown that carbohydrate induction of hypertriglyceridemia in normal subjects occurs at night and appears to be related to a rise of free fatty acids after diurnal feeding of high-carbohydrate formula diet. The present investigation was undertaken to observe the effect on 24-h triglyceride, free fatty acid, blood sugar, and plasma insulin profiles of inhibition of nocturnal lipolysis by glucose or nicotinic acid in normal subjects and in patients with type IV hyperlipoproteinemia.

In 10 normal subjects and 10 patients with primary type IV hyperlipoproteinemia, plasma triglyceride, free fatty acid, blood sugar, and insulin levels were followed in short intervals for 24 h while a 2,400 cal, 80% carbohydrate, fat-free formula diet was given in six equal portions during the day (control experiments). This procedure was repeated in the same subjects, 10 of whom (5 normal subjects and 5 patients) received additional feedings of glucose between 2000 and 0600 h while the other 10 persons (5 normal subjects and 5 patients) were given nicotinic acid by intravenous infusion during the same time interval. Both procedures resulted in maintained lowering of free fatty acid levels over 24 h. Mitigation of carbohydrate-induced hypertriglyceridemia appeared to result from the additional glucose in normals and in patients. Nicotinic acid abolished the nocturnal rise of plasma triglyceride levels which in the control studies of normal subjects had resulted in approximate doubling of triglyceride levels in 24 h.

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The effectiveness of nicotinic acid in inhibiting nocturnal lipolysis and preventing carbohydrate-induction of hypertriglyceridemia might have consequences for management of endogenous hypertriglyceridemia.

INTRODUCTION

In 1961, Ahrens, Hirsch, Oette, Farquhar, and Stein (1) introduced the concept of carbohydrate-induced hypertriglyceridemia. They showed that a number of patients with primary hypertriglyceridemia responded to high carbohydrate feeding with sustained elevation of fasting plasma triglyceride levels. Subsequently, it has been shown, that carbohydrate induction may be observed in several types of primary hyperlipoproteinemias (types III, IV [2]) and that it also occurs in normals (3, 4), in whom it appears to be a transient phenomenon, with approximate doubling of plasma triglyceride levels within 5-7 days. With continued high carbohydrate feeding, triglycerides return to normal levels in the course of days or weeks (5).

While the phenomenon of carbohydrate induction of hypertriglyceridemia had usually been described in terms of fasting plasma triglyceride levels, we have been interested in the study of diurnal changes of plasma lipids. In 1969, we reported (6) that carbohydrate induction of hypertriglyceridemia in normal subjects occurs at night and appears to be related to a rebound rise of free fatty acids after diurnal feeding of a high carbohydrate formula diet. This biphasic response of plasma triglycerides to high carbohydrate feeding on a 24 h basis has since been confirmed by Barter, Carroll, and Nestel (7).

TABLE I
Data on Patients and Control Subjects

Patient	Sex	Age	Body wt	Height	Weight index*	Plasma TG‡
			kg	cm		mg/100 ml
Type IV patients (glucose study)						
F. T.	M	39	96	180	1,200	165§
G. R.	M	40	73	175	973	349
R. R.	M	48	108	195	1,137	266
J. K.	M	21	84	166	1,273	343
G. S.	M	40	87	174	1,176	478
Mean		37.6	89.6	178	1,152	320
Normal subjects (glucose study)						
R. L.	M	30	61	174	824	86
K. B.	M	25	65	178	833	56
G. E.	M	25	66	172	916	76
T. K.	F	23	59	167	880	70
G. W.	M	25	83	187	954	59
Mean		25.6	66.8	175.6	881	69
Type IV patients (nicotinic acid study)						
A. Sp.	M	49	82	178	1,051	285
W. H.	M	39	97	170	1,386	1,123
H. H.	M	33	104	173	1,425	1,080
L. W.	M	50	85	170	1,214	400
A. Sc.	M	65	75	165	1,154	699
Mean		47.2	88.6	171.2	1,246	717
Normal subjects (nicotinic acid study)						
F. F.	M	28	68	171	958	94
A. M.	M	23	63	172	875	55
W. F.	M	26	65	170	929	31
M. W.	M	25	83	185	976	70
K. S.	M	29	80	184	952	83
Mean		26.2	71.8	176.4	938	67

* Weight index = weight (kg)/height (cm) - 100.

‡ Fasting values of first experiments. TG, triglyceride.

§ This patient, on four previous occasions, always had TG > 200 mg/100 ml.

The present investigation was undertaken in order to study the effect on 24-h triglyceride, free fatty acid, blood sugar, and insulin profiles of inhibition of nocturnal lipolysis by glucose or nicotinic acid. Since this experimental procedure provided for quite different conditions with regard to plasma insulin levels which were high in the first and low in the second study, it should yield information not only on free fatty acid and triglyceride interrelationships on a short-term basis, but also whether substantial differences of plasma insulin levels would influence 24-h plasma triglyceride concentrations.

METHODS

Glucose study. Participants of this study were five healthy male subjects on the one hand and five patients with primary endogenous (type IV) hyperlipoproteinemia on the other. Data on sex, age, weight, and initial triglyceride levels are given in Table I.

Each subject was studied twice in randomized order. For control experiments, the subjects were admitted to the hospital in the morning, after they had been fasting for at least 12 h. They were put to bed where they stayed for the following 24 h. A plastic cannula was placed in a large vein of one forearm and kept open by means of a stylet. Starting at 0800 hours, these subjects were given formula diets in six divided portions of 400 cal each. The composition of the diet was 79% of total calories from carbohydrates, 20% protein, and 1% fat (Table II). While portions of this diet were consumed at 0800, 1000, 1200, 1400, 1600, and 1800 h, blood samples for determination of plasma triglyceride, free fatty acid, blood sugar, and insulin concentrations were obtained hourly during the day and, after 2230 h, every 2 h during the night. The blood samples were taken without a tourniquet into EDTA tubes, immediately chilled to 4°C until, always within a few hours, the plasma was separated by centrifugation in a cold room and immediately frozen to -25°C.

The second experiment, either after or preceding the control experiments by intervals of at least 5 days, were per-

TABLE II
Composition of Formula Diet

	Grams	Carbo- hydrate	Fat	Protein	Calories
Fat-free milk solids	320	166	3	115	1,184
Maltidextrose	270	262			1,080
Vanilla sugar	30	30			118
Total of nutrients		458	3	115	
Calories (~2,400)		1,878	28	472	
Percent of calories		79	1	20	

formed in a similar manner. Here, in the *normal subjects*, only 1,800 cal of the same formula diet were given during the day in six divided portions (300 cal each). Starting at 2000 h and then every 2 h during the night, this was followed by the oral administration of six portions of 120 ml 50% glucose solution, amounting to 1,440 cal at night and a total of 3,240 calories for 24 h. The *patients* received identical amounts of the formula diet during the day (2,400 cal) in the control and glucose experiments. In the latter 6 × 120 ml 50% glucose solution were given at night in addition, to make 3,840 cal in 24 h.

Nicotinic acid study. Participants of this study were again five healthy young male subjects and five patients with primary (type IV) endogenous hypertriglyceridemia. The control experiments were identical to those of the glucose study, the subjects remaining in bed for 24 h, consuming a high carbohydrate, fat-free formula diet of 2,400 cal in six divided portions and having blood samples drawn as described. On another day, either preceding or after the control experi-

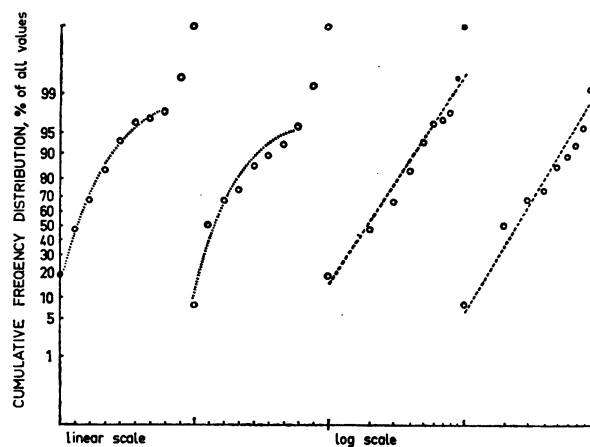


FIGURE 1 Frequency distribution of plasma triglyceride levels. More than 96% of values conform to log normal distribution.

ment, the subjects were treated in an identical manner from 0800 to 1800 h, while, starting at 1800 h, an intravenous infusion of nicotinic acid (2 g/500 ml 0.9% NaCl solution) was started and continued until 0600 h of the following day.

Laboratory methods. While blood sugar values were determined from venous blood samples on the day after each experiment by the AutoAnalyzer (Technicon Corp., Tarrytown, N. Y.), triglyceride, free fatty acid, and insulin levels for the two experiments of each patient were always determined on the same day, triglycerides by the fluorimetric method of Kessler and Lederer using the AutoAnalyzer (8),

TABLE III
Data of Statistical Analysis

	Glucose study				Nicotinic acid study				$\alpha(0.05)$	$\alpha(0.01)$
	BS*	Ins.	FFA	TG	BS	Ins.	FFA	TG		
Variance‡										
Source										
A	598.44	6,627.28	2,845.91	443.29	761.92	12,093.87	3,695.57	120.66		
B	4,522.56	21,345.20	18,865.02	251.22	70.56	479.60	3,074.70	2,943.06		
C	147.62	37,558.44	12,690.02	381,615.00	361.00	103,555.19	29,189.72	829,283.19		
AB	405.24	4,419.49	2,314.89	97.37	17.26	178.17	2,275.40	315.57		
AC	102.50	542.82	220.73	103.04	97.65	638.60	100.72	107.18		
BC	1,417.52	17,004.16	2,425.56	113.42	14.44	129.96	5.52	1,132.32		
ABC	38.65	363.06	79.12	40.56	21.93	191.77	47.44	100.83		
E	51.87	469.26	187.16	221.82	45.92	700.86	142.17	570.17		
F-Test										
A/E	11.53§	14.12§	15.20§	1.99	16.59§	17.26§	25.99§	0.21	1.62	1.97
B/AB	11.16	4.83¶	8.15¶	2.58	4.08	2.69	1.35	9.32	4.38	8.18
C/AC	1.44	69.19§	57.49§	3,703.56§	3.70	162.16§	289.81§	7,737.29§	4.38	8.18
AB/E	7.81§	9.42§	12.37§	0.44	0.38	0.25	16.00§	0.55	1.62	1.97
AC/E	1.97	1.16	1.18	0.46	2.13	0.91	0.70	0.19	1.62	1.97
BC/ABC	36.67§	46.83§	30.65§	2.78	0.66	0.68	0.12	11.23	4.38	8.18
ABC/E	0.74	0.77	0.42	0.18	0.48	0.27	0.33	0.18	1.62	1.97

The original data from which these correlations were made have been placed in the National Auxiliary Publications Service (ID no. 02010).
* BS, blood sugar; Ins., insulin; FFA, Free fatty acids; TG, triglycerides.

‡ Results of three way analysis of variance: A, times; B, procedures (control vs. experimental); C, diagnoses (normal vs. type IV patients); AB, interaction time/procedure; AC, interaction time/diagnosis; BC, interaction procedure/diagnosis; ABC, interaction time/procedure per diagnosis; E, error.

Statistical significance:

§ $\alpha < 0.001$.

|| $\alpha < 0.01$.

¶ $\alpha < 0.05$.

free fatty acids after extraction according to Dole according to Lorch and Gey (9), and insulins by a modification of the radioimmunoassay of Yalow and Berson (10). All measurements were made in duplicate.

Statistical evaluation¹ was performed by three-way analysis of variance after logarithmic transformation of the data. Transformation was necessary to reduce skewness to the right and achieve "normality" of distribution (Carlson and Lindstedt [11] (see Fig. 1).

The formulas used were: blood sugar, $100 \log x - 150$ ($x = \text{mg}/100 \text{ ml}$); triglycerides, $100 \log x - 140$ ($x = \text{mg}/100 \text{ ml}$); insulin, $100 \log (x + 10) - 100$ ($x = \mu\text{U}/\text{ml}$); free fatty acids, $100 \log x - 200$ ($x = \mu\text{eq}/\text{liter}$). Results of statistical analysis are given in Table III.

RESULTS

Glucose study—normal subjects (Fig. 2)

Blood sugar and insulin profiles. The blood sugar concentration spiked during the day according to meal intake and was slightly higher in the control experiments when more calories and carbohydrates were consumed during the day. At night, the curves became divergent due to the consumption of glucose in divided portions in the glucose part of the study (significant at 0.1% level).

Insulin profiles closely reflected blood sugar changes, the control curve during the day again being higher than the glucose curve. The difference between the two 24-h patterns is statistically significant at the 0.1% level.

Free fatty acid profiles. Mean fasting free fatty acid levels were slightly higher in the control experiments. Free fatty acid levels fell upon initiation of feeding and remained low during the day. In the control experiments, free fatty acid levels rose during the night. They remained low with continued glucose feeding. The difference of patterns is statistically significant at the 0.1% level.

Triglyceride profiles. Triglycerides started from similar values in control and glucose experiments. There was little change of plasma triglyceride levels during the day, the control curve being slightly lower than the glucose curve. At night, in the then fasting control group, triglycerides approximately doubled as described previously (12), while in the glucose group, the nocturnal rise appeared to be diminished. The difference between the two experiments does not reach significance.

Glucose study—type IV patients (Fig. 3)

Blood sugar and insulin profiles. During the day, blood sugar profiles were identical in the two experiments. They diverged during the night according to the patterns of food intake. The difference is statistically significant at the 0.1% level.

The insulin profiles closely reflected those of the blood sugar concentrations. Again, the difference between the

¹Kindly performed by Professor H. Immich, Abteilung für Medizinische Dokumentation und Statistik, Universität Heidelberg.

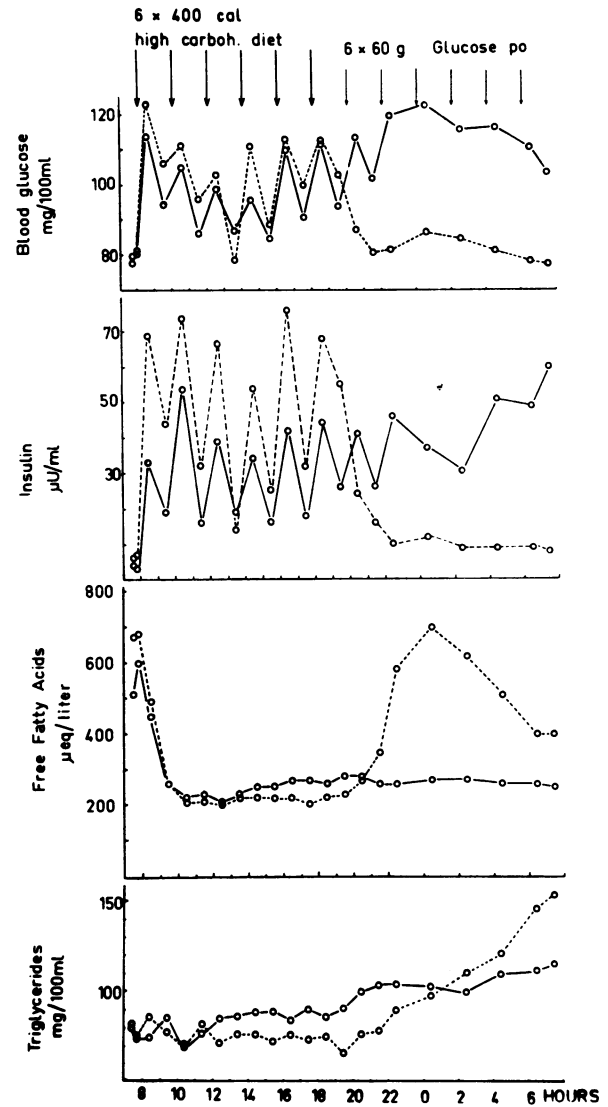


FIGURE 2 Mean 24-h blood sugar, insulin, free fatty acid, and triglyceride profiles in normal subjects on high carbohydrate diet without (dotted lines) and with (solid lines) additional glucose. Large arrows denote intake of formula diet, small arrows intake of glucose.

two 24-h experiments was statistically significant at the 0.1% level. Fasting as well as postprandial levels were about two times as high as in the normal subjects (difference significant at 0.1% level).

Free fatty acids. During the day free fatty acid profiles were very similar in the two experiments and slightly higher than in the normal subjects. At night, in the control experiments, there was a rebound rise of free fatty acids after the last meal, while concentrations remained low with continued glucose administration. The difference is significant at the 0.1% level.

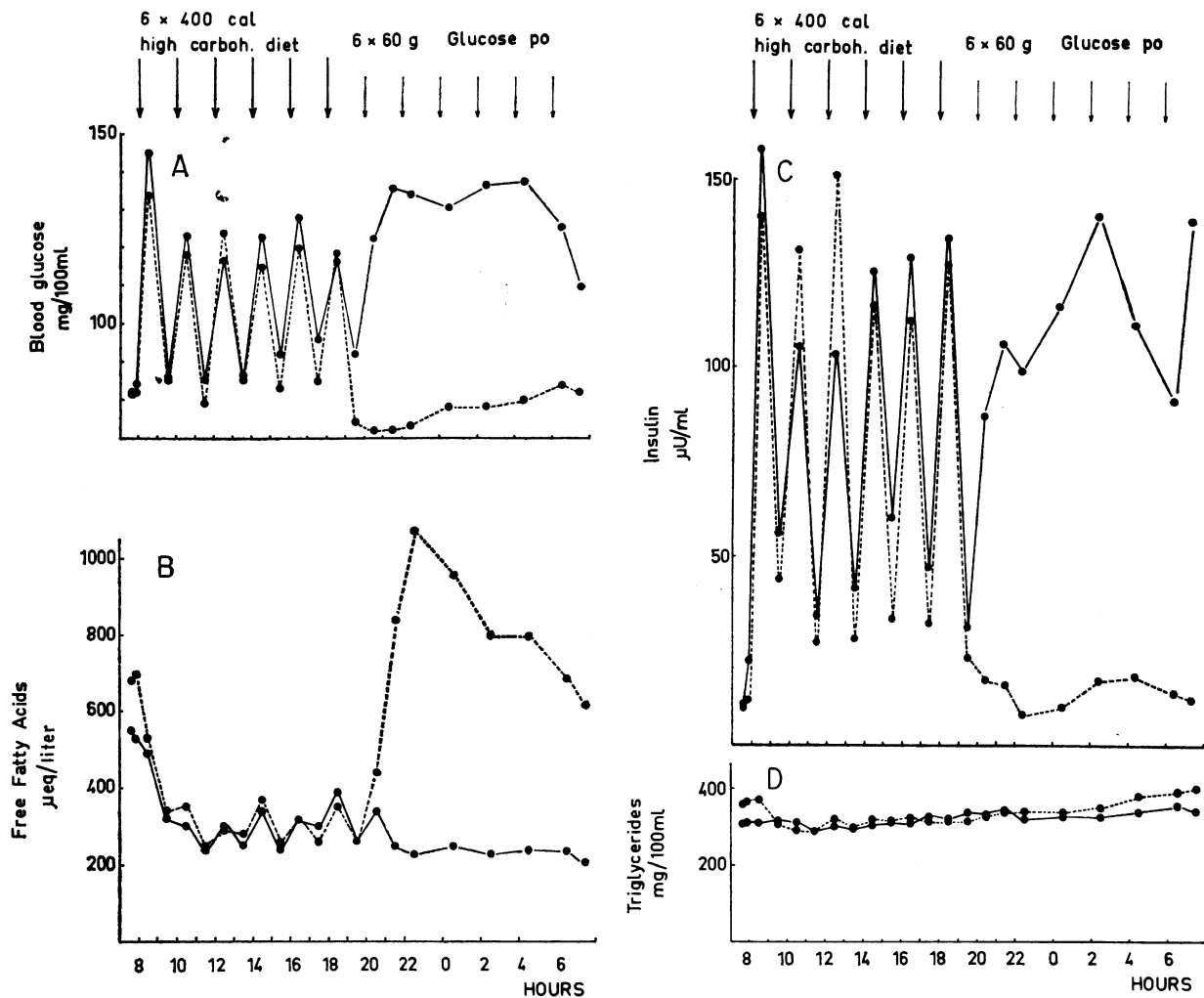


FIGURE 3 Mean 24-h blood sugar, insulin, free fatty acid, and triglyceride profiles in patients with type IV hyperlipoproteinemia on high carbohydrate diet without (dotted lines) and with (solid lines) glucose. Large arrows denote intake of formula diet, small arrows intake of glucose.

Triglycerides. Triglyceride profiles with the two experiments were identical during the day and slightly lower in the glucose experiment at night. This difference is not statistically significant.

Nicotinic acid study—normal subjects (Fig. 4)

Blood sugar and insulin profiles. The blood sugar values of this study were very similar to the control part of the glucose study in normal subjects. Insulin levels reflected changes in blood sugar concentrations. There was no difference between the control and nicotinic acid experiments.

Free fatty acids. In the control study free fatty acids behaved as described previously (12) showing the rebound rise after cessation of feeding and returning to preexperiment concentrations at the end of 24 h. With nicotinic acid, free fatty acids remained low until the

end of the infusion at 0600 h and rose immediately afterwards to very high levels. The difference between the two experiments is statistically significant at the 0.1% level.

Triglycerides. In the control study triglycerides rose at night, approximately doubling their concentration from 2000 to 0600 h. With nicotinic acid there was a slight fall of triglycerides during the night hours. The last two samples, which had been taken after cessation of the nicotinic acid infusion, showed a tendency to rise. The difference between the two experiments is statistically significant at the 1% level.

Nicotinic acid study—type IV patients (Fig. 5)

Glucose and insulin profiles. Glucose profiles in the control and nicotinic acid experiments were identical and very similar to those of the control experiments in the

glucose study with the patient group. 24-h insulin levels reflected the sugar changes. The profiles were identical in the two experiments.

Free fatty acids. Free fatty acid concentrations started from fasting levels slightly above 600 $\mu\text{eq/liter}$, were low during the day and rose in the control experiments after cessation of feeding, which observations are similar to those in normal subjects. With nicotinic acid, free fatty acids remained low up to the end of the infusion, when they showed a steep rebound rise up to 1,900 $\mu\text{eq/liter}$. The difference between the two studies is statistically significant at the 0.1% level.

Triglycerides. Triglycerides, in the control study, showed some variation during the day and rose slightly during the night, similar to their behavior in the control experiment of the glucose study. With nicotinic acid, as in normals, there was a continued fall of plasma triglyceride concentrations during the night until the end of the infusion, when two samples with rising values were noted. The difference is significant at the 1% level.

DISCUSSION

Blood sugar-insulin relationships. In 15 of the 20 experiments involving normal subjects, the time-courses of blood sugar and insulin levels during the day showed similar patterns: in spite of identical meal size, the first glucose peaks were considerably higher than the following ones, while plasma insulin levels showed an opposite behavior. Carbohydrate tolerance apparently improved during the morning and slightly deteriorated again in the afternoon, in agreement with findings of Jarrett and Keen (13) that there are significantly higher postglucose blood sugar levels in afternoon glucose tolerance tests than in tests performed in the morning. This diurnal variation of carbohydrate tolerance was less evident in the patients.

Another finding in our study, which might have been related to the obesity in the patient groups (14), was slightly higher blood sugar levels and considerably higher fasting as well as postprandial insulin levels. Therefore insulin glucose ratios were significantly higher in the patients than in the normals.

Free fatty acids. In all experiments free fatty acid levels became quite low during the day as a result of inhibition of lipolysis by elevated glucose and insulin levels (15). Lowest values in individual subjects lay around 150 $\mu\text{eq/liter}$ which may be the amount irreversibly bound to albumin and thus not affected by changing rates of lipolysis or free fatty acid consumption (16). Approximately 2 h after cessation of feeding, in the control studies, free fatty acid levels rose, rebounding considerably in some subjects, and then fell slightly again, but always remained considerably higher at night than during the day. With low glucose and insulin levels

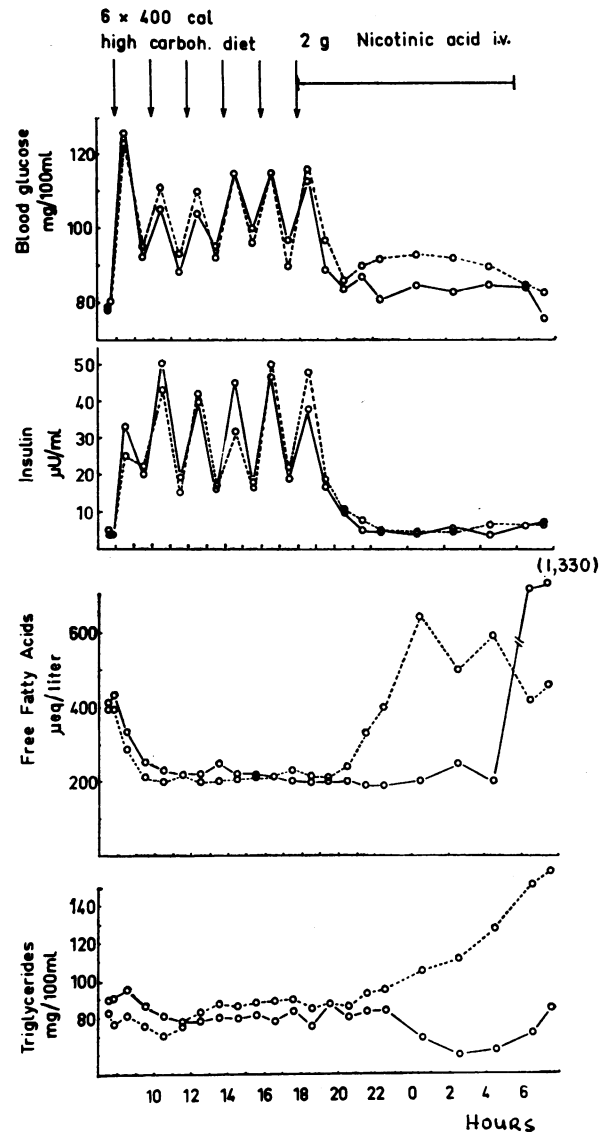


FIGURE 4 Mean 24-h blood sugar, insulin, free fatty acid, and triglyceride profiles in normal subjects on high carbohydrate diet without (dotted lines) and with (solid lines) nocturnal infusion of nicotinic acid. Arrows denote intake of formula diet.

during the night hours, lipolysis proceeds with an accelerated rate supplying fuel for many energy-consuming processes. One of the lipolytic forces at night might also be growth hormone (17) which in many subjects shows spikes at night.

In contrast to the control experiments, glucose or nicotinic acid administration at night resulted in maintained lowering of free fatty acid levels for the period of administration of the respective substances. Cessation of nicotinic acid infusion at 0600 h resulted in a very

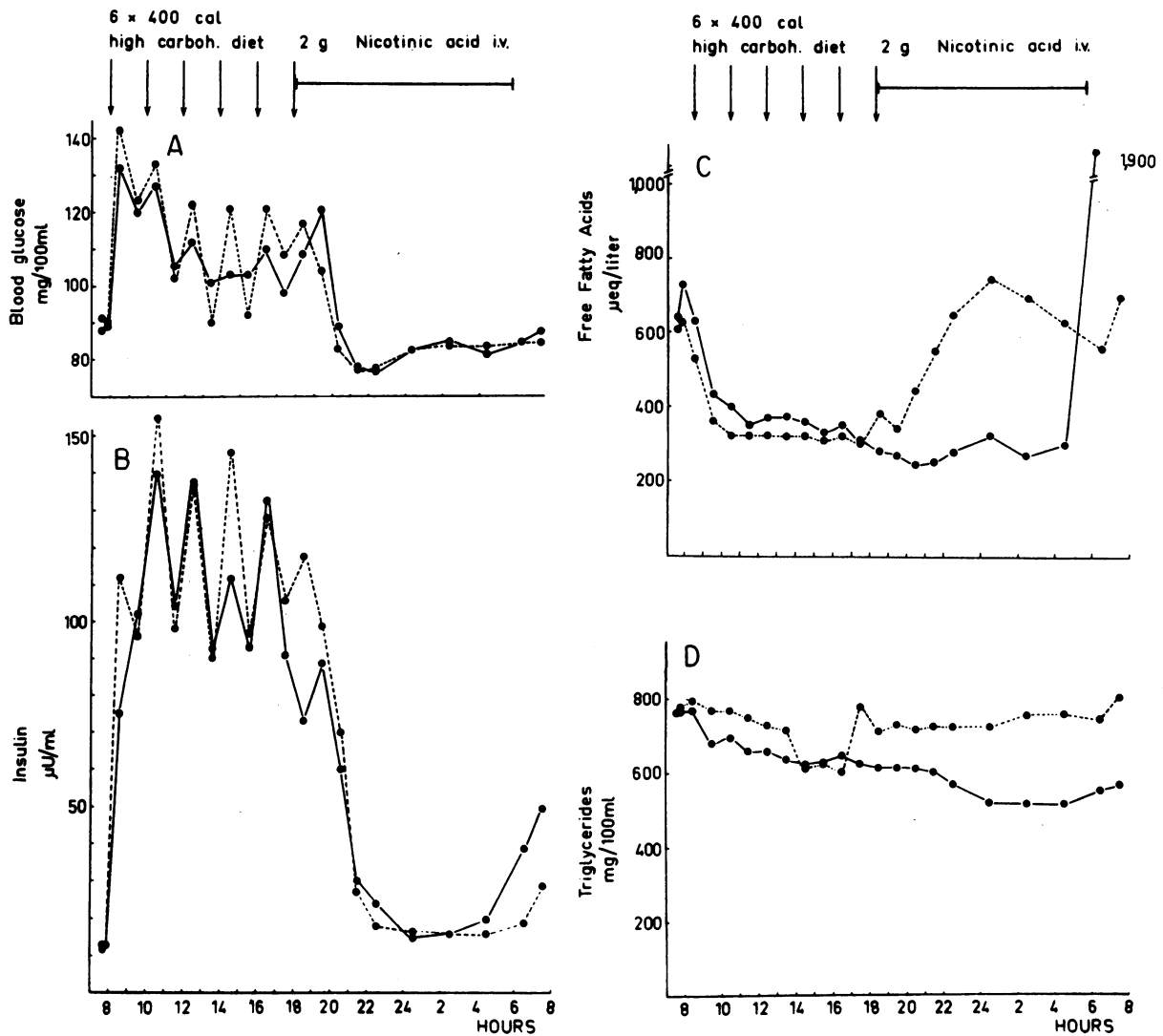


FIGURE 5 Mean 24-h blood, insulin, free fatty acid, and triglyceride profiles in patients with type IV hyperlipoproteinemia on high carbohydrate diet without (dotted lines) and with (solid lines) nocturnal infusion of nicotinic acid. Arrows denote intake of formula diet.

marked rebound rise of free fatty acids measured as early as 30 min after the end of the infusion.

In the patients fasting free fatty acid levels were not different from those of normals, but diurnal levels were significantly higher (0.1% level) indicating less efficient suppression of lipolysis by carbohydrate feeding or decreased free fatty acid removal.

Diurnal triglycerides. In normal subjects plasma triglyceride profiles during the day with high carbohydrate feeding showed little change and were similar in all studies. At night, in the control experiments, there was a considerable rise of plasma triglyceride levels which resulted in doubling of the values from evening to morn-

ing and was related to the rise of free fatty acid levels which occurred during that time (12). When free fatty acids were kept low during the night by administration of additional glucose, the rise of triglycerides appeared to be mitigated, although this impression is not substantiated by statistical analysis. It is nevertheless surprising that a combination of conditions, which are generally thought to result in increased plasma triglyceride levels, i.e. hypercaloric intake (18), glucose feeding (19), and high insulin levels (20), did not result in higher triglycerides in the glucose as compared with the control experiments. Our results are thus in agreement with those of Barter et al. (7) who, by administra-

tion of insulin at night, observed slightly lower triglyceride levels on a sucrose diet as compared with control studies. They tend to confirm previous findings (21, 22) that infusion of insulin actually slightly lowers triglyceride levels during the course of several hours.

When free fatty acids were suppressed by infusion of nicotinic acid at night, plasma triglycerides stayed significantly lower for the period of the infusion and only started to rise when the infusion was terminated. Carbohydrate induction in normals was thus inhibited by nicotinic acid.

Hyperlipemic subjects. In patients of the glucose group, as in normals, the nocturnal rise of plasma triglycerides appeared to be mitigated by additional glucose administration in spite of an even higher total calorie level for 24 h (3,840 cal). If there is increased production of triglycerides by hyperinsulinemia as suggested by Reaven, Lerner, Stern, and Farquhar (20), this effect either requires more time, or removal must have been accelerated in excess of production to give a net change as observed.

In the nicotinic acid group which started from a rather high mean level of above 700 mg/100 ml, there was a slight fall of plasma triglyceride during the day in both control and nicotinic acid study and a slight rise during the night in the former. Infusion of nicotinic acid resulted in further lowering of plasma triglycerides and, at the end of the experiment, in a difference between mean values of control and drug studies of more than 200 mg/100 ml. The difference from the starting level was thus greater than 25%. The mechanism of triglyceride lowering appears to be related to inhibition of lipolysis, although increased removal by activation of lipoprotein lipase cannot be excluded (23).

When the first and last triglyceride levels (0800 h and 0730 h of the following day) of the control experiments in both patient groups are compared (Fig. 3 and Fig. 5), there was within 24 h no significant carbohydrate induction of triglyceridemia in the patients, quite contrary to the observation in normals, who, within 24 h, doubled their triglyceride levels on the identical dietary regimen. One of several possible explanations for these findings might be that, whatever mechanisms were responsible for carbohydrate induction of triglyceridemia in the patients have already been operating on their usual diets before entrance into the study. The absence in patients with endogenous hypertriglyceridemia of the normal biphasic response of 24-h triglyceride levels to high carbohydrate feeding has been previously reported by our group (6).

There appear to emerge at least two sets of conclusions from the studies described. The first would be that, with frequent sampling of blood and lipid determinations under conditions of feeding and fasting during 24 h,

there is no evidence that elevation of plasma glucose and insulin levels, either in normals or in type IV patients, results in increased plasma triglyceride levels. The second conclusion is that dietary and drug management of hypertriglyceridemia (type IV hyperlipoproteinemia), in view of the strong correlation of free fatty acid and plasma triglyceride levels (24, 25), should aim at maintained lowering of the free fatty acid fraction. Although our studies were performed with diets of rather unusual and extreme makeup, a basically similar diurnal free fatty acid pattern appears to prevail with formula diets of ordinary (20% protein, 37% fat, 43% carbohydrate) composition (26) in that highest levels are found at night. If, for drug treatment of these disorders, substances are used, the mode of action of which appears to be related to inhibition of lipolysis, it may be useful to find a way for their administration at night, when lipolysis appears to be most active.

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