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Research Article

SERUM LIPOIDS IN MALNUTRITION[1]

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In previous studies of the blood lipoids in relation to various disease syndromes most authors have not considered the rôle which malnutrition in itself may play in determining the amount of these substances. For example, patients with hyperthyroidism usually lose a great deal of weight and may develop an extreme degree of malnutrition. The fall in the cholesterol and fatty acids that frequently occurs may be related to the general effect of the malnutrition and not to any direct action of the thyroid principles on lipoid metabolism. There is some experimental work on animals which indicates that malnutrition may reduce the level of blood lipoids. In the present paper the relationship between malnutrition and the serum lipoids in patients with a variety of diseases is presented. The disease syndromes that are suspected of directly disturbing fat metabolism, and particularly the blood lipoids, have been avoided.

MATERIALS AND METHODS

Cholesterolemia and lipemia have been studied in 31 emaciated patients with or without an authentic history of weight loss and in 5 patients who appeared well nourished in spite of recent weight loss. The lipoids have also been followed in 10 subjects while they were undergoing marked changes in nutritional status. The subjects studied were patients with diabetes, tuberculosis, arteriosclerosis, carcinoma and abnormalities of the gastro-intestinal tract. Patients with nephritis, nephrosis, liver cirrhosis, hyperthyroidism, hypothyroidism or manic-depressive psychosis are omitted. Serum from venous blood taken from patients in a postabsorptive state was analyzed by methods previously described (3, 10, 12) for cholesterol, fatty acids, lipoid phosphorus, protein, albumin and globulin. The errors of these methods and the range of normal values have been discussed (10, 11, 12, 13, 17).

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DATA

In Table I are given the serum lipoids and proteins of 10 patients who were studied while their nutritional states changed. Nine improved clinically but one (824) refused to eat and lost weight. The intervals of time during which these patients were followed varied from 9 days to 11 months. The last 6 patients in the table were diabetics, but 3 (A30909, 824, A32215) usually did not require insulin, and A36853 only needed 25 units daily. The insulin dosage of each patient at the time of discharge from the hospital is included in the protocols. In the column labeled "food intake" is listed the approximate number of calories per day eaten since the preceding blood study. Whenever possible, body weights have been included in the table as an indication of the degree of improvement of the subject's nutrition. Unfortunately, several of the patients were too ill to be weighed when they entered the hospital, and two (98170, A32215) had so much edema that weights were of no significance. One patient (A36853) went through a stormy course after gastrectomy so that in spite of clinical improvement in nutrition at the time of the second blood study his body weight was actually less than it had been at admission. The patient was so ill that postoperative blood studies and body weights were not obtained when he was at his lowest point of nutrition.

In Table II*A* are presented the serum lipoids and proteins of 31 emaciated patients, some of whom had repeated blood studies even though no changes in nutrition were noticeable clinically. In the first group are patients who, either because of poverty or a non-malignant pathological condition of the gastro-intestinal tract, had taken inadequate diets. These are followed by emaciated patients with tuberculosis or lung abscesses and then by malnourished diabetics without the extreme arteriosclerosis of old age. At the end of the table are patients with extensive arteriosclerosis and carcinoma, some of whom had diabetes. Throughout the table patients who died

TABLE I

Serum lipoids in changing nutritional states

Case number	Date	Serum								Food intake
		Cholesterol	Lipoid phosphorus	Non-phospholipoid fatty acids	Total fatty acids	Total protein	Albumin	Globulin	Weight	
		mgm. per 100 cc.	*mgm. per 100 cc.*	*m.eq.*	*m.eq.*	*per cent*	*per cent*	*per cent*	*kgm.*	
A28867	September 11, 1933	83	5.6	4.9	8.5	7.13	4.65	2.48	42.8	Inadequate 1–2 years
	September 26, 1933	129	7.7	6.3	11.3	6.74	4.32	2.42	45.2	High calory
	October 5, 1933	168	10.1	6.6	13.2	6.98	4.23	2.75	45.	High calory
98170	December 7, 1933, 1:00 p.m.	125	7.9	10.2	15.3					Inadequate 2 years
	December 29, 1933	198	9.5	8.1	14.2	6.34	3.84	2.50	47.7	High calory
A13839	October 29, 1934	104	6.2	5.3	9.3	8.02	3.99	4.03	50.0	
	November 7, 1934	124	8.3	3.8	9.2	8.37	4.14	4.23	50.0	3800 calories
	November 19, 1934	139	7.1	3.1	7.7	7.88	4.01	3.87	57.0	3800 calories
	December 11, 1934	133	6.7	5.2	9.5	7.72	4.46	3.26	56.6	3800 calories
	September 17, 1935	107	4.9	4.8	7.9	7.53	4.24	3.29	54.5	
863	February 1, 1935	108	7.6	9.1	14.1	5.49			36.7	
	February 8, 1935	168	8.4	6.4	11.8	6.27	3.85	2.42	36.7	3000 calories
	February 18, 1935	197	10.0	7.3	13.8	6.22	4.25	1.97	37.7	3000 calories
	March 4, 1935	209	12.0	5.2	13.0	6.44	3.96	2.48	39.5	3000 calories
	April 4, 1935	200	9.8	8.8	15.2	6.61	4.49	2.12	42.7	3000 calories
A30909	June 29, 1933	117	5.6	4.5	8.1	6.39	3.47	2.92		2750 calories daily between these dates
	July 14, 1933	158	7.4	4.4	9.2	7.44	4.09	3.35	49	
A32215	November 15, 1933	90	7.3	9.7	14.4	4.87	3.12	1.75	*	1400 calories daily
	December 29, 1933	122	8.2	11.3	16.6	5.58	3.24	2.34		
A36853	January 19, 1934, 7:50 p.m.	146	7.2	3.7	8.4	6.08			56.4	
	February 24, 1934	207	10.4	6.5	13.2	6.98	4.41	2.57	54.3	† 3000 calories
A33706	April 16, 1934	181	8.1	7.6	12.8	5.15	3.23	1.92		Inadequate 1 month
	April 25, 1934	236	11.2	8.4	15.6	5.98	4.50	1.48	49.0	2300 calories
A30940	July 11, 1933	138	7.9	8.1	13.2	5.33				
	July 19, 1933	154	8.8	7.2	12.9	6.03	2.67	3.36		
	September 12, 1933	204	8.5	6.7	12.2	6.51	3.14	3.37	55.0	2700 calories
	September 29, 1933	220	10.5	7.5	14.3	7.29	3.59	3.70	58.5	3100 calories
824	November 22, 1933	211	9.8	9.5	15.8	6.92	4.10	2.82	113.2	Approximately 800 calories daily
	January 16, 1934	146	8.4	7.5	13.0	6.51	3.67	2.84	103.0	
	February 3, 1934	155	8.8	7.6	13.3	6.94			100.0	

* Edema.
† This diet had been eaten for one week only.

shortly after examination are marked with asterisks. Whenever possible the period of time during which the body weight decreased or the dietary was inadequate has been included in the columns giving weight loss and food intake. Actual body weights are included in the protocols.

In Table II*B* are presented data similar to those in Table II*A* except that the 6 patients included were not malnourished in spite of marked loss of body weight.

At the end of the paper are protocols arranged in the order in which the patients occur in Tables I and II. Abnormal temperatures and white blood cell counts are included.

In Figure 1, serum cholesterol and lipoid phosphorus and in Figure 2, cholesterol and non-phos-

pholipoid fatty acids, are compared. All determinations in Table II*A* and *B* are included. In Figure 3 are graphically represented the changes in serum cholesterol, total fatty acids, lipoid phosphorus, protein and albumin of Case 863 throughout a period of two months. This figure has been selected as representative of the course of lipemia and proteinemia of the patients in Table I.

OBSERVATIONS

The range for normal serum cholesterol as determined by the method of Man and Peters was found previously to be 150 to 256 mgm. per cent (12). More recent studies of the relation of body build to lipemia indicate that in males with extremely slender (leptosomatic) physiques the serum cholesterol may be much lower than 150 mgm. per cent. In one 26 year old man studied at intervals during 6 months one observation was as low as 128 although his cholesterol was usually between 150 and 160 mgm. per cent. The cholesterol of five normal individuals in stable nutritional states, studied throughout a period of 6 to 13 months, varied from the mean by 5 to 24 mgm. per cent.

In Table I there was an increase of 32 to 101 mgm. per cent in the serum cholesterol of each of the nine patients whose nutritional state improved

TABLE II

Serum lipoids in undernourished patients

Case number	Date	Serum								Food intake
		Cholesterol	Lipoid phosphorus	Non-phospholipoid fatty acids	Total fatty acids	Total protein	Albumin	Globulin	Weight loss	
		mgm. per 100 cc.	*mgm. per 100 cc.*	*m.eq.*	*m.eq.*	*per cent*	*per cent*	*per cent*	*kgm.*	
A. EMACIATED PATIENTS										
Patients who ate insufficient calories †										
A41714	October 31, 1934	70	5.1	3.8	7.1	4.80	2.55	2.25	34 in 2 years	Diminished for 2 years
14616	January 2, 1933	96	6.6	6.3	10.6	6.90	3.64	3.26		Poor
	January 31, 1933	120	6.4	7.4	11.5	7.68	3.67	3.63		
79865	* May 28, 1935	123	6.4	5.7	9.8	5.95	3.64	2.31	Marked	Poor for 6 years
A34091	* July 2, 1934	105	7.7	9.4	14.4	4.40	2.48	1.92		Poor for 7 months
Patients with tuberculosis or lung abscess										
A12902	November 23, 1934	105	6.1	5.2	9.1	5.98	2.65	3.33	12	Poor for 1½ years
	* December 6, 1934	90	5.0	5.3	8.5	5.76	2.65	3.11		
A18058	November 23, 1934	121	6.3	5.0	9.1	6.01	2.56	3.45	24	Poor for 3 months
	* December 6, 1934	110	6.5	4.9	9.1	5.69	2.77	2.92		
A52555	December 6, 1934	184	7.8	5.5	10.5	6.72	3.41	3.31	14	Fair
A36436	January 24, 1935	137	7.8	5.5	10.5	6.83	3.43	3.40	16	Poor
A32258	July 2, 1934	71	5.1	3.4	6.6	6.09	2.56	3.53	8	Poor
	July 19, 1934	76	5.4	4.3	7.8	6.72	2.70	4.02		
684	October 26, 1933	136	6.8	5.1	9.4	6.09	3.89	2.20	Marked	Poor
Patients with diabetes ‡										
61682	January 16, 1933	170	9.2	6.2	12.1	6.74	4.14	2.60	15 in 1 month	Poor
A32829	* January 14, 1934, 10:00 p.m.	83	5.8	6.8	10.5	5.01	3.73	1.28		Poor for 3 months
	January 15, 1934	80	5.1	5.6	8.8	4.70				
A30304	May 4, 1933	615	21.1	15.4	28.9	5.81	3.98	1.83	9 in 1 year	Poor
A32114	November 1, 1933	513	16.4	18.7	29.2	5.68	3.74	1.94	18 in 4 months	Poor for 4 months

TABLE II—*Continued*

Case number	Date	Serum								Food intake
		Cholesterol	Lipoid phosphorus	Non-phospholipoid fatty acids	Total fatty acids	Total protein	Albumin	Globulin	Weight loss	
		mgm. per 100 cc.	*mgm. per 100 cc.*	*m.eq.*	*m.eq.*	*per cent*	*per cent*	*per cent*	*kgm.*	
Senile patients §										
46000	April 2, 1934	51	3.8	3.2	5.6	4.95			8 in 2 weeks	
	* April 23, 1934	92	5.7	5.0	8.7	5.99	2.60	3.39	23 in 9 years	
A33395	* March 14, 1934	85	6.0	2.9	6.8	4.69	2.67	2.02		
29923	* March 21, 1934	117	6.2	6.4	10.4	5.17			18	
A 9017	* December 31, 1932	139	7.1	6.6	11.2	6.37	3.03	3.34		Poor
A32655	* December 27, 1933	105	6.0	5.2	9.1	5.09	3.43	1.66	21	Very poor for 6 months
A30333	May 6, 1933		6.6	4.2	8.4	4.08	2.89	1.19	Marked	6 months minimal
	May 18, 1933	96	6.5	3.5	7.7	5.41	3.68	1.73		
	* May 31, 1933	104	5.3	4.1	7.5	5.97	3.96	2.01		
A 9797	* March 16, 1933	46	5.5	4.1	7.7	4.76	2.27	2.49	Marked	
A30081	* April 13, 1933	105	6.8	4.2	8.6	3.99	2.38	1.61		Poor for 6 months
4590	* October 3, 1932	64	4.4	2.5	5.3	5.64	3.75	1.89		
B. PATIENTS WITH WEIGHT LOSS WITHOUT EMACIATION ||										
A38178	March 14, 1934	147	6.9	5.7	10.1	6.09	3.82	2.27	5.5	
91497	February 21, 1933	137	7.4	5.4	10.2	6.43				
	February 22, 1933	146	8.6	6.4	11.9	6.77				10 days limited
A33650	April 14, 1934	186	8.9	7.9	13.6	5.83	3.80	2.03	9	Poor for 1 month
A33628	April 14, 1934	218	8.4	8.7	14.1	6.33	4.17	2.16	16 in 4 months	Small for 4 months
	May 3, 1934	210	10.3	9.5	16.2	5.46	2.97	2.49		

* Patient deceased within a few days.
† To this group should be added the initial studies in Table I on A28867, 98170, A13839 and 863.
‡ To this group should be added the initial studies in Table I on A33706 and A30940.
§ To this group should be added the initial studies in Table I on A30909 and A32215.
|| To this group should be added the initial studies in Table I on A36853 and 824.

and a decrease in the serum cholesterol of the one patient (824) who lost 13 kgm. Cholesterol in all nine patients except A33706 was below, or in the lowest limits of, normal, at the time of the initial blood study. The cholesterolemia rose to a level within the normal range in all but two of the nine patients (A13839, A32215).

Of the three patients who had the smallest increases in serum cholesterol A30909 was followed for only 15 days, while A32215 had eaten only 1,400 calories daily and was still markedly undernourished at the time when he was discharged from the hospital. A13839, a woman with Raynaud's disease, weighed 56.6 kgm. even after a month on 3,800 calories daily. She was readmitted to the hospital 9 months later after a loss of weight probably caused by excessive housework and a poorly balanced diet. At this time her cholesterol had fallen to the same minimum level as at her previous admission eleven months before. It is possible that the duration in 1934 of the high calory diet was not sufficient to permit the serum lipoids to rise to the normal range. Patient A33706, whose initial cholesterol was within normal limits, may not have been as emaciated as she appeared because she was of a tall, lean build. This twenty-five year old woman, had had recognized diabetes for 3 months and during 1 month of an extremely inadequate diet her weight had decreased from 53.5 to 47 kgm. The one patient whose serum cholesterol fell (from 211 to 146 mgm.) lost 10 to 13 kgm. because she refused to eat more than about 800 calories daily during an interval of about two and

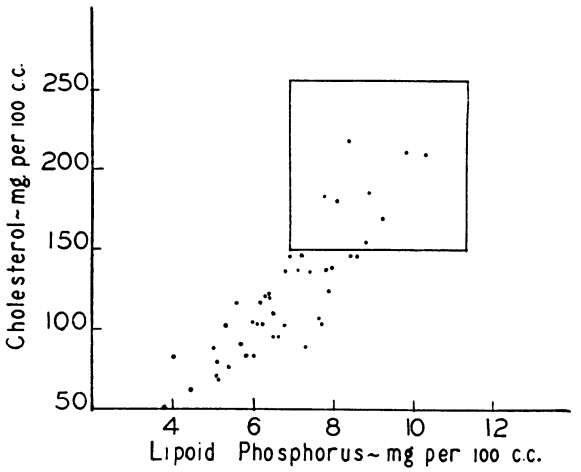

FIG. 1. RELATION BETWEEN CHOLESTEROL AND LIPOID PHOSPHORUS. DETERMINATIONS IN TABLE II.

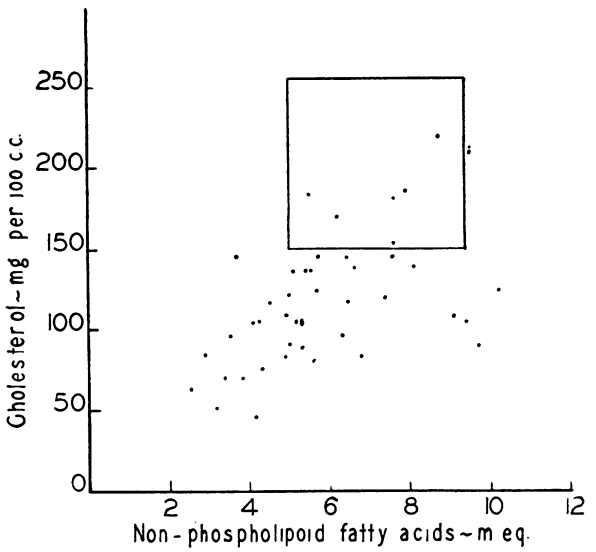

FIG. 2. RELATION BETWEEN CHOLESTEROL AND NON-PHOSPHOLIPOID FATTY ACIDS.

one-half months, but was still decidedly obese (weight 100 kgm.) at the time of the last blood study.

Only 4 of the 8 patients who had low cholesterols had fatty acids below the normal limits of 10 to 16 m.eq. (11). Furthermore, the fatty acids rose with the cholesterol during improvement in nutrition in only 4 and fell with cholesterol in the patient who lost weight. In the other 5, changes in fatty acids did not exceed 0.5 to 1.0 m.eq., the limits of variation from the mean found in a study of normal individuals in stable nutritional states.

Initially lipoid phosphorus was below the normal minimum of 6.9 mgm. per cent (12) in only 3 (A28867, A30909, A13839) of the 9 patients. It increased with improvement in nutrition and decreased with loss of weight in all. The changes in 5 (824, 98170, A13839, A30909, A32215) do not exceed the variation observed in the normal individuals mentioned above, 0.4 to 1.0 mgm. per cent from the mean.

Serum cholesterol in Table II*A* was below normal in 26 of the 31 undernourished patients, within the normal range in 3 (61682, A33706, A52555) and above normal in 2 (A30304, A32114). These last were diabetics with symptoms of autonomic instability who had been on insufficient diets. Their hypercholesterolemia has been discussed previously in relation to their metabolic disorders (14). Of the 3 undernourished patients with normal cholesterolemia no history of insufficient diet could be secured from A52555. Patient A33706 who has already been mentioned in connection with the change in lipemia during nutritional improvement, as well as Patient 61682, belong to the group of individuals whose emaciation is difficult to judge because of the lean build.

In 16 of the 31 undernourished patients fatty acids were below normal, in 13 normal, in 2 above normal. In 19, lipoid phosphorus was below normal, in 2 above normal and in 10 normal. In all 16 subjects with fatty acids below normal the lipoid phosphorus was also below normal, and in 3 cases (14616, 29923, A32829) hypophospholipoidemia accompanied normal fatty acids. The 2 patients with fatty acids and lipoid phosphorus above the normal range were those who had hypercholesterolemia (A30304, A32114). The 3 patients (61682, A33706, A52555) with normal cholesterols had normal fatty acids and phospholipoids.

In Table II*B* only one patient (91497) had a cholesterol below normal, one patient (A36853) fatty acids below normal and all had phospholipoids within the normal range.

DISCUSSION

One purpose of this investigation was to learn about the interdependence in metabolism of the

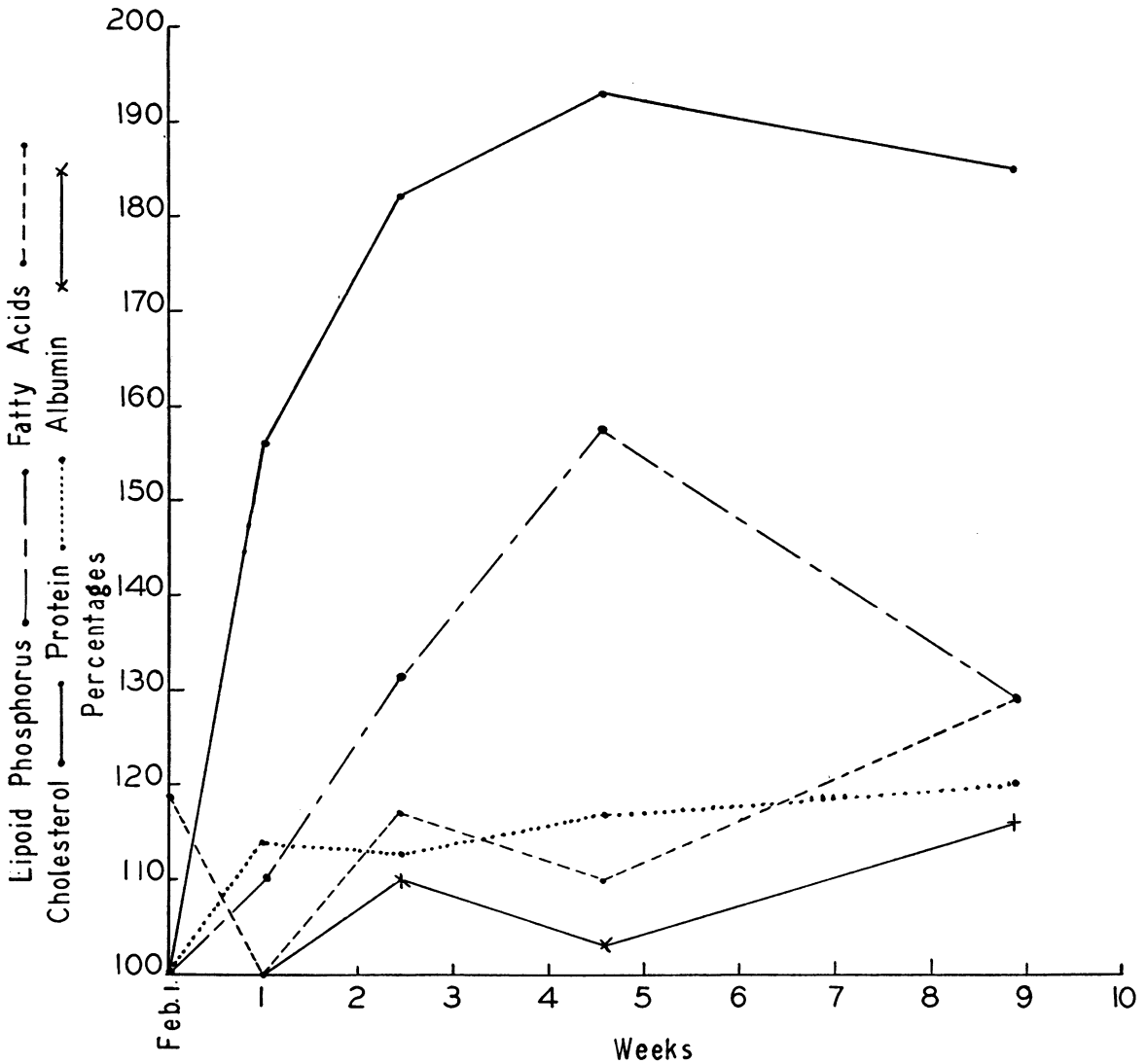

FIG. 3. RELATION BETWEEN SERUM CHOLESTEROL, LIPOID PHOSPHORUS, TOTAL FATTY ACIDS, PROTEIN AND ALBUMIN IN PATIENT 863 DURING COURSE OF RECOVERY FROM MALNUTRITION.

three lipoid fractions, phospholipoids, cholesterol and non-phospholipoid fatty acids. Many of the early studies concerning lipemia in malnutrition were confined to only one or two of the constituents. In Figure 1 a definite correlation between the levels of serum cholesterol and lipoid phosphorus is demonstrated. A similar relation between the cholesterol and lipoid phosphorus in the blood serum of diabetic patients has been emphasized previously (14). In Figure 3 the cholesterol, lipoid phosphorus, total fatty acids and proteins of Case 863 have been charted during a two month period. This curve, which is representative of the group, illustrates the parallel variations in serum cholesterol and lipoid phosphorus of the patients who were followed during changes in nutrition. Examination of the non-phospholipoid fatty acids and cholesterol values in Table II*A* and *B* and Figure 2 reveals wide discrepancies. Similarly in Figure 3 the fatty acid curve does not follow that of cholesterol or lipoid phosphorus. It is difficult to choose a curve representative of the fatty acids and cholesterol of the 10 patients because the fatty acids agreed in

6 (824, A28867, A30909, A32215, A33706, A36853), but in 4 varied independently of lipoid phosphorus, cholesterol and nutritional state. It is possible that the fatty acids may rise more rapidly than cholesterol. In the following discussion the relation of various factors to the level of serum cholesterol is therefore applicable to phospholipoids, but only occasionally to non-phospholipoid fatty acids.

The reduction of the blood lipoids in these cases might be attributed to the underlying diseases which caused the malnutrition rather than to the undernutrition itself, except for the fact that in this heterogeneous group of whom 84 per cent exhibited hypocholesterolemia no single disease or symptom predominated except emaciation. In Table II*A*, the first 4 patients (footnote 1), who had eaten an inadequate and poorly balanced diet suffered from anemia, 98170 from scurvy, 863 from polyneuritis and A13839 from symptoms of Raynaud's disease. The next 3 patients (A41714, 14616, 79865) had abnormalities of the gastro-intestinal tract which in the second and third patients resulted in intractable diarrhea. Patient A34091 for months retained little food because of vomiting, probably associated with thrombi of the pial vessels around the brain stem. Patients A18058 and A32258 had lung abscesses. Pulmonary tuberculosis was diagnosed in the 3 subjects, A52555, A36436, A12902, and also in the diabetic 684. King and Bruger (5), Warnecke (22), Llopis (9), Marino (15) and Rosenthal and Patrzek (18) have been unable to relate the occurrence of hypocholesterolemia to the duration, extent or severity of tubercular lesions, although von Babarczy (21) and Warnecke (22) have reported extremely low cholesterols in toxic cases. King and Bruger (5) consider hypocholesterolemia an indication of poor prognosis because, of the 34 patients studied by them, 13, who had cholesterols below 150 mgm. per cent, died within 10 days of the blood study. Whether it was the tuberculosis or the accompanying malnutrition which was related to the hypolipemia is difficult to ascertain from the published data. In this series of patients, A52555 who had tuberculosis was 1 of the 31 emaciated patients who did not have a cholesterol below the normal minimum. In Table II*A*, after 32114, arteriosclerosis complicated the condition of all of the remaining patients, who with the exception of the last four, were diabetics. Of these last four A30333 and A30081 had carcinoma while the other two A9797 and 4590 died with the exact cause of death undetermined. That the carcinoma of A30081 and A30333 was responsible for the hypocholesterolemia cannot be substantiated from our data because both A33682 and A33650, with normal cholesterols, listed in Table II*B*, had carcinoma, the latter possibly with metastases to the liver. Kingreen (6) found normal or high cholesterols in patients with carcinoma, except in advanced stages of the disease.

Although no single disease can be related to the hypocholesterolemias of the patients in Table II*A*, it seemed possible that the hypolipemia might be related to the degree of hyperpyrexia. Many previous investigators (Boyd (2), Lavergne and Kissel (7), McEachern and Gilmour (16), King and Bruger (5), Schemensky and Mrugowsky (19)) have reported that febrile conditions are attended by a diminution in cholesterol and that during convalescence the cholesterolemia rises to normal or above normal levels, although Kaiser and Gray (4) who studied children recovering from scarlet fever found no deviation from the normal range of lipemia. Four patients (4590, A41714, A32829, A13839) with serum cholesterols of 64, 70, 83 and 104 mgm. per cent had temperatures which did not exceed 98.0 to 99.6° F. Patient A52555, in spite of a temperature ranging from 98.6 to 102, had a serum cholesterol of 184 mgm. per cent, while other patients with approximately the same or less hyperpyrexia exhibited much lower serum cholesterols (A36436, A18058, A32258, 684, A33395, A9017, A30081, 14616, A30333, 98170). In Table I certain patients (98170, A13839, A33706), all of whom showed increases in serum cholesterol had no marked change in temperature range. This lack of relation between hypolipemia and degree of hyperpyrexia is in accordance with the observations of Stoesser and McQuarrie (20) who have studied the influence of acute infections and artificial fever on plasma "lipids."

These investigators found that in spite of the lack of relation of lipemia to pyrexia, the plasma "lipids" varied inversely with the white count in any one individual but that from child to child there was no consistent relation between the num-

ber of leukocytes and the level of the serum cholesterol. It is difficult to judge from their data whether the diet was adequate, or continued long enough, for the establishment of a steady nutritional state. In the present study there were no significant changes in white counts and final serum lipoid determinations of A28867, 98170, A30909, A36853 and A33706, all of whom had increases in cholesterol. Between July 17 and September 3 the white count of A30940 diminished from 12,200 only to 11,750 but the serum cholesterol rose from 154 to 204 mgm. per cent. There were insufficient counts on Patient 824 to permit any conclusion. Patient A32215 was, therefore, the only one of 9 adult patients who showed the inverse ratio between serum lipoids and white counts which is postulated by Stoesser and McQuarrie (20) in infectious diseases of children. Moreover, from a study of Table II*A* and the white counts which, whenever abnormal, are included in the protocols, 11 of the 26 patients with hypocholesterolemia had white counts below 10,000 at the time of the initial blood study.

The low level of serum cholesterol and phospholipoids bears no relation to age or to the outcome of the disease. The patients in Table II*A* ranged from 19 to 80 years in age, with 2 patients aged 19, 3 between 20 and 30, 3 between 30 and 40, 2 between 40 and 50 and all the rest above 50. Patients with cholesterols as low as 71 (A32258), 70 (A41714) and 83 (A28867) all recovered, while several of the patients who died had higher cholesterols than these, as can be judged by examining Table II, in which the patients who did not survive are marked with asterisks.

The effect of emaciation on cholesterolemia may be judged best by a comparison of the level of serum cholesterol with the actual weight loss and previous food intake of a patient, because the criteria of malnutrition, thinness, muscular tone and condition of the skin are difficult to define. Every patient in Table II, except 14616 and A13839, showed signs of marked weight loss. To the patients in this series might be added the 5 diabetics of a previous communication in whom nutritional improvement after the severe tissue wasting of diabetic acidosis was attended by increases in serum lipoids (13). That loss of weight is closely proportional to the degree of hypocholesterolemia cannot be demonstrated by the data in Table II. Patient A52555 lost 14 kgm., 26 per cent of his original weight, but his lipemia remained within the normal range; while A36436 with hypocholesterolemia had lost 16 kgm., or 23 per cent of his original weight. Again 61682, who had lost 15 kgm. or 23 per cent of his original weight, still had serum lipoids within the normal range. If each patient is considered in relation to both weight loss and food intake the correlation is better. Thus A36436 who had a marked hypocholesterolemia in spite of a loss of only 23 per cent of his original weight had eaten poorly, but A52555 with a loss of 26 per cent of his weight had no history of poor food intake and had a normal cholesterolemia. That weight loss and small food intake for a short period of time result in hypocholesterolemia is disproven by studies of two normal individuals and of A33650 and A33682 in Table II*B*. Both of the latter had been on inadequate diets, although they still appeared obese and had normal serum lipoids. Of two vigorous but slightly overweight men, who on a low calory diet lost about 7 kgm., one showed no change in lipemia, the other, three weeks after commencing the diet, showed a reduction in all serum lipoids (total fatty acids fell from 13.8 to 11.4 m.eq., cholesterol from 215 to 160 mgm. per cent, and lipoid phosphorus from 8.2 to 7.6 mgm. per cent). Two weeks later with continuation of the same diet the lipoids returned almost to the original level (fatty acids rose to 12.5 m.eq., cholesterol to 192 mgm. per cent, lipoid phosphorus to 7.7 mgm. per cent).

A decrease in serum cholesterol after a reduction in food intake is not at variance with the repeated demonstration that in man and the carnivores cholesterol can be produced endogenously. In malnutrition the cells important in the formation of cholesterol may be less active, or the balance between the exogenous and endogenous supplies may merely be upset. Bloor (1) has already shown the direct correlation between fat in the diet and the level of serum lipoids. Rosenthal and Patrzek (18) have published data on low cholesterolemia in war times. Wendt (24) fasted two dogs and after several days found a diminution in cholesterol. Ling (8) who fed dogs on a fat free diet and then fasted the dogs for 7 days found a diminution in whole blood total fat, in lecithin and in cholesterol, both after

the dogs were transferred to the fat free diet and again after the seven days of fasting.

Peters and Eisenman (17) have shown that serum proteins and especially serum albumin are low in malnutrition and increase as nutrition improves. An argument for the relation of the nutritional state to the level of serum cholesterol is afforded by examination of the data in Tables I and II which demonstrates a close correlation between serum albumin and cholesterol and between the serum albumin and nutritional status of each patient. In Table I when the cholesterol increased the serum proteins rose in 6 patients (A30909, A36853, A30940, 863, A32215, A33706) and diminished in 2 (A28867, A13839). At the same time the serum albumin increased in 6 (A30909, A30940, A13839, 863, A32215, A33706), diminished only once (A28867) and was undetermined twice. In one patient (824) who was studied before and after low food intake and weight loss the proteins and albumin had fallen at the time of the second blood study. When the blood serum was examined the third time the albumin was not determined so that the increase in total proteins may have been caused by an increase in globulin. In Figure 3 a qualitative relation between serum proteins and cholesterol is apparent. This curve was considered representative because the correlation was closer quantitatively in 5 (A36853, A30909, A30940, A32215, A33706) and was less precise in 3 (A28867, A13839, 824). That serum globulin bears no definite relation to the changes in serum cholesterol is deduced from the fact that the globulin decreased while the cholesterol increased in 3 (A13839, 863, A33706) of the 7 patients in Table I whose protein fractions were studied and remained the same in the 1 patient, 824, who was studied when losing weight. In Table II*A*, 26 of the 31 patients had serum cholesterols below the normal range and 25 of the 26 had serum albumin below normal. The exception was A28867 whose total protein and albumin were both within the limits of normal variation. These limits are set by Peters and Eisenman (17) as 6.0 to 8.0 per cent for total protein and 4.0 to 5.5 per cent for albumin. The correlation in Table II between hypocholesterolemia and hypoproteinemia is less definite chiefly because of the elevation of globulin in several patients with infections or hyperpyrexia. Of the 3 patients (61682, A52555, A33706) in Table II*A* with normal cholesterols the first had serum albumin within normal limits and the first two normal total proteins. In the obese patients such as A33650, A33682, and 824 the effect of malnutrition, which is considered by Peters and Eisenman (17) to imply protein starvation, may conceivably effect the serum proteins and lipoids in widely different degrees. Peters has called attention to the paradox of apparent obesity and hypoproteinemia in "subjects who had undergone wasting with an inadequate protein diet." On such an inadequate diet, the obese patient who has large reserves of fat to mobilize might be expected to develop hypoproteinemia earlier than hypolipemia. It is true in the initial studies on all the patients included in this paper that only A13839 and A28867 exhibited hypolipemia with normal albuminemia although several had normal serum lipoids simultaneously with diminution of serum albumin (A52555, A33706, A33650, A33628, and the border-line cases A38178, 824).

To establish that malnutrition and hypocholesterolemia are related, it must be shown not only that all patients with low cholesterols are malnourished unless there is some recognized pathological condition to account for an abnormal lipemia, but also that patients with malnutrition have low serum cholesterols. In the course of the last four years no patients with hypocholesterolemia without malnutrition have been observed except five, three of whom also had abnormally low basal metabolisms without any symptoms of myxedema. One was a young, slender (leptosomatic) male and one a thin female with recent weight loss, and hypoproteinemia. In the last four years 4 patients who appeared emaciated had normal serum proteins and lipoids, but as has been pointed out by Peters the distinction between emaciation and leanness is extremely difficult. Similar to the occasional lack of hypolipemia in malnutrition is the absence at times of hypoproteinemia in emaciation. Weech and associates (23) state that in spite of the fact that "plasma protein deficits are generally associated with malnutrition the reverse is not true and severely malnourished individuals are frequently encountered in whom the plasma proteins have a normal value." They cite the case of one of their experimental dogs the

serum albumin of which diminished to 1.95 per cent after 64 days on a low protein diet. The dog refused to eat for about ten days and lost 3 kgm. but was given sufficient salt, glucose and water to prevent dehydration. Meanwhile the serum albumin rose to 3.17 per cent although the serum globulin remained constant. They found also that on a low protein diet normally nourished dogs showed marked diminution in serum albumin as rapidly and in some instances more rapidly than animals which were poorly nourished at the beginning of the feeding experiment. It is certainly evident from the observations of Weech and the present data that some chronically undernourished individuals do not have hypoproteinemia and hypolipemia. On the other hand if the state of malnutrition is brought on rapidly enough and is severe enough, reduction of serum proteins and lipoids will eventually occur.

From this point of view part of the hypoproteinemia and hypolipemia associated with debilitating diseases such as nephritis, tuberculosis and possibly hyperthyroidism may be attributed to the state of malnutrition.

CONCLUSIONS

Serum has been analyzed for lipoids in 31 emaciated patients, in 6 patients with weight loss without emaciation, and in 10 patients who have been studied during changes in nutritional state.

In the 10 malnourished patients who were followed for some time the cholesterol varied with the state of nutrition. Cholesterol was below normal in 26 of the emaciated patients, and was within normal limits in 5 of the 6 non-emaciated patients. Although the initial cholesterols varied throughout a wide range, improvement in nutrition was accompanied by an increase even when the first observations were not below the normal range.

The fatty acids were below normal in 16, normal in 13 and above normal in 2 of the 31 patients; were only below normal in one of the 6 patients with weight loss; and varied with nutrition in 5 of the 10 subjects studied for some time.

Concentrations of lipoid phosphorus were proportional to those of cholesterol.

The hypocholesterolemia could not be related to the various diseases of the patients, to tuberculosis, to increased body temperature and white blood cell count, to the age of the subject or to the outcome of the disease.

When there was hypocholesterolemia there were usually low values for protein and albumin. The reduction in these 3 substances was directly related to the state of malnutrition and previous inadequate food intake of the patients.

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PROTOCOLS

A28867, female, age 39, weight 42.5 kgm. Extremely malnourished. Inadequate diet for 1 to 2 years, with only potatoes and beans for one year. Idiopathic hypochromic anemia, menorrhagia. Temperature September 11, 1933, 102° F., subsequent temperature 100.5° F. September 28, 1933, W.B.C. 12,320, at times of all other blood studies below 8,000.

98170, male, age 60, weight 47.7 kgm. Poor nutrition, scorbutus. With orange juice and iron in addition to diet the anemia and malnutrition diminished, initial edema disappeared and patient was greatly improved. Temperature 99.4° F.

A13839, female, age 30, admission weight 50 kgm. Poor nutrition, varicose veins. Ulcer of left leg, questionable Raynaud's disease. Nutrition and peripheral circulation improved on treatment with theelin and a high caloric diet (3,700 to 3,900 calories daily), with extra vitamins. Temperature 100.1° F.

863 (Psychiatric Clinic), female, age 43, height 158 cm., admission weight 36.7 kgm. Extreme emaciation, alcoholism, avitaminotic and alcoholic neuritis, hyperchromic, macrocytic anemia. Patient improved greatly on high calory diet (approximately 3,000 calories daily) with extra vitamins, iron and liver extract. Temperature February 1, 1935, 102.5° F. February 8, 101.0° F. February 18, 1935, 100° F., normal thereafter.

A30909, male, age 70, weight 49.7 kgm. Diabetes, extreme emaciation, arteriosclerosis without hypertension, multiple ulcers of feet. Temperature June 29, 1933, 103.5° F., July 14, 1933, 99.5° F. Discharged on 15 units insulin daily.

A32215, male, age 78. Diabetes, extremely wasted during postoperative recovery from appendicitis and peritonitis. Arteriosclerosis with hypertension (178/90), auricular fibrillation and heart failure, edema. Temperature November 15, 1933, 103.0° F. December 15, 1933, W.B.C. 11,500. Discharged on 20 units of insulin daily.

A36853, male, age 63, weight 56.4 kgm. Mild diabetes, poor nutrition. At admission patient had vomited for 2 weeks. On January 29, 1934 a partial gastrectomy was performed for pyloric obstruction due to peptic ulcer. Until February 6, 1934 caloric intake

small. February 6 to 17, 1934, approximate daily intake 2,200 calories. February 17 to 24, 1934, 3,000 calories. Temperature January 19, 1934, 101° F.

A33706, female, age 25, weight 48.9 kgm. Diabetes during improvement from malnutrition induced by starvation diet. Temperature April 16, 1934, 100.0° F. W.B.C. April 15, 1934, 11,200; April 23, 1934, 10,000. Discharged on 30 units of insulin daily.

A30940, female, age 57. Poor nutrition. Diabetes, multiple subcutaneous abscesses (*Staphylococcus aureus hemolyticus*) which finally ceased draining about September 1, 1933. Approximate daily intake during August, 2,700 calories, during September, 3,100 calories. Temperatures July 11, 1933, 103.0° F.; July 19, 1933, 101.7° F.; September 12, 1933, 101.2° F.; September 29, 1933, 99.5° F. Discharged on 85 units of insulin daily. W.B.C. July 10, 1933, 21,160; July 17, 1933, 12,200; September 3, 1933, 11,750; September 23, 1933, 9,040.

824, female, age 61, weight 100.2 kgm. Diabetes, extreme obesity, arteriosclerosis with heart disease. During recovery from pneumonia and coronary occlusion she refused to eat and lost much weight. Moderate edema. Temperature rose to 99.8° F. frequently throughout this time.

A41714, male, age 80, weight 41 kgm. Extreme emaciation with hyperchromic anemia, congenital hernia of stomach through diaphragm which for two years had resulted in diminishing food intake and loss of 34 kgm. Condition improved with soft diet.

14616, male, age 21, weight 37.8 kgm. Malnourished, underdeveloped. Idiopathic steatorrhea, pulmonary tuberculosis. Temperature 100.0° F. W.B.C. January 5, 1933, 9,200; January 27, 1933, 13,900.

79865, male, age 19, weight 32 kgm. Extreme emaciation, anemia, chronic glossitis, chronic ulcerative enterocolitis and appendicitis with multiple fistulae, fibrous adhesions of peritoneum following an intractable diarrhea of 6 years' duration, demyelinization of tracts of spinal cord and peripheral nerves, axonal change in Betts cells of motor cortex, atrophy of skin with scaling of face. Temperature 104.0° F. Died May 31, 1935.

A34091, female, age 55, weight unrecorded. Extreme undernutrition with edema following 7 months of vomiting and of liquid diet. Clyses of saline and glucose for 3 weeks before this blood study with nothing by mouth. Blood pressure 210/110. Temperature 103.0° F. Died July 7, 1934. Autopsy findings:—Organized thrombi in pial vessels around medulla; organizing arachnoiditis in region of cisterna magna with block of foramina of Luschka, probably due to thrombus associated with hypertensive heart disease; internal hydrocephalus; subdural hematoma, submucous hemorrhages of esophagus and stomach; pleural effusion (bilateral); subcutaneous edema.

A12902, male, age 28, weight unrecorded. Extreme emaciation, pulmonary tuberculosis, inadequate diet 1½ years due to poverty. Temperature 104.0° F. Died January 2, 1935. W.B.C., November 20, 1934, 10,900; December 7, 1934, 13,700.

A18058, male, age 40, weight 50 kgm. Extreme malnutrition, chronic bronchitis, multiple abscesses of lungs. Temperature 102.0° F. Died January 4, 1935. W.B.C. November 23, 1934, 13,800; December 9, 1934, 24,300.

A52555, male, age 54, weight 39 kgm. Emaciation, pulmonary tuberculosis with question of pneumoconiosis. Until 4 weeks before blood study patient worked strenuously. His food intake, though unrecorded, was probably fair. Temperature 102.0° F. W.B.C. December 5, 1934, 15,000.

A36436, male, age 54, weight 58 kgm. Fair nutrition, bilateral pulmonary tuberculosis and intestinal tuberculosis. Condition improved with bed rest, and a regular diet supplemented by high caloric extras. Temperature 102.0° F. W.B.C. December 27, 1934, 13,600.

A32258, male, age 19, weight 39 kgm., height 167 cm. Extreme emaciation, bronchiectasis (right) pleural empyema (right), bronchopleural fistula (right). Temperature 101.5° F. W.B.C. July 3, 1934, 14,200.

684, male, age 55, weight 42 kgm. Marked emaciation (starvation diet for many months), pulmonary tuberculosis, pneumoconiosis, facio-scapulohumeral atrophy (Landouzy-Déjerine type), adenoma of prostate, chronic cystitis. Temperature 102.0° F.

61682, male, age 57, weight 51.2 kgm. Malnutrition, mild diabetes, inadequate dietary for 3 months. Temperature 99.5° F. W.B.C. January 16, 1933, 11,300. Discharged on 15 units of insulin daily.

A32829, male, age 57. Diabetes, extremely emaciated with intestinal obstruction. Died January 15, 1934.

A30304, female, age 50, weight 44.5 kgm. Diabetes, extremely wasted, with tachycardia, sweating and vasomotor instability with normal blood pressure. One kidney had been removed in 1932. Glycosuria could not be completely eliminated without precipitating insulin shock. Basal metabolism May 12, 1934, + 11 per cent. Temperature 99.5° F. 145 units of insulin daily when discharged from hospital.

A32114, female, age 70, weight 48 kgm. on admission, increasing to 52.4. Diabetes, senile cataracts and general arteriosclerosis without hypertension. She had a persistent tachycardia, and her carbohydrate metabolism was quite unstable. November 24, 1933 discharged from hospital on 55 units of insulin daily.

46000, female, age 65. Diabetes, extreme emaciation, arteriosclerosis with hypertension (170/110) and previous amputation of foot. Temperature 102.8° F. W.B.C. April 2, 1934, 21,500; April 23, 1934, 28,800. Died May 16, 1934.

A33395, female, age 55. An extremely emaciated diabetic, one day before death from staphylococcus septicemia. Temperature 102.0° F. W.B.C. March 14, 1934, 10,850.

29923, female, age 68. An extremely emaciated diabetic one day before death from staphylococcus septicemia. Temperature 105.5° F. W.B.C. March 20, 1934, 16,400.

A9017, female, age 55. Diabetes, extreme emaciation, arteriosclerosis without hypertension, gangrene of foot, spreading cellulitis, 5 days before death. Temperature 102.0° F. W.B.C. December 30, 1932, 40,200.

A32655, male, age 71, weight 60.5 kgm. Diabetes, extremely wasted with bleeding duodenal ulcer, 8 days before death from acute hemorrhage. Temperature 99.5° F. W.B.C. December 26, 1933, 13,200.

A30333, male, age 76. Extremely malnourished, carcinoma of stomach, secondary anemia, arteriosclerosis with hypertension (220/65) and arteriosclerotic heart disease with congestive failure. Temperature 100.0° F.

A9797, female, age 64. Extremely emaciated. Died March 17, 1933. Bronchopneumonia, peritonitis, acute, etiology undetermined, arteriosclerosis. No autopsy. Temperature 103.0° F.

A30081, female, age 73, markedly emaciated, edema, carcinoma of ovary, generalized arteriosclerosis with hypertension (185/80). Temperature 100.5° F. W.B.C. April 12, 1933, 13,950. Died a few months later after rapid downhill course.

4590, male, age 68. Extreme malnutrition, anemia. Expired October 10, 1932. Generalized arteriosclerosis involving coronary arteries. Cardiac dilatation and hypertrophy, chronic passive congestion of viscera, carcinoma of cecum. Temperature 99.6° F. W.B.C. October 2, 1932, 15,750.

A38178, male, age 75, weight 62.2 kgm. Average nutrition, but evidences of weight loss, hematuria, secondary anemia, benign papilloma of bladder. Temperature 99.5° F.

91497, male, age 31, weight 58 kgm. Average nutrition. Recurrent attacks of pain and vomiting, duodenal ulcer with pyloric obstruction. Temperature 100.0° F.

A33650, female, age 68, weight 56.4 kgm., height 151 cm. Fair nutrition, carcinoma of stomach with regional metastases. Temperature 100.0° F.

A33628, female, age 68, obese in spite of recent weight loss. Mild diabetes. Carcinoma at head of pancreas and around common duct with no evidence of metastases to liver. Temperature 100.0° F. Died May 16, 1934. Between April 14 and May 16, 1934 nutrition depended on infusions of salt and glucose.

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