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Metabolic Observations during the Treatment of Obese Patients by Periods of Total Starvation

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Ten very obese female patients were treated by periods of total starvation lasting 10 days each. In the interval between these starvation periods, a diet of 600 calories was given. Twenty-one periods were completed, 6 patients went through 3 periods each. The fasting was generally well tolerated; with the appearance of ketone bodies in the urine the feeling of hunger diminished. The average weight loss during total starvation was 447 Gm./day ranging from 290 to 600 Gm. Nitrogen excretion was on the average 4.15 Gm./day (2.6–7.2). There was no significant decrease in BMR neither a lowering of body temperature. During the third starvation period weight loss was less than during the other two, but the BMR did not decrease. There were no changes in serum electrolytes, HCO_3–, pH, urea, creatinine or serum proteins. The excretion of 17-OHCS dropped significantly but remained within the normal range. The excretion of 17-KS dropped to subnormal values. Plasma FFA were elevated at the start of the experiment. Generally there was some rise from the first to the seventh day of the starvation periods. In the patients who completed 3 periods the FFA values were lower during the third than during the first period. Serum cholesterol, total fat and phospholipids did not show significant changes. The blood sugar values showed some decrease during starvation which was statistically not significant. The implications of these findings are discussed. We are of the opinion that our patients did not exhibit signs of a disturbance in fat mobilization.

IN 1959 Bloom[1] introduced periods of total fasting of 4–9 days as an effective means of a reducing scheme in obese patients. Recently, Duncan[2,3] et al. reported on a large number of obese patients treated in the same way for periods of 4–14 days. Since 1962 we have used this method for the treatment of 10 very obese female patients who previously had failed to respond to other forms of therapy. In total, 22 starvation periods of 10 days each were completed. Only 1 patient abandoned the fast. During the fasting periods several metabolic observations have been made which will be described below.

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Materials and Methods

The age of the patients varied between 18 and 52 years. Before admission the scope and purpose of the treatment and of the investigation were explained to each patient in order to insure their willingness to cooperate. After hospitalization the patients were placed on a 600 calory diet for a period of 7 to 21 days. During this period routine studies were done to exclude complicating diseases.

In 2 patients who were suspected of having Cushing's syndrome, detailed endocrinological studies were performed.

In the fasting periods, in this article also called periods of total starvation, only water, tea and coffee without milk or sugar were allowed. Vitamin preparations were prescribed. During the initial period anorexigenic drugs were given to alleviate sensations of hunger. This medication could generally be stopped after the first 3 or 4 days of the starvation regimen. Physical activity was not restricted. During the intervals between the starvation periods the patients were given a 600 calory diet which consisted of 53 Gm. carbohydrate, 65 Gm. protein and 15 Gm. fat.

In 3 patients in whom a nitrogen balance was performed during feeding periods, a standard diet of Metrecal (Mead Johnson) 600 cal. daily was also used. For study of protein loss stool collections were made. To delineate the start and the end of the collection periods the patients were given charcoal, respectively, carmine markers. During the periods of study daily 24-hour urine specimens were collected also. Both stools and urine were analyzed for nitrogen with Kjeldhal's method.

BMR was estimated by the diaferometric method of Noyons.

One Gm. barbital was administered orally to the patients 1 hour prior to the determination.

Determinations of cholesterol were performed by a modification of the method of Zlatkis and Zak;[4] phospholipids were measured by the method of Connerty et al.;[5] total fat determinations were carried out by performance of a gravimetric method;[6] serum was deproteinated with alcohol 96 per cent, the filtrate evaporated and then extracted with petroleum-ether, the residue was then weighed. FF9 were determined according to the method of Dole, as modified by Dole and Meinertz;[7] titrations were carried out with thymol blue as indicator.

Glucose and urea values were measured with the autoanalyzer. Sodium, potassium, chloride, HCO_3, creatinine and serum proteins were determined by current methods of our routine laboratory. Acetone in urine was determined by using Acetest reagent tablets (Ames Company of Miles Lab. Ltd., England); acetyl-acetic acid in urine by the method of Gerhardt. Serum pH measurements were carried out by the micromethod of Astrup.[8] Urinary excretion of total 17-OHCS was determined by the method of Norymberski;[9] 17-KS by a modification of the Drekter method.[10]

Results and Discussion

I. *Weight Reduction, Protein Loss and Calory Requirement*

The periods of total starvation were well tolerated by all patients, except 1 who abandoned the treatment.

Complaints during the total fast consisted of headache, lightheadedness and a slight feeling of weakness. Hunger was felt mainly in the first 3 to 4 days and could be alleviated by 5 mg. dextroamphetamine thrice daily; with the development of ketonuria hunger disappeared. Ketonuria increased each day and at last acetyl-acetic acid was found also.

Figure 1 shows the weight reduction in our patients.

During the initial period, especially on the first days after admission most of the patients showed a considerable loss of weight on a diet of 600 calo-

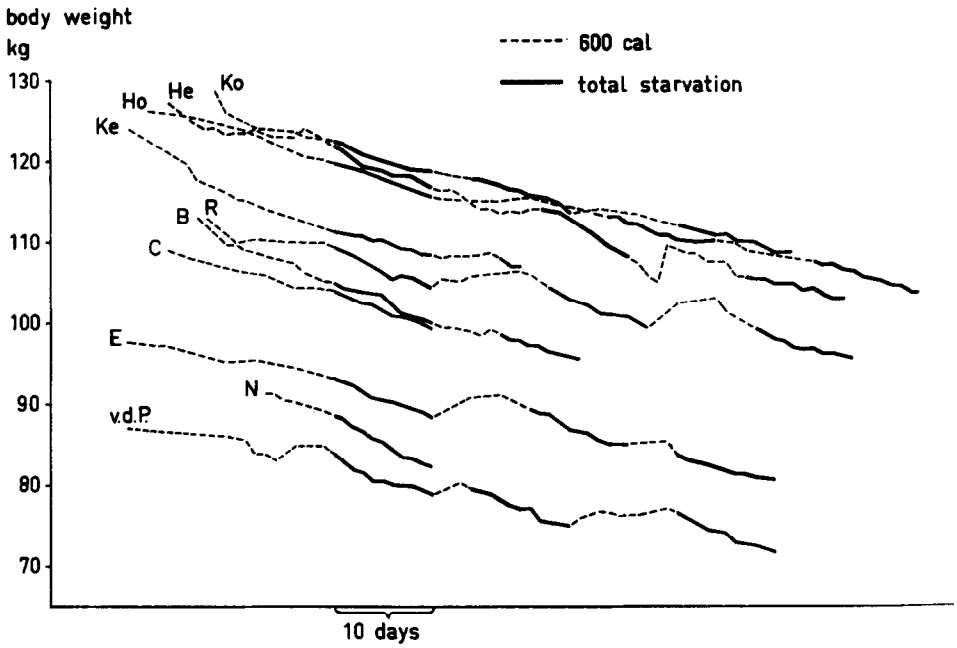

Fig. 1.—Weight reduction in 10 obese female patients. The thick lines represent the weight loss during total fasting, weight loss in the 600 caloric periods is given in dotted lines.

ries. In 5 patients the weight reduction was even greater than during the starvation periods which followed. On the other hand, during the periods between those of total starvation the 600 calory diet produced a weight gain in nearly all patients. These facts demonstrate clearly the role fluid retention and fluid loss are playing in such experiments. (Newburg[11] has shown that the ability of obese patients to maintain weight on a low calory diet is due to fluid retention). During total starvation the average weight loss amounted to 447 Gm./24 hours with a range of 290 to 600 Gm.

Undoubtedly, this weight reduction was partly caused by loss of body fluid. Nevertheless, it is interesting to compare the results of the 3 periods in the 6 patients who completed 3 courses of total starvation (table 1).

It appears that generally the weight reduction was less in the third period than in the first. The difference is significant ($p < 0.05$ Wilcoxon two sample test).

Daily nitrogen excretion in urine and feces during the starvation periods was on the average 4.15 Gm. (2.6–7.2). The mean protein loss was calculated from these figures to be 26 Gm. daily (range 16.2–45 Gm.). The nitrogen balance in the 600 calory periods has been calculated in 3 patients.

In 1 patient (pat. N.) a negative balance was found (N-intake 44.6 Gm., N-output 59.7 Gm. in 6 days), in the other two there was a positive balance: pat. B. (N-intake 52 Gm., N-output 46.8 Gm. in 7 days) and pat. K. (N-intake 80.1 Gm., N-output 50.7 Gm. in 11 days).

Table 1.—*Mean Weight Loss (Gm./24 hr.) of 6 Obese Patients*

Case No. plus Initials	Starvation Periods			Mean of 3 Periods
	I	II	III	
1. Ko.	430	480	300	413
2. Ho.	450	270	310	343
3. R.	550	620	340	503
4. E.	440	430	280	383
5. He.	570	750	270	530
6. v.d.P.	590	510	550	550

The nitrogen loss was not greater during the last than during the first starvation period.

BMR values, determined on the first and seventh day of starvation and just before feeding was resumed, are shown in table 2. There is no consistent tendency of the BMR during each period (sign test). The rather low RQ values indicate a relatively high fat metabolism. The BMR is in the range to be expected in obese patients.[12] In some instances the BMR decreased somewhat during starvation. Theoretically this must be expected as body surface diminishes, but this would be of no practical importance in our patients. There is no indication of increased body economy by lowering basal caloric consumption, neither was there a decrease in body temperature as is seen in patients with severe emaciation, e.g., anorexia nervosa.

During total starvation our patients had to live on protein breakdown and on energy derived from depot fat. The carbohydrate stores of the body are so small that they can be neglected. The rather low RQ values found in our patients (table 2) are in good agreement with this theory.

Calculation of the daily calory requirement should be possible from weight reduction and protein loss if fluid equilibrium could be assumed. This is clearly not the case for short periods like the starvation periods (see fig. 1).

If, however, the whole time from the first day of the first starvation period until the last day of the last period is taken (27–60 days), it can be assumed that there is no undue loss or gain of body fluid, at least not to an extent which would influence our calculation.

In the following calculation the water content of "fat tissue" is taken to be 20 per cent, of "protein tissue" 70 per cent; 1 Kg. of "fat tissue" therefore yields 7,200 calories, 1 Kg. of "protein tissue" 1,200 calories. The daily calory requirement is then found by the formula:

$$\text{Cal. Req.} = \frac{7.2\ A - 6\ ap + 600\ b}{a + b}, \text{ in which}$$

A = total weight loss
a = days 0 cal.
b = days 600 cal.
p = protein loss per day in Gm.

The specific dynamic action during the feeding periods is neglected. The calculation could be done for 7 of our patients. We found an average of 2,125 calories per day with a range from 1,647 to 2,449 calories.

Table 2.—*BMR and RQ Values in 9 Obese Patients during Treatment with Total Starvation (Determined on the First, Seventh and Eleventh Day just before Feeding was Resumed)*

Case No. plus Initials	Starvation Period	BMR	RQ	Case No. plus Initials	Starvation Period	BMR	RQ
		2,093	—			1,588	0.77
	I	1,699	0.73		I	1,388	0.73
		1,602	0.80			1,562	0.74
		1,577	—			1,536	0.75
1. Ko.	II	1,488	0.70	5. He.	II	1,478	0.82
		1,627	0.70			1,361	0.77
		1,588	—			1,764	—
	III	1,446	0.77		III	1,676	0.74
		1,809	—			1,714	—
	I	1,627	0.76			1,932	0.89
					I	1,606	—
		1,636	0.71			1,378	0.81
2. Ho.	II	1,814	0.79				
		1,454	0.86			1,470	0.76
				6. v.d.P.	II	1,616	0.80
		1,638	0.74			1,510	—
	III	1,651	0.78				
		1,657	—			1,486	0.74
					III	1,071	0.77
		1,701	0.73			1,356	0.77
	I	1,508	0.72				
		1,779	—			1,454	0.71
				7. C.	I	1,520	0.80
		1,638	0.73			1,739	0.75
3. R.	II	1,725	—				
		1,355	0.72			1,645	0.74
		1,455	0.76	8. N.	I	1,588	—
	III	1,172	0.86			1,487	0.74
		1,570	0.76				
						1,645	0.74
		1,588	—	9. B.	I	1,606	0.76
	I	1,462	0.70			1,452	0.82
		1,478	0.73				
		1,371	0.89				
4. E.	II	1,420	0.76				
		1,468	0.83				
		1,631	0.81				
	III	1,388	0.76				
		1,554	0.76				

From these data and the mean BMR, the amount of energy used for daily activities can be approximated (table 3). In patient E. the result is peculiarly low. The only explanation we can think of are dietary indiscretions which escaped notice. This girl had in fact an exceptionally great increase in weight during one of the 600 calory periods. The other patients needed between 468 and 881 calories for their daily activities in the hospital ward. These

Table 3.—*Calculated Data for Caloric Requirement of 7 Obese Patients during a Starvation Regimen. Figures for Physical Activity were Obtained by Subtraction of the Mean BMR Values*

Case No. plus Initials	Calc. Cal. Req./Day Calories	BMR (Mean of 9 Determ.) Calories	Phys. Act./Day Calories
1. Ko.	2,233	1,659	574
2. Ho.	2,130	1,639	491
3. R.	2,046	1,545	541
4. E.	1,647	1,484	163
5. He.	2,423	1,563	784
6. v.d.P.	1,960	1,492	468
7. B.	2,449	1,568	881

values are higher than those estimated by Lusk,[13] but seem to be reasonable in view of the fact that our patients participated in activities as walking, dish washing, etc., in the ward. There is a remarkable difference between our findings and those of Bloom[1] and Duncan.[2,3] These authors report that the weight loss of their fasting patients amounted to more than 1 Kg. daily on the average. The maximum we have seen during one of the fasting periods was 750 Gm. Even if excessive fluid loss is taken into consideration this difference is difficult to explain. The physical activity of their patients appeared to be of the same order as of our patients as far as can be judged from the reports. Bloom states that the weight loss exceeded that which could be explained by caloric energy expenditure and urinary water loss. The findings of Bloom and Duncan that the feeling of hunger disappears when ketonuria develops is corroborated by this study.

Adaptation to undernutrition in normal persons has been extensively dealt with by Keys.[14] He found a marked reduction of the BMR; in the Minnesota Experiment the total rate of basal metabolism at the end of semistarvation was 40 per cent less than in the control period. Keys reported a small decrease in body temperature. If decrease in BMR and lowering of body temperature are taken as objective signs of real starvation, it appears that our patients were not really "starved" and probably had free access to their depots of body fat.

II. *Electrolytes, HCO_3^- pH Urea, Creatinine and Serum Proteins*

Serum values were determined on the first, seventh day and at the end of total starvation. Apart from a slight decrease of the HCO_3^- no changes in electrolyte values were seen. The pH remained on a normal level and varied between 7^{53} and 7^{32}. Urea and creatinine values were always normal. The serum proteins also remained constant. This could be expected as the nitrogen loss of our patients was not considerable; only in patients wth severe emaciation serum proteins appear to be decreased as is known from famine victims and patients with debilitating diseases.

III. *Steroid Excretion*

Elevation of the excretion of 17-KS and 17-OHCS in obesity and return to normal values after weight reduction has been shown by several authors.[15-17]

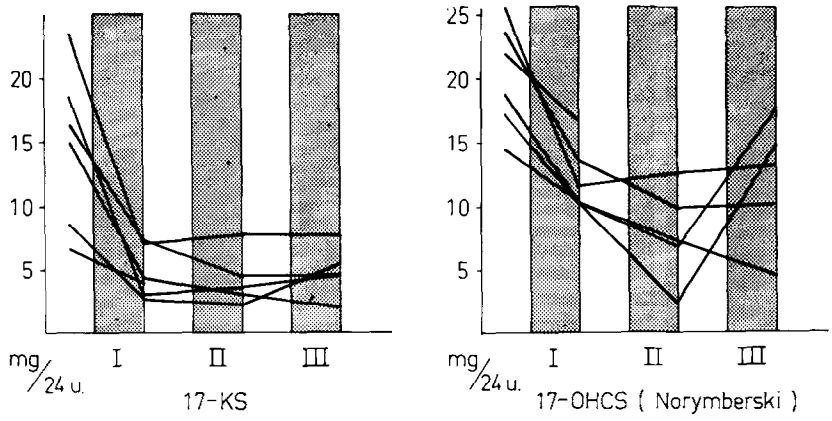

Fig. 2.—(Left) Excretion of 17-KS in 6 obese female patients during 3 periods of total starvation.

Fig. 3.—(Right) Excretion of 17-OHCS in 6 obese female patients during 3 periods of total starvation.

The same trend has been observed by De Waard and Schwarz[18] for adrenal estrogens. Recently, Migeon et al.[19] reported on an elevated cortisol production rate in obesity.

In our study 17-KS and 17-OHCS excretions were high in 1 patient (v.d.P.), normal in the others. In all patients during the period of treatment the values dropped rather uniformly (fig. 2 and 3). It is noteworthy that the 17-OHCS excretion stayed within the normal range, while 17-KS dropped to definitely low values.

In the case of patient v.d.P., a girl of 18 who was initially suspected of having Cushings syndrome, not only the steroid values decreased, but the GITT which showed a pathologic curve returned to normal during the starvation period.

Nine patients had normal menstrual cycles, 1 (pat. E.) had secondary amenorrhea for half a year prior to admission. This amenorrhea still persists.

IV. *Serum Lipids and Blood Sugar*

The course of the FFA concentration in the plasma during the time of observation is shown in figure 4.

In all except 2 patients the FFA level was above the normal range at the start of the first starvation period. Generally the FFA were less elevated during the third starvation period than during the first.

The mean FFA values on the seventh day of total starvation are significantly higher than those on the first day ($0.01 < p < 0.02$ Students t test $t = 3.19$) (fig. 5). But as can be seen in figure 4, analyses of the curves of the individual patient show no general trend. In some patients there is a definite rise from the first to the seventh day of starvation followed by a decline towards the end of the period. The blood sugar values showed some decline from the first to the seventh day but the difference is not significant.

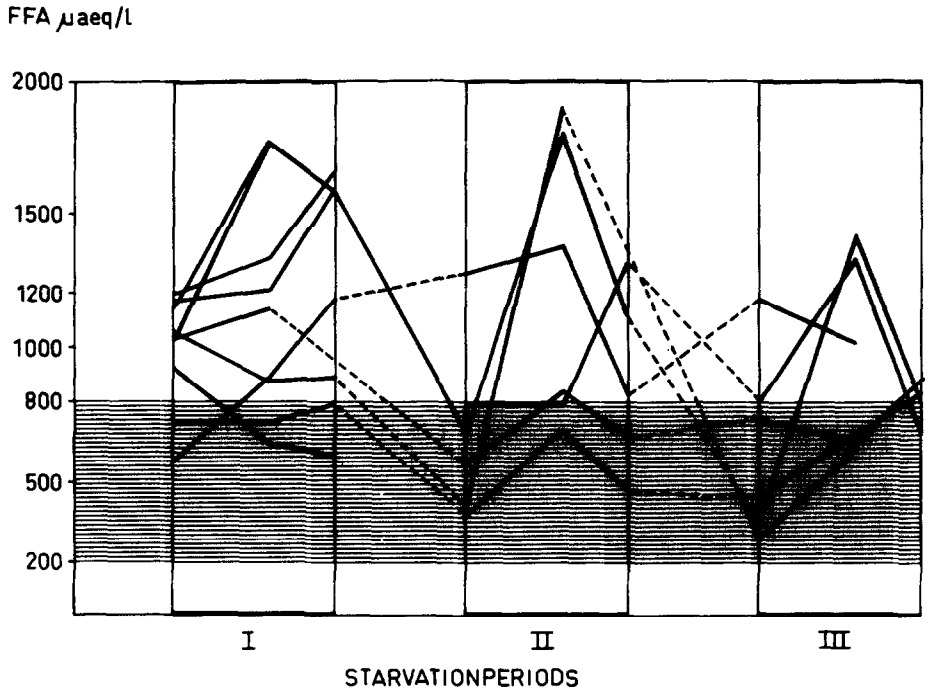

Fig. 4.—Course of plasma FFA concentration in the individual patient during the treatment. The striated area represents the range of FFA levels determined in venous blood of normal subjects after an overnight fast.

It must be kept in mind that the fasting first day values reported, were obtained from patients who had been on a semi-starvation diet (600 cal.) for a prolonged period. The fact that elevated FFA and cholesterol values were found is therefore not surprising.

The mean cholesterol values did not show an increase during the starvation periods, they were all above the normal range. Neither did determinations of total fat and phospholipids reveal any changes, these values remained within the normal range.

Analysis of the response of the individual patient showed no correlation between FFA changes and those of the other serum lipid fractions.

General Comment

Obesity is obviously caused by an imbalance between calory intake and calory expenditure. The reason for this imbalance has been sought either in a disturbance of appetite regulating mechanisms or in a metabolic disturbance causing an impaired mobilization of body fat. In this study we are not concerned with the first possibility, but want to discuss the theory about a fault in fat mobilization.

If obese individuals have difficulties in deriving energy from their stores of adipose tissue, this must necessarily show up during periods of prolonged fasting like those to which our patients have been submitted. They would

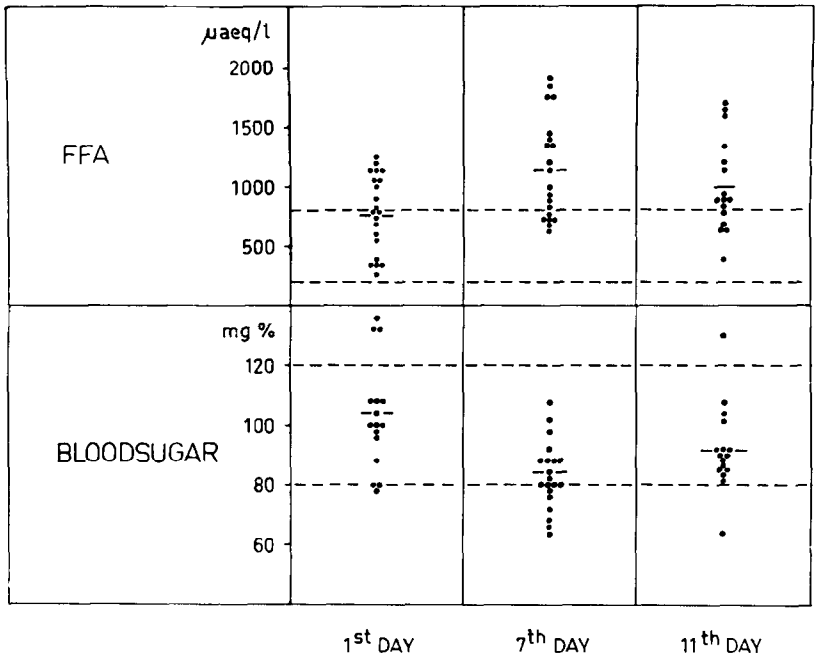

Fig. 5.—FFA and blood sugar levels in 10 obese patients during treatment with starvation periods, all periods taken together. The last blood sample is taken just before resumption of feeding. The horizontal bars indicate the mean value, broken lines indicate the normal range.

either be forced to break down large quantities of body protein, or to economize sharply in caloric expenditure.

In the patients presented herein the nitrogen excretion remained low during the whole period of study, indicating that no appreciable amount of energy was derived from protein breakdown, neither was there an increase in nitrogen excretion from the first to the third of the starvation periods. Keys has shown, that normal persons who were placed on a semi-starvation diet for a long time exhibited a marked decrease in BMR together with a lowering of body temperature. The same reaction is well known in the clinical picture of anorexia nervosa. This would, in our opinion, represent the real signs of starvation, caused by depletion of body stores and the urgent need of body economy. In our patients, however, there was no significant decrease of the BMR and no lowering of body temperature was noted. Although some patients complained of a feeling of weakness, muscular strength was not impaired. One of the patients was suffering from secondary amenorrhea for several months, in the others the menstrual cycles continued undisturbed. These facts indicate that during the time when feeding was insignificant or insufficient, our patients had free access to their fat stores and thereby could satisfy their metabolic needs.

Arguments in favor of a deficient fat mobilization have been given by several authors. Dole[20] and Gordon[21] found elevated FFA levels in the

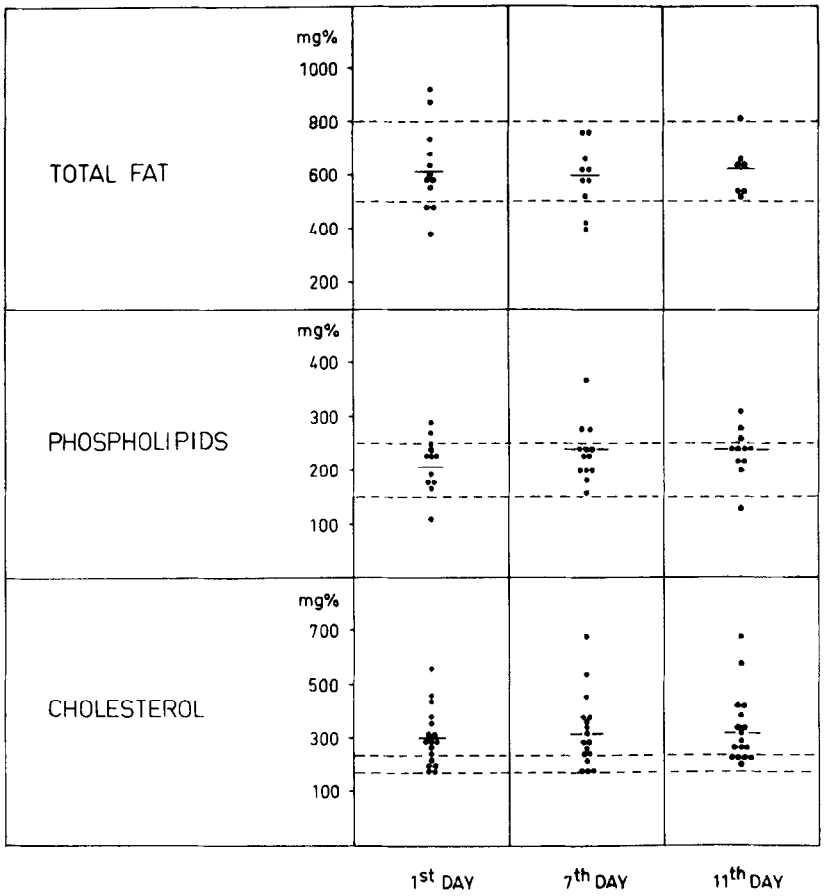

Fig. 6.—Levels of total fat, phospholipids and cholesterol in venous blood of 10 obese patients during treatment with starvation periods, all periods taken together.

plasma of obese persons, but the increase in FFA during short-term fasting was less in the obese than in the normal.[21] In our study we also found high FFA levels at the start of the experiment.

It must be remembered, however, that our patients had been on a very low caloric diet for some time before the first determinaton was done. Armstrong et al.[22] have shown in dogs that changes in FFA uptake by the tissues are simple mass action effects of plasma FFA concentration. If this can be applied to man, it would be reasonable to expect that an individual would adapt his plasma FFA level in such a way that the metabolic needs of the tissues can be met. This means that in an obese patient on a reducing diet high values will be found. The findings in our patients can be explained in this way. Unfortunately, Dole and Gordon give no information about the diet used by their obese patients during the time before the FFA determinations. On fasting the increase in plasma FFA would have to be only sufficient to compensate for the amount of calories omitted. In our patients in whom this difference was only 600 calories no big rise could be expected.

We found some increase between the first and the seventh day of starvation but on the average it was barely significant.

Opie et al.[23] calculated the absolute amount of FFA mobilization from the plasma levels and found that per Kg. of adipose tissue less was mobilized in the obese than in the normal. If there is a regulation of FFA release depending on the energy requirements of the moment there is no reason why the obese should release per Kg. of adipose tissue as much as the normal. Figure 4 shows that during the first starvation period of our patients plasma FFA levels were on the average higher during the third period, when weight loss was also less (table 1). Probably the patients decreased their physical activity during this period to some extent. The question, however, whether this difference in FFA levels was due only to a decrease in metabolic needs or was caused by some adaptation of tissue metabolism, facilitating FFA oxidation, cannot be answered at the moment and will be the subject of further investigation.

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