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BLOOD KETONES AND SERUM LIPIDS IN STARVATION AND WATER DEPRIVATION^{1,2,3}

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Few observations of the behavior of serum lipids in acute human starvation have been reported and no studies using present improved analytical methods are available. The occasional published reports of changes in serum lipids in fasting experimental animals are often contradictory (1 to 9). Increases in the blood ketone bodies during starvation are well recognized (10 to 15), but have never been systematically related to serum lipid changes.

In this study, serum lipids and blood ketones were determined simultaneously in 14 fasting normal male human subjects, some of whom were also deprived of water. These have been supplemented with experiments on fasting mon-

keys and dogs. Some effects of feeding carbohydrate or fish to otherwise fasting subjects have also been included.

EXPERIMENTAL PROCEDURE

Fourteen normal adult male subjects were starved for periods of 2 to 6 days. Three of them, Yale medical students, were subjected only to a 2-day fast and were allowed water or black coffee *ad libitum*. The other 11 volunteers, members of the Army of the United States, were subjected to water restriction or deprivation. Some of them were subjects of carbohydrate and of fish feeding experiments as well. The organization of these experiments has been described in detail in an accompanying paper (16), and is summarized in Table I of that paper. Serum proteins were not determined in the medical students and serum lipids were not determined in the subjects eating fish. Intravenous glucose tolerance tests (17) with simultaneous blood ketone determinations were made at the end of 8 starvation periods in Experiments II and III and blood ketones were repeated in 3 of them after 24 hours of carbohydrate ingestion. After 2 periods of fasting, blood ketones were determined before and after 24 hours of sugar eating. Intravenous glucose tolerance tests were also carried out at the end of 4 experiments with fish feeding.

Four male *rhesus* monkeys (*macaca mulatta*) and 7 dogs were studied. The monkeys were starved for 3 to 6 days, the dogs for longer periods. All animals, with the exception of 2 dogs, were permitted to drink water *ad libitum*. In other experiments, the monkeys were allowed to eat varying amounts of sugar for 3 to 8 days.

CHEMICAL METHODS

Serum separated from clotted venous blood drawn under oil was used for all lipid analyses, while oxalated whole blood was used for the ketone determinations. In Experiment I, most of the analyses were carried out on blood or serum which had been transported for about 24 hours in special cooled containers. This procedure was justified by control experiments in which determinations of serum lipids and blood ketones in blood samples precipitated immediately were compared with those in blood samples precipitated after 48 hours of refrigeration. No significant change was found. The extra manipulations and transportation prevented duplicate analyses in a few instances and may have been responsible for some inconsistencies in the data of Experiment I.

¹ Lt. Col. D. B. Dill, Q. M. C., A. U. S., was responsible for the inception of this work and guided it through its initial stages. Capt. J. M. Quashnock, M. C., A. U. S., assisted in the management of the experiments and in the analysis of the data, as well as serving as a volunteer subject. Capt. Wilson, A. C., A. U. S., Lt. Holmes, Sn. C., A. U. S., Lt. Chovnick, A. C., A. U. S., Sgts. Tressler and Roberts, and Pvts. Perzanowski, Leyzorek, and McHugh, all of the A. C., A. U. S., served as volunteer subjects. We are indebted to Dr. T. S. Danowski, Dr. A. J. Eisenman, Dr. J. R. Elkinton, and Dr. E. A. H. Sims of the Department of Internal Medicine of Yale University School of Medicine, for their cooperation and help. Sugar and protein analyses were done by members of the laboratory staffs at Wright Field and at Yale. Miss Barbara Russell of the Yale University School of Nursing and Dr. S. C. Harvey of the Department of Surgery provided proper facilities for the care of the subjects. The work was carried out in connection with an Army Air Corps Contract.

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Serum lipids, proteins, and blood sugars were determined by methods previously described (17 to 23). Neutral fat concentration was calculated by the formula of Peters and Man (24). The values for neutral fat calculated in this way are less accurate than are the values for the other lipid fractions, since the calculation introduces cumulative errors from 3 chemical methods and from variations in composition of phospholipids. Nevertheless, in each of 3 normal males, the greatest individual deviation from the average neutral fat of that individual was only ± 0.8 m.eq. per liter (24, 25). Whole blood ketones were determined by the method of Weichselbaum and Somogyi (26), with a combination of the procedures used in deproteinization and desaccharification. Results are expressed as mgm. per cent of acetone. At concentrations below 1 mgm. per cent, the proportion of known amounts of acetone recovered from blood was considerably less than that reported by the original authors. This is not a serious practical difficulty, however, since in this range a large percentage error represents only a small absolute one. At higher concentrations, the proportion recovered was similar to that reported by Weichselbaum and Somogyi (26). Nitrogen, water, and electrolyte balances were also measured in the military subjects and are reported elsewhere (16).

RESULTS

A. Normal human subjects

The data from all fasting normal subjects are contained in Table I. Subject T was atypical throughout, in that his carbohydrate tolerance, urinary nitrogen excretion, blood ketones, and serum lipids were little affected by starvation. Subjects D and H drank large amounts of dilute salt water on the fifth day of Experiment I, thereby certainly affecting the concentration of serum lipids at the close of the period. Data from all experiments with T and from these experiments with D and H are therefore considered separately, and the general statements made below concerning the results do not apply to them. In analyzing the data concerning lipids and proteins of serum, each change is referred to the initial concentration in the blood of the individual in the experiment under consideration.

Total cholesterol increased progressively in starvation. At the end of 2 days, the average rise did not usually exceed the average variation observed in normal subjects, ± 13 mgm. per cent (derivation of normal average variations of cholesterol and lipid phosphorus is given under Figure 1). After 3 to 6 days, however, it amounted to 36 ± 13 mgm. per cent, a highly significant increment. This is illustrated in

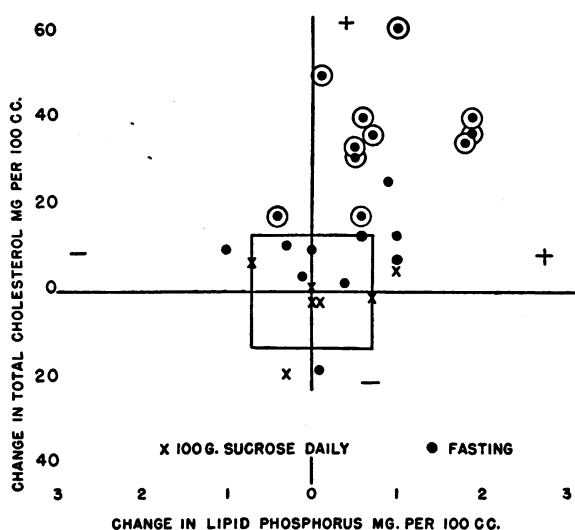


FIG. 1. THE RELATIONSHIP OF CHANGES IN SERUM TOTAL CHOLESTEROL TO THE CHANGES IN LIPID PHOSPHORUS

Dots represent the changes in fasting human subjects, crosses the changes in humans who ingested 100 grams of sugar daily. Circled dots denote values after 3 or more days of starvation. The square in the center denotes the average individual variation for the respective lipid fractions.

The probable error of the averages of duplicate total cholesterol determinations is 5.42 mgm. per cent (25). However, the variation in the individual from day to day is probably larger and would include the error of the method. In our own experimental work on 3 healthy male adults, in each subject, the average deviation from his average value did not exceed ± 13 mgm. per cent of serum total cholesterol (24, 25). Sperry (27), in 25 normal adults, found the variation of the individual from the average not to exceed ± 12.3 mgm. per cent, a value in close agreement with our value of ± 13 mgm. per cent.

In the same 3 normal males, the greatest average deviation from the average lipid phosphorus of any one individual was ± 0.7 mgm. per cent (24, 25). This includes the error of the method of ± 0.13 mgm. per cent (25).

Figure 1 in which the 11 observations after 3 or more days of starvation are distinguished by circled dots. In addition, it will be noted in this figure that cholesterol increased to some extent in all but 1 of 21 determinations, irrespective of the duration of starvation. The increase affected both free and esterified fractions of cholesterol. Although in the experiments of 3 or more days, the average increment of esterified cholesterol, 24 ± 11 mgm. per cent, is the greater, the average increase of free cholesterol, 13 ± 3.6

TABLE I
Serum lipids and blood ketones of human subjects

Subject	Days	Serum lipids					Ketones as acetone	Total proteins	Food***	Fluid****
		Cholesterol		Lipid phosphorus	Fatty acids					
		Total	Free		Total	Neutral fat				
		<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>	<i>m. eq. per 1000 cc.</i>	<i>m. eq. per 1000 cc.</i>	<i>mgm. per 100 cc. whole blood</i>	<i>grams per 100 cc. serum</i>		
Experiment I										
L	0	206	50	8.9	11.8	2.6	0.3	6.79		
	2	210	52	8.8	11.6	2.4	8.9	7.32	O	R
	5	219	63	9.5	11.6	2.0	13.9	7.53	O	R
F	0	147	43	8.5	7.1*	-0.5*	0.3	6.56		
	2	129	44	8.6	8.3*	1.1*	7.2**	6.90	O	R
	5	209	58	9.5	9.8	0.4	14.8	7.34	O	R
Q	0	185	49	8.7	10.5	1.9	0.4	7.01		
	2	203	67	9.3	9.6	0.7	0.3	7.40	O	O
	5	203	56	8.3	9.3	0.7	2.5	7.61	O	A. L.
D	0	172*	42	7.6	12.5*	4.7*	0.3	7.10		
	2	174	56	8.0	8.9	1.2	16.6**	7.49	O	R
	5	171	48	8.2	11.7	3.7	23.9**	7.30	O	D. S.
P	0	192	61	8.9	12.6	4.0	0.3	6.79		
	2	190	63	9.0	11.7	3.2	2.3	7.48	C	R
	5	193	47	8.9	10.8	1.9	3.0	7.41	C	R
R	0	141*	33	6.5	6.2*	-0.4*	0.3	6.38		
	2	140	46	7.2	8.0	1.4	2.5	7.03	C	R
	5	146	42	7.5	8.3	1.2	3.2	7.46	C	R
W	0	170	52	9.1	9.7	1.4	1.1	6.63		
	2	177*	47	8.4	9.7	1.5*	1.9	7.28	C	R
	5	151	40	8.8	8.6	0.6	3.0	7.10	C	R
H	0	215*	56	8.5	11.4*	2.3*	0.3	6.97		
	2	213	60	8.5	10.0	1.1	2.5	7.37	C	R
	5	165	47	7.6	8.1	0.6	3.4	6.70	C	D. S.
Experiment II										
A, Q	0	205	57	10.4	11.6	1.7	0.2	7.33		
	2						16.6		O	O
	3	246	76	11.0	15.8	4.9	15.5	8.09	O	O
	4						3.1		C	A. L.
B, Q	3						0.6		F, C	A. F. J.
A, C	0	163	46	8.5	9.3	1.3	1.1	6.38		
	2						12.6		O	O
	3	197	56	9.0	11.3	2.4	9.8	7.35	O	O
	4						3.2		C	A. L.
B, C	3						6.1		F	A. F. J.
A, H	0	218	55	8.7	9.9	0.6	0.3	6.99		
	3	255	67	9.4	12.7	2.4	13.9	7.74	O	O
	4						2.4		C	A. L.
B, H	3						7.8		F	A. F. J.

TABLE I—Continued

Subject	Days	Serum lipids					Ketones as acetone	Total proteins	Food***	Fluid****
		Cholesterol		Lipid phosphorus	Fatty acids					
		Total	Free		Total	Neutral fat				
		<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>	<i>m. eq. per 1000 cc.</i>	<i>m. eq. per 1000 cc.</i>	<i>mgm. per 100 cc. whole blood</i>	<i>grams per 100 cc. serum</i>		
Experiment II—Continued										
A, T	0 3 4	172 185	43 55	9.6 9.6	10.1 12.7	1.2 3.8	0.3 3.7 0.9	7.32 7.88	O	O
B, T	0 3	156 149	44 39	9.2 8.4	11.3 11.6	3.1 3.9	4.7	6.68 7.68	O	A. F. J.
A, R	0 3	117 168	32 49	7.9 8.0	8.1 14.3	1.3 6.6	0.2 20.8	6.28 6.93	O	O
B, R	0 3	141 173	39 46	7.8 8.3	8.8 11.9	1.7 3.1	37.4	6.22 6.85	O	0.6% NaCl
Experiment III										
H	0 2 4 5 6 7	213 223	52 55	8.2 8.2	10.8 11.2	1.8 2.1	0.3 17.6 4.5 3.9 2.9 5.0	7.12 7.31	O F F F C	R O O O O A. L.
C	0 2 4 5 6 7	195 203 230 232 236 202	52 55* 64 66 65 56	8.2 9.2* 10.0 10.1 10.1 9.1	9.4 10.9 11.6 12.2 12.6 11.3	1.0 1.7* 1.5 2.0 2.4 2.2	0.6 11.9 17.7 22.4 33.0 20.5	7.07 7.31 7.79 7.82 7.70 7.26	O O O O C	R O O O O A. L.
T	0 2 4 5	200 196 200 203	55 54 54 55	11.7 10.9 10.0 9.7*	15.7 13.3 14.2 14.1	5.2 3.3 4.6 4.6*	0.3 3.0 6.5 6.6	7.23 7.49 7.98 7.76	O O O	R O A. L.
M	0 2 4 5	189 199	47 48	10.4 9.4	13.3 13.0	3.6 3.6	0.3 9.0 11.1 25.8	7.11 7.20	O F O	R A. L. A. L.
Experiment IV (Students)										
B	0 2	211 224	50 63	8.8 9.8	11.6 15.6	2.3 6.4	0.4 29.6		O	A. L.
Bl	0 2	232 243	60 62	10.5 10.2	18.2 17.0	7.6 6.4	0.2 12.5		O	A. L.
F	0 1 2	163 189	48 60	6.7 7.6	7.8 10.5	0.9 2.8	0.3 3.9 13.7		O O	A. L.

* Single determination. All others average of duplicate determinations.

** Poor checks between duplicates.

*** In the food column, C stands for carbohydrate, F for fish in the previous period.

**** In the fluid column, R stands for restricted and A. L. for *ad libitum* water intake, D. S. for dilute seawater, and A. F. J. for artificial fish juice.

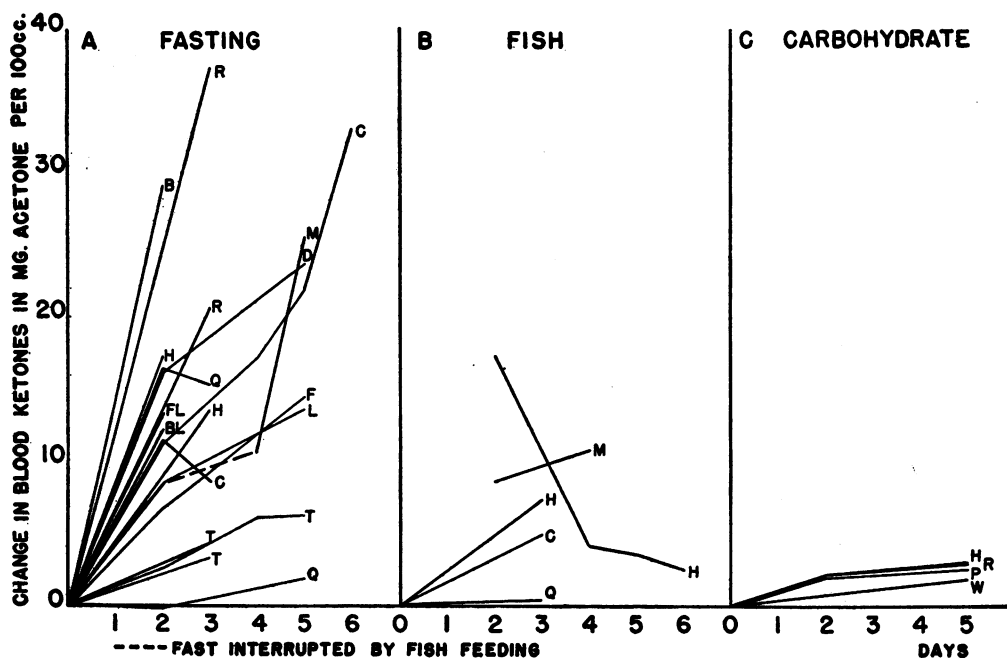


FIG. 2. BLOOD KETONE CHANGES IN HUMAN SUBJECTS

FIG. 2A. DURING STARVATION

The interrupted line indicates that the starvation was interrupted in one subject by feeding of fish for 2 days.

FIG. 2B. DURING FEEDING OF FISH

In the 2 instances in which there are no initial values, the subject has been fasted for 2 days prior to the feeding of fish.

FIG. 2C. DURING CARBOHYDRATE INGESTION

mgm. per cent, is relatively larger and more significant.⁴

Lipid phosphorus rose in all but 5 instances, exceeding the range of normal variability, ± 0.7 mgm. per cent, on 7 occasions (see Figure 1). The average increase after 3 or more days was 0.8 ± 0.7 mgm. per cent.

The average increase of total fatty acids was 1.5 ± 2.2 m. eq. per liter; for periods of 3 days or more, it was 2.5 ± 1.9 m. eq. per liter. Changes of neutral fat were quite irregular. In several instances, it decreased. Only at the 3-day interval was it consistently elevated. In all of 5 determinations at this interval, neutral fat was definitely above its initial concentration.

⁴ The normal average variation of free cholesterol has been calculated from Sperry's data (28). Free cholesterol was determined on 9 separate occasions in one subject and on 7 occasions in another. Some specimens were taken in the absorptive and others in the post-absorptive state. The average variation of one subject from his own average was 3 mgm. per cent, of the other 4 mgm. per cent.

Whole blood ketone bodies rose consistently and usually progressively during starvation (see Figure 2A). The average initial concentration in the 14 subjects was 0.4 mgm. per cent of acetone; after 2 days, it was 11.1 mgm. per cent. In most longer studies, it rose further from the second to the fifth day, reaching 37.4 mgm. per cent in Experiment II B-R after 3 days and 33.0 mgm. per cent in Experiment III C after 6 days. In no instance, however, did ketosis attain sufficient severity to produce a significant bicarbonate deficiency (16).

The degree of ketonemia varied from subject to subject and in different experiments on the same subject. There was no exact correlation between ketonemia and hyperlipemia. For example, the greatest ketonemia, 37.4 mgm. per cent, occurred in Experiment II B-R, in which cholesterol rose only 32 mgm. per cent; whereas a cholesterol increment of 41 mgm. per cent in Experiment II A-Q was associated with a blood

ketone of only 15.5 mgm. per cent. Nevertheless, a rough relation between the two functions is implicit in the fact that both rose progressively as starvation was prolonged.

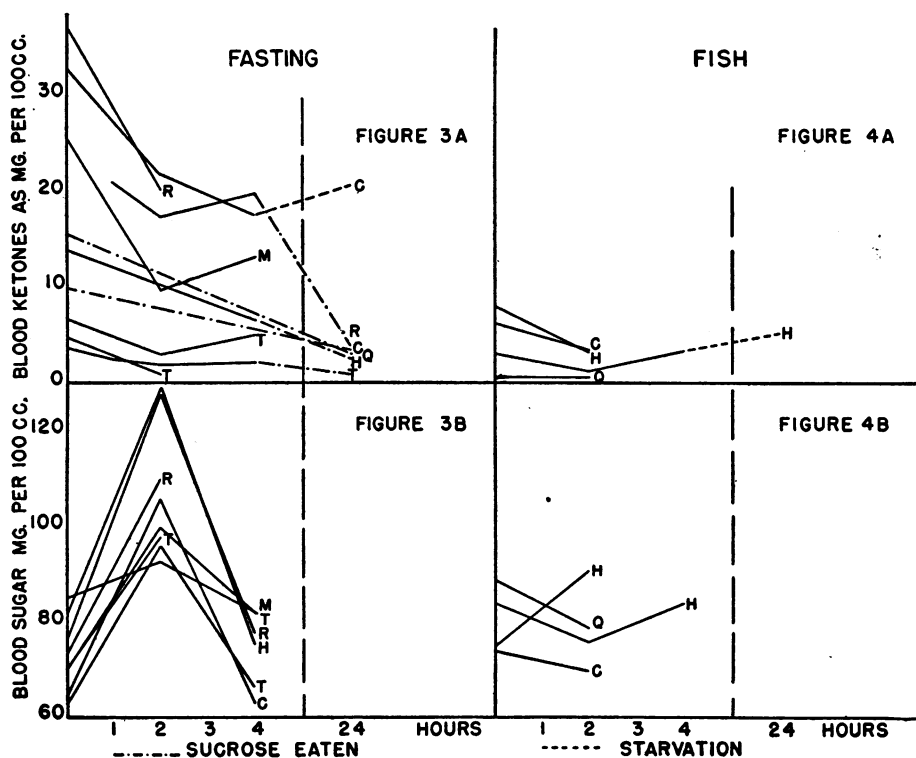
None of the lipid fractions of the serum, except the lipid phosphorus of R, rose definitely in the 4 experiments in which subjects took 100 grams of sucrose daily (Experiment I, P, R, W, and H). In these experiments, blood ketones did not exceed 3.4 mgm. per cent, even after 5 days without other food (Figure 2 C), although 2 of the same subjects, H and R exhibited considerable ketonemia and increases of serum total cholesterol on starvation.

The intravenous injection of 25 grams of glucose at the close of starvation regularly and rapidly reduced the ketonemia of subjects who

had starved or received fish (Figures 3A and 4A). Subsequent ingestion of carbohydrate during the remainder of the first 24 hours after starvation further depressed blood ketones, although they did not return to normal.

In 3 experiments in which fish was eaten for 3 days (Experiment II B-Q, C, and B), there was less ketonemia than in the comparable control experiments (II A-Q, C and H (see Figure 2B)). Of the 2 subjects who ate fish after a preliminary 2-day fast, only 1 (Experiment III-H) was able to eat considerable quantities. The ketones in this case diminished considerably, but did not return to normal.

Glucose tolerance of all subjects, except T, was distinctly low after 3 to 6 days of complete starvation, but was normal in subjects who had



FIGS. 3 AND 4. CHANGES IN (A) BLOOD KETONES AND (B) BLOOD SUGAR VALUES, DURING AND FOLLOWING INTRAVENOUS GLUCOSE AND FEEDING OF SUCROSE
 FIG. 3. FOLLOWING STARVATION

FIG. 4. FOLLOWING EXPERIMENTS IN WHICH FISH HAD BEEN EATEN

Solid lines indicate changes following the intravenous injection of 25 grams of glucose at zero time. Dash line extensions indicate continued starvation during the next 24 hours. Dot-dash lines refer to experiments in which 100 to 150 grams of sucrose were ingested at intervals during the period indicated.

eaten fish (Figures 3B and 4B). No blood sugar below 64 mgm. per cent was found in any subject, even after 5 or 6 days of fasting.

B. Experiments with monkeys

Data from these experiments are given in Table II. Fasting invariably provoked striking hyperlipemia and ketonemia. The serum lipids were elevated at the end of 2 days and rose further subsequently. Cholesterol was most af-

ected, increasing on the average 58 mgm. per cent, or 49 per cent of the initial value. The increment consisted chiefly of cholesterol esters; consequently, the ratio of free to total cholesterol fell. Lipid phosphorus rose proportionally less than cholesterol, an average of 2.4 mgm. per cent, or 30 per cent of the initial value. Neutral fat did not change consistently.

Blood ketones rose markedly, but to a variable extent, in all starved monkeys. The ketonemia

TABLE II
Serum lipids and blood ketones of monkeys

Monkey	Days	Serum lipids					Ketones as acetone	Total proteins	
		Cholesterol		Lipid phosphorus	Fatty acids				
		Total	Free		Total	Neutral fat			
		mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	m. eq. per 1000 cc.	m. eq. per 1000 cc.	mgm. per 100 cc. whole blood	grams per 100 cc. serum	
1545	0	105	24	7.8	7.8	1.4	1.1*	7.1	Control study, eating normally but in post-absorptive state After 84 hours without food
	3	155	30	10.7	10.7	0.8	12.9	7.7*	
2156	0	141	33	8.7	9.0	1.1		7.6	Control, eating normally, but in post-absorptive state
	5	134	30		8.9		0.9		
	0	157	45	8.8	9.0	1.0		7.2	After 2 days without food After 6 days without food
	2	181	46**		10.7		36.6*		
	6	225	51	9.9	10.6	2.3	46.9	7.4	
	0	132	25	8.4	6.9	-0.8	0.7		Control study, eating normally After 1 week of 15 grams of sucrose daily
	7	176	46	8.1	8.6	0.5	0.8		
	0	117	25	7.7	8.2	1.4	1.0*	6.2	Control, eating normally After 5 days of starvation
	5	220	45	10.4	13.2	2.6	58.8	7.1*	
	0	152	38	9.7	9.3	0.8	0.9*	6.6	Control, eating normally 15 grams sucrose daily for 4 days 40 grams sucrose daily for 4 days
4	197	46	10.5	10.2	0.5	5.2	7.3		
8	155	39	8.5	9.6	0.6	0.8	7.2		
0	145	31	8.5	9.7	1.8	1.3	6.4	Control 15 grams sucrose daily 40 grams sucrose for 4 days	
3	157	39	9.2	9.5	1.1	4.3	6.8		
7						1.2			
1739	0	113	30	8.4	7.3	0.3		6.6	Control, eating normally but in post-absorptive state After 2 days without food After 6 days without food
	0	119	29		6.9		0.8		
	0	119	32	7.2	6.5	0.1		6.7	
	2	172	40	10.7	9.5	-0.2	12.6	6.9	
	6	189	46	9.2	8.8	-0.3	9.7	6.4	
	0	124	29	7.5	6.6	-0.3	0.6		
	7	191	49	9.0	8.7	-0.2	1.4	6.6	
	0	162	40	9.2	8.7	0.2	0.7*	6.0	Control After 4 days 15 grams sucrose daily
	4	171	44	9.2	9.8	1.2	4.0	6.9	
	1567	0	144	32	8.9	9.5	0.9	1.6	7.3
0		134	39	9.1	9.2	1.3	1.3		
4		157	41	7.9	7.4	-0.1	2.8		
7		107	31	7.4	7.7	1.5		7.2	

* One determination.

** Hemolysis.

usually was greatest in the animals that starved longest. No definite quantitative correlation between hyperlipemia and ketonemia could be established in these experiments.

Ingestion of 15 to 20 grams of sugar daily for from 3 to 7 days prevented the rise of lipid phosphorus, but not of cholesterol, and diminished ketonemia. When 40 to 50 grams of sugar were given daily, ketonemia was abolished and serum cholesterol fell to or below its initial concentration. This is distinctly less than the daily amounts of carbohydrate given to monkeys in their regular diets.

C. Experiments with dogs

Seven dogs were starved for from 4 to 14 days. The data are not presented in detail because there were no consistent changes of the serum lipids. In one animal, after 14 days, blood ketones rose to 1.5 mgm. per cent.

DISCUSSION

It has been rather generally stated that starvation is attended by hyperlipemia in which neutral fat is particularly involved. Evidence for these statements is, however, largely inferential, based on studies of diabetes uncontrolled by insulin and on the well-established fact that the lipids of the liver increase in starvation. In the present studies, a slight, but significant, increase of serum lipids has been demonstrated in normal men during starvation. A more pronounced hyperlipemia was observed in monkeys. The serum lipids of the dog were unaffected by starvation. In all species, neutral fat was only slightly altered. In both man and monkey, the lipid increment consisted of cholesterol and phospholipid, the former predominating.

The human experiments are somewhat complicated by the presence of hemoconcentration which regularly attends starvation and was exaggerated in the majority of these experiments by water deprivation. It has been shown by Man and Peters (29) that, when acute hemoconcentration is induced by prolonged maintenance of the erect posture, serum lipids and proteins rise proportionally. Evidence has also been adduced that the hyperlipemia of diabetic acidosis may be referable in part to hemoconcentration (30). During recovery after the acute

phase of this condition, serum lipids and proteins parallel one another in their descent. Hemoconcentration may have been responsible for some part, but not all, of the increases of lipids in the human starvation experiments. Cholesterol rose proportionally more than the serum proteins. In addition, ingestion of carbohydrate in Experiment I inhibited hyperlipemia without greatly mitigating dehydration, while the lipids of Br, Bl, and Fl (Experiment IV) rose, although the subjects were allowed to drink water *ad libitum*. In the monkeys, lipids rose so much more than proteins that the reality of the hyperlipemia cannot be questioned.

The general concept that the hyperlipemia of starvation arises merely from the rapid mobilization of fat seems hardly tenable in view of these observations. Already there is a wealth of evidence that the concentrations of lipids in the serum are little influenced by the quantity of fat in the metabolism mixture. After fatty meals, there is a transient hyperlipemia, affecting chiefly neutral fat (31 to 36). On the other hand, the serum lipids—and especially cholesterol—of a given individual remain remarkably constant throughout a day and over long periods despite variations of diet (24, 25, 34, 35, 37 to 39). Starvation lipemia must, therefore, be attributed to a change in the character, rather than the quantity of fat metabolism.

The most obvious phenomenon with which to connect it is ketosis. The dog, inured to a carbohydrate-free diet, does not change the character of its metabolism radically with starvation. It also develops neither ketosis (10) nor lipemia (1 to 5, 8, 9). In the diabetic dog, however, both ketosis (40 to 42) and lipemia (43 to 47) occur. The human male, when starved, exhibits mild ketosis and a comparably slight lipemia. The two phenomena tend to parallel one another. The monkey is somewhat more susceptible to ketosis (42, 48) and has a proportionally greater lipemia.

In both man and monkey, lipemia can be abolished by the administration of quantities of carbohydrate altogether too small to alter radically the quantities of fat oxidized, but large enough to reduce ketosis to minimal proportions. Reduction of ketosis by administration of carbohydrate has been repeatedly reported (11, 15, 41).

Transfer from a mixed diet to 100 grams of carbohydrate, in the case of an adult male, for example, which must involve the consumption of at least 1200 additional Calories from fat per day, had no appreciable effect on serum lipids. Nevertheless, removal of 400 Calories in the form of sugar, thereby provoking ketosis, elicited distinct hyperlipemia. The fatty meals given by Man and Gildea (36) contained as much as 2500 Calories of fat. In the monkey, also, amounts of carbohydrate too small to reduce considerably the quantities of fat metabolized, but large enough to mitigate ketosis, reduced hyperlipemia.

Greater ketosis and lipemia might have been demonstrable in women and in children than in adult males. Deuel and Gulick found greater ketonemia in fasting women than in men (49). McQuarrie, Husted, and Bloor (50) have reported striking elevations of cholesterol, phospholipids, and fatty acids in the serum of epileptic children receiving ketogenic diets. The lipids fell when enough carbohydrate was given to eliminate ketosis. Hypercholesterolemia has also been reported by Tolstoi and his associates (51, 52) in an adult male who subsisted for prolonged periods on diets consisting solely of fat and protein. This is at variance with the report of Corcoran and Rabinowitch (53) of diminished rather than elevated serum cholesterol and phospholipids in Eskimos. The latter, however, did not have ketonemia, while Tolstoi's subjects did.

In the acidosis of human diabetes, in which both ketosis and hyperlipemia attain a severity never reached in starvation, neutral fat is usually affected as much or more than are cholesterol and lipid phosphorus (30). In this respect, for some reason, the lipemia differs from that of starvation. The distinction is not, however, an absolute one. Although cholesterol and lipid phosphorus are always elevated, neutral fat sometimes escapes. This is illustrated by comparison of the first 3 and last 3 cases in Table III (cases and treatment described previously (30)). What determines the participation of neutral fat is not clear. It may be the severity of the ketosis or the nutritive state of the patient; but it is impossible to establish a clear correlation with either of these features from the data now available. The consistent rises of cholesterol and lipid phosphorus, in contrast to the capricious

TABLE III
Serum lipids in diabetic acidosis of humans

Case number, sex	Days, Hours	Blood sugar	Serum			
			Carbon dioxide	Cholesterol	Lipid phosphorus	Fatty acids of neutral fat
A700 F	3 1, 11 3, 11 5, 11	per 100 cc.	volumes per cent	mgm. per 100 cc.	mgm. per 100 cc.	m. eq. per 1000 cc.
		686		673	18.9	8.2
		480		680	16.3	5.6
		375		456	12.7	6.4
		530		559	13.3	4.3
360		503	12.8	5.7		
A30940 F	7	1080	26.9	157	8.8	3.1
		94	46.4	110	5.7	3.1
A30929 F	12	649	27.1	454	13.4	3.9
		474		452	12.8	4.4
A25652 M	3	418	11.6	490	19.9	14.4
		492		212	10.6	12.0
A5815 F	5 9½ 14 1 2 11	713	11.4	304	20.9	30.1
		476	29.3	281	14.5	12.0
		168	41.6	213	10.0	8.2
		60	42.7	208	9.5	5.5
		267	44.9	203	10.1	6.3
		486	43.2	190	9.5	7.2
		275		209	11.4	7.1
29923 F	1 2	716	11.7	233	16.3	32.3
			32.1	161	8.5	4.2
			34.5	117	6.2	4.0

action of neutral fat, are common to both starvation and diabetic acidosis.

The lipid disturbances of acute starvation contrast sharply with those of chronic undernutrition. In the latter, the serum lipids are characteristically reduced (54, 55). Administration of carbohydrate in starvation causes a rapid decline of the lipids; during recovery from malnutrition, the lipids rise from subnormal to normal concentrations. Nevertheless, there is reason to believe that starvation will cause the lipids of a chronically malnourished patient to rise as do those of normal subjects. During acidosis in malnourished diabetics, Man and Peters (30) observed normal or high concentrations of lipids that fell below normal on recovery. An illustration is found in Case A30940 of Table III. The course of the serum lipids during starvation in a malnourished patient without diabetes is illustrated in Figure 5. The woman had an inoperable gastric carcinoma causing pyloric obstruction. On admission, she had taken little food for many

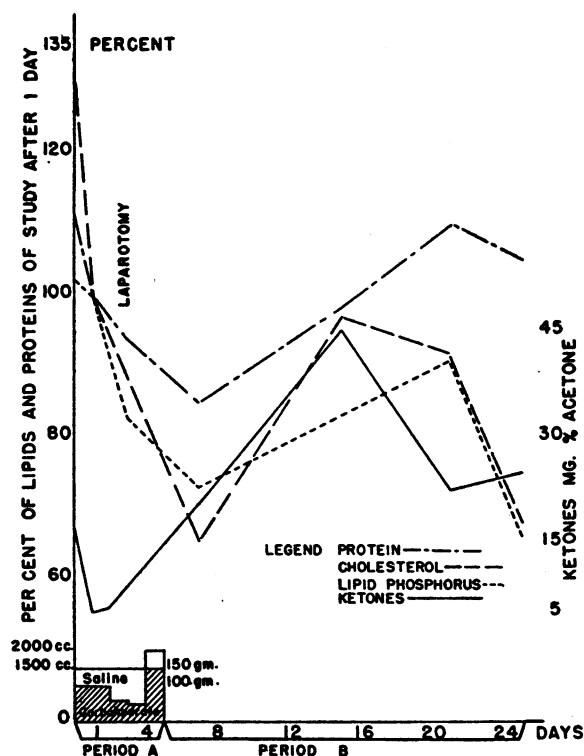


FIG. 5. BLOOD KETONES AND SERUM PROTEINS, LIPID PHOSPHORUS AND TOTAL CHOLESTEROL OF A PATIENT WITH AN INOPERABLE, OBSTRUCTING GASTRIC CARCINOMA

To represent proportionately the changes in serum lipid fractions and proteins, the values on the first morning after parenteral fluid and glucose have been selected as 100 per cent. These relative values can be translated into absolute terms from the following data: at 100 per cent, protein equals 5.58 per cent, cholesterol 163 mgm. per cent, and lipid phosphorus 10.4 mgm. per cent. Blood ketones are presented in absolute terms.

weeks and had vomited everything for 4 days or more. During the first few days (period A of Figure 5), while she received parenteral saline and glucose, all the serum lipid fractions fell considerably and progressively. Cholesterol diminished more than lipid phosphorus did, finally falling below the normal range. Serum proteins also declined, but relatively less than the lipids. Blood ketones diminished within 24 hours, but never to normal values. With resumption of starvation (period B), blood ketones and lipids again rose for a time. The initial study in period B is difficult to evaluate because no blood study was obtained soon after carbohydrate ad-

ministration was stopped. As starvation was prolonged and wasting became extreme, both ketones and lipids gradually decreased again.

These experiments and the other scanty data which can be found in the literature strongly suggest that the hyperlipemia of carbohydrate starvation is not simply an indication that fat is being burned more rapidly, but that a larger proportion of fatty acids is being converted to ketone bodies in the process of combustion. There is ample evidence that the quantity of fat in the metabolism mixture can be varied greatly without any demonstrable variation of serum lipids so long as it is burned directly by the tissues and no unusual amounts of ketone bodies are formed. When, however, ketogenesis exceeds certain limits, hyperlipemia appears. In this, cholesterol and phospholipids seem to play a major role, presumably serving as vehicles to convey the fatty acids to the liver. It may be that they are required to facilitate the entrance of the fatty acids into the liver and participate in the reactions by which ketone bodies are formed. It is well recognized that the hepatic metabolism of fat is greatly influenced by phospholipids and cholesterol.

SUMMARY AND CONCLUSIONS

A study has been made of the serum lipids and blood ketones of adult human males, dogs, and monkeys during starvation.

Dogs developed no appreciable ketosis and no hyperlipemia.

In men, blood ketones increased progressively throughout the periods of starvation, which varied from 2 to 6 days. Serum cholesterol rose slightly, but unequivocally, as fasting was prolonged; lipid phosphorus rose perceptibly; neutral fat changes were equivocal.

In monkeys both blood ketones and serum lipids rose more rapidly and further than they did in men. Again cholesterol was most affected, while neutral fat did not change appreciably.

In both man and monkey, the hyperlipemia was abolished by administration of sufficient carbohydrate to mitigate or to extinguish the ketosis.

From this and other evidence, it is suggested that the hyperlipemia of carbohydrate starvation arises not merely because a larger quantity of

fat is being utilized, but because an unusually large amount of fat is being converted to ketone bodies.

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