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I. L. Chaikoff, … , T. H. McGavack, A. Kaplan

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Research Article

THE BLOOD LIPIDS IN THE POSTABSORPTIVE STATE AND AFTER THE INGESTION OF FAT IN NORMAL HUMAN SUBJECTS AND IN A CASE OF DISSEMINATED CUTANEOUS XANTHOMATA[1]

By I. L. CHAIKOFF, T. H. McGAVACK AND A. KAPLAN

(From the Division of Physiology, Berkeley, and the Division of Medicine, San Francisco, University of California Medical School)

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The presence of hypercholesterolemia in xanthomatosis attracted the attention of early workers, but it was soon shown that an increased blood cholesterol did not necessarily accompany this condition. Bloch (1) in a recent review of the literature on this subject found an increased cholesterol content of the blood in 71 per cent of the cases, while in 20 per cent the cholesterol level was normal, and in 9 per cent subnormal. A rise in the concentration of the cholesterol of the blood is usually associated with pathological lipemias, and it seems reasonable to suppose that the hypercholesterolemia found in most cases of xanthomatosis is part of a general disturbance in lipid metabolism. Moreover, it has been repeatedly observed in such cases that not only is there an increased amount of cholesterol in the blood, but the fatty acids and phospholipids are present in greater concentration than normal. Although the significance of the changed level of the blood lipids in relation to the onset of cutaneous xanthomata is still largely a matter for speculation, it is interesting to note that Eckstein and Wile (2) have found no direct parallelism between blood and tumors with regard to the percentages of the different lipids present.

The present study was undertaken with a view to obtaining more information concerning the variations in the blood lipids in xanthomatosis under various physiological conditions. It seemed to us that such an experimental approach might throw light on the nature of the lipid disturbance in xanthomatosis. The metabolism of a patient presenting cutaneous xanthomata was therefore investigated in the following respects: (1) the levels of the blood lipids in the postabsorptive state during a prolonged period of observation; (2) the effect of a short fast upon the blood lipids; (3) the quantitative relation of total fatty acids, free cholesterol and ester cholesterol of the blood; (4) the response of the blood

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lipids to ingested fat. A somewhat similar study was made on several normal subjects to serve as a basis for comparison.

EXPERIMENTAL

Twelve young adults, 10 males and 2 females, varying in age from 17 to 39 years, served as subjects for the study of the normal fat metabolism. No attempt was made to regulate the previous diet or nutritional state of the subjects other than to withhold all food for 10 to 14 hours before the beginning of the experiment. After a sample of blood had been taken for the determination of the fasting lipid values, 7 of the subjects received 100 cc. of olive oil flavored with a few drops of oil of spearmint. They were also permitted to drink 200 cc. of tap water immediately after the ingestion of the oil. Blood was taken as a rule at 2-hour intervals over a period of 10 hours. During the period of observation the subjects either slept or rested.

The history of the patient who suffered from cutaneous xanthomata follows:

E. W., an unmarried, white American male, a carpenter, 27 years of age, was admitted to the medical clinic on September 19, 1931, complaining of a papular and nodular eruption on both knees, which had begun 2 years prior to the date of his entry and had at first manifested itself by a slight pain on flexion of the knee. Within 6 months after the appearance of the tumors in the region of the knee similar lesions became visible on the fingers and palmar surfaces of both hands and about the extensor surfaces of the elbows. During the 6 months prior to his admission nodules also appeared over the buttocks and along the entire posterior surface of both thighs. These tumor-like masses were firm, yellow or saffron colored, and varied in diameter from 2 mm. to 1.5 cm. The lesions were painless, although discomfort was experienced upon pressure. It is worthy of note that the patient had an aversion to fats, milk, and eggs. His weight on admission was 72 kilos and his height 162.5 cm., indicating a well developed male. Past illnesses included measles and whooping cough in childhood, appendicitis at the age of 17, and a Neisserian infection of 6 to 7 weeks' duration at the age of 18. The family history was negative. At the time of admission the urine was normal and the fasting blood sugar was 110 mgm. per cent. The glucose tolerance test was normal. As judged by the rose-bengal test, there was no liver dysfunction and cholecystography showed a normally functioning gallbladder. The basal metabolic rate was minus 6 per cent. X-ray examination revealed no bony changes in skull, chest, feet, or legs.

The treatment of E. W. previous to and during the ingestion of 100 cc. of olive oil was similar to that recorded above in the case of the normal subjects. The procedure in the fasting experiment was similar to that of the other experiments, except that no oil was ingested.

With 2 exceptions, the ingestion of oil was without ill effects upon normal subjects and patients. W. H. and E. W. (the latter during his first experiment only) were slightly nauseated for a short time following the administration of the oil.

A single fat rather than a diet high in fat was used, inasmuch as this procedure presented less danger of variation in the fat content of the test meal from time to time.

Sampling and storage of blood. Venous blood taken from the forearm was oxalated and pipetted with continuous stirring into a flask containing 25 cc. of redistilled 95 per cent alcohol. Ten cc. of blood were taken from normals and 5 cc. from the patient with xanthomata. The flasks were stoppered with tinfoil-covered corks and stored in the dark at minus 1° C. until analyzed.

Extraction of blood. The blood was extracted by a modification of Bloor's method (3). Peroxide-free, redistilled ethyl ether was added until the volume of solvent reached 75 cc. The mixture was refluxed in a water bath for one hour at 55° ± 5° C., with vigorous rotation of the contents at intervals. An all-glass coil, which at the same time served as a cover to the flask, was used as a condenser. After cooling, the entire mixture was transferred quantitatively to a 100 cc. glass-stoppered volumetric flask. The contents were made up to volume at 20° C. and then filtered through fat-free filter paper into glass-stoppered flasks. While samples were removed for analyses, the extract was kept at 20° C. All determinations were done in duplicate, and the figures reported are averages of values which checked within 5 per cent.

Determination of cholesterol (free and total). Free cholesterol and total cholesterol were determined after the manner of Okey (4), with a few modifications suggested to us by Dr. Okey herself. Carbon dioxide was used instead of air as the agent for removing the last traces of solvent. In the first analysis on E. W. a saturated solution of potassium hydroxide was used as the saponifying agent instead of sodium hydroxide. Sodium ethylate, freshly prepared according to Bloor (5), was substituted in all other work. The time of oxidation was extended to 40 minutes.

Determination of total fatty acids. Total fatty acids were determined by the method of Bloor (5).

Determination of total lipid. This was calculated as the sum of total fatty acids and total cholesterol.

Okey and Stewart (6) point out that slight irregularities in the effects produced by anticoagulants and by centrifugation make plasma less desirable than whole blood for comparative lipid studies. Moreover, it has been shown that the corpuscles participate in lipid transport, for the administration of fat to dogs invariably results in an increase of the fatty acid content of the corpuscles as well as of the plasma. In this investigation, therefore, the use of whole blood for comparative lipid determination was adopted.

RESULTS

Normal subjects

The blood lipid studies in normal subjects are summarized in Tables I and II.

1. In the postabsorptive state. The total lipid content of whole blood varied from 448 mgm. to 610 mgm. per 100 cc., while the minimum and maximum values for fatty acids were respectively 310 and 432. These figures are in close agreement with those obtained in recent years by the oxidative procedures (7, 8, 9). Okey and Boyden (10) have made the interesting observation, later confirmed by Kaufmann and Mühlbock (11) and by Okey and Stewart (6), that a definite fall in the blood cholesterol of women occurs during or near to the menstrual period, and in a few cases a similar tendency for cyclic changes in the fatty acids of the blood

TABLE I

Constituents of whole blood lipids in normal fasting subjects

Subject	Sex	Total lipid	Total fatty acids	Cholesterol		
				Free	Ester	
		mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*per cent of total*
B. S.	Male	594	400	122	72	37.1
C. E. H.	Male	600	432	101	67	39.9
		610§	424	111	75	40.3
W. H.	Male	488	310	98	80	45.0
A. K.	Male	561	370	112	79	41.4
I. L. C.	Male	459	316	95	48	33.6
T. H. M.	Male	607	412	102	93	47.6
A. Ki.*	Female	518	365	95	58	37.9
B. L.	Male	477	333			
R. C.†	Male	563	425			
E. M.‡	Female	448	331			
H. L.	Male					
Maximum		610	432	122	93	47.6
Minimum		448	310	95	48	33.6
Average		539	374	105	72	40.4

* 18 days after cessation of menstruation.
† Blood clotted very rapidly.
‡ 17 days after cessation of menstruation.
§ Samples taken 5 months apart.

was also noted. Hence blood-lipid figures in women can be of comparative value only if obtained during the intermenstrual period. Such observations in the plasma lipids of 8 young women have recently been reported by Boyd (12).

The total cholesterol values obtained in 12 normal subjects were 117 mgm. per 100 cc. of whole blood for the lowest and 195 for the highest; the free or uncombined portion of this consisted of 95 mgm. in the case of the minimum value and 122 mgm. in the case of the maximum, whereas the esterified portion varied from 48 to 93 mgm. The average figures for total, free, and ester cholesterol were 166, 105, and

72 respectively. The latter agree closely with the mean values reported by Okey and Stewart (6).

Total fatty acids were present to the extent of 70 per cent of the total whole blood lipids in the normal subjects examined. In plasma, Boyd (12) found that fatty acids constituted 60 per cent of the total lipids, whereas McQuarrie, Bloor, et al. (9) found 65 per cent as fatty acids. Total cholesterol, which amounted to 30 per cent of the total whole blood lipids, had in our normal subjects an average ester content of 40 per cent. This proportion of ester to total cholesterol corresponds closely with the mean values in whole blood, namely, 39, 42, and 42 per cent, reported for 3 different diets by Okey and Stewart (6), but is lower than that obtained for plasma by Boyd (12).

2. The influence of fat ingestion. The influence of a single meal of fat upon the concentration of lipids in the blood of normal subjects is shown in Table II. The greatest change was demonstrated in the fatty acid component, but considerable non-uniformity was observed in the behavior of the latter in different individuals. Thus, the greatest increase in the total fatty acids was obtained in B. L., in whom this lipid rose 35 per cent above the fasting value at the end of 2 hours, while lesser increases varying from 11 to 27 per cent were observed in B. S., C. E. H., W. H., H. L., and E. M. The time of onset of the rise of the fatty acids and its duration varied in the different subjects examined. In a single case (R. C.) no rise in the level of the fatty acids was observed. The concentration of the fatty acids in the latter subject, however, did not remain constant for at the third and eighth hours decreases were obtained.

With a single exception, no significant change in the cholesterol content of the blood, either free or combined, was produced after a fat meal consisting of 100 cc. of olive oil. In the exception already noted (E. M.), the total cholesterol content of the blood rose slowly and progressively, reaching a maximum value in the fourth hour and showing but a slight decrease from the latter at the end of the period of observation.

Xanthomatosis

1. In the postabsorptive state. The fasting level of the lipids in the subject suffering from cutaneous xanthomata is shown in Table III. This patient was observed over a period of 14 weeks, during which time estimations of the fasting blood lipids were made on 5 different occasions. From January 20th to April 28th a rise in the fasting level of all the lipid components of the blood took place. The fasting lipid content of the blood on January 20th was 1160 mgm. per 100 cc., but by April 28th it had risen to the enormous figure of 2180 mgm. per 100 cc. of whole blood, an increase of 88 per cent above the first value. On May 1st the total lipids had dropped to 1920 mgm., a decrease of 260 mgm. per cent in 3 days. As one would expect, the major portion of the total lipids consisted of fatty

TABLE II

The influence of the ingestion of 100 cc. olive oil on the lipids of whole blood in normal human subjects

Subject	Sex	Weight	Oil ingested per kilo body weight	Hours after fat ingestion	Total fatty acids	Cholesterol		Total lipids
						Total	Free	
		kgm.	*grams*	*hours*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
B. S.	Male	77.1	1.2	0	400	194	122	594
				2	409	198	122	607
				4	364	188	120	552
				6	422	170	121	592
				8	486	182	120	668
				10	390	190	124	580
C. E. H.	Male	78.9	1.2	0	432	168	101	600
				2	479	172	100	651
				4	340	172	101	512
				6	373	170	101	543
				8	361	163	103	524
				10	356	168	99	524
W. H.	Male	73.9	1.2	0	310	178	98	488
				2	392	181	108	573
				4	369	180	102	549
				6	339	186	106	525
				8	360	184		544
				10	360	156	106	516
H. L.	Male	69.4	1.3	0	Lost	186		
				2	434	186		620
				4	424	176		600
				6	435	182		617
				8	519	187		706
				10	476	190		666
B. L.	Male	68.0	1.4	0	333	144		477
				2	449	146		595
				4	340	143		483
				6	397	149		546
				8	372	150		522
				10	396	151		547
R. C.	Male	72.6	1.3	0	425	138		563
				3	339	144		483
				6	414	141		555
				8	367	146		513
				10	401	144		545
E. M.*	Female	64.9	1.4	0	331	117		448
				2	377	138		515
				4	416	158		574
				6	412	158		570
				8	355	158		513
				10	324	154		478

* 17 days after cessation of menstruation.

acids, and during the marked rise and sudden fall in the total lipids, the fatty acid portion of the latter varied from 72 to 79 per cent, a small but definite increase in this percentage being observed as the total lipid concentration of the blood rose. The percentage increase in total cholesterol was not as great as that which had occurred in fatty acids, for on April 28th, when the fatty acids had already risen by 104 per cent above the value of January 20th, cholesterol had risen by 46 per cent. Throughout the experiment the ester varied from 43 to 53 per cent of the total cholesterol. In the fluctuations of total cholesterol that occurred during the 14 weeks of observation, both free and esterified cholesterol participated, although the percentage increase of each was not the same on different days. On February 5th, a marked increase in ester was found as compared with the value obtained on January 20th, whereas the free cholesterol was practically the same on both days. On April 28th and May 1st, when the total cholesterol rose and fell respectively, free and ester cholesterol shared in these changes to almost an equal degree.

TABLE III

Components of whole blood lipids in fasting xanthomatosis (E. W.) (Observations over a period of 14.5 weeks)

Date	Total lipids	Total fatty acids	Cholesterol		
			Free	Ester	
	mgm. per 100 cc.	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*per cent of total*
January 20	1160	840	185	137	42.6
February 5	1500	1090	190	216	53.2
February 26	1650	1210			
April 28	2180	1710	229	241	51.3
May 1	1920	1520	198	204	50.8

2. The influence of fasting and of fat ingestion. In Table IV are shown the effects of a 10-hour fast and of the ingestion of 100 cc. of olive oil upon the blood lipids in the case of xanthomatosis. Throughout the period of fasting, a drop in the level of the blood fatty acids was found. As compared with the initial value, the fatty acid concentration of the blood showed a decrease varying from 10 to 19 per cent from the fourteenth to the twenty-second hour of fasting. The cholesterol values remained fairly constant throughout this period. Four experiments were carried out with olive-oil feeding. Although the results were not similar in all details, they show, when compared with the fasting control, that the ingestion of oil did not markedly affect the content of the blood lipids in the patient in question. The cholesterol level remained steady during the periods of observation. In one case, the level of the blood fatty acids was below the fasting value throughout the 10-hour interval. In the experi-

ment of April 28th, after a decrease had occurred at the third hour following the meal, there was a slow rise in the concentration of fatty acids till the 8.5-hour interval, at which time the latter had risen by 12 per cent above the fasting level. Following the ingestion of fat on February 5th,

TABLE IV

The influence of fat on the whole blood lipids of a patient with cutaneous xanthomata (Patient, E. W.; Sex, male; Age, 29)

Date	Hours after fat ingestion	Total fatty acids	Cholesterol		Total lipids
			Total	Free	
1933	*hours*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
February 26	* No fat ingested	1210	436		1650
		1090	432		1520
		980	434		1410
		1040	440		1480
		1080	458		1540
		1040	440		1480
January 20	0	840	322	185	1160
	1½	748	348	184	1100
	3	810	320	188	1130
	5	764	334	188	1100
	7	894	336	182	1230
February 5	0	1090	406	190	1500
	2	944	402	190	1350
	4	944	428	195	1370
	6	1140	404	189	1540
	8	1050	384	188	1430
	10	1060		188	
April 28	0	1710	470	229	2180
	3	1500	446	227	1950
	5	1790	456	220	2250
	6½	1830	476	231	2310
	8½	1920	460	231	2380
	10	1830	478	238	2310
May 1	0	1520	402	198	1920
	2	1420	398	202	1820
	4	1200	404	205	1600
	6½	1430	398	197	1830
	8	1140	415	198	1560
	10	1240	408	208	1650

* Samples taken at 2-hour intervals, starting 12 hours after last meal.

the fatty acids of the blood dropped 13 per cent in the second and fourth hours, and at the other intervals the values fluctuated between a decrease of 4 per cent and an increase of 5 per cent. On January 20th an increase of 6 per cent above the initial value occurred at the seventh hour.

DISCUSSION

If we take the results as a whole, the conclusion seems warranted that no typical or uniform response in the blood fatty acids is produced in normal man by the ingestion of a single fat. When olive oil up to 1.4 gram per kilo of body weight is fed, the effect upon the fatty acids of the blood during the course of the experiment may vary from no rise whatsoever to one involving an increase of 35 per cent. The absence of a typical blood lipid curve may be ascribed in part to the fact that the previous diet of these subjects had not been controlled, or in part to the fact that an interval of 14 hours from the last meal was insufficient to establish a constant nutritional state in the normal subjects. There are numerous other factors, however, which may influence the behavior of the blood lipids towards ingested fat, for this depends not only on the rate of intestinal absorption of the fat, which again is probably dependent upon many factors, but also on the rate at which the tissues remove the absorbed fat from the blood. It is the intestinal factors—as yet poorly understood—that account in part, no doubt, for the normal variability in the response of the blood lipids during the absorption of fat. Rony and Ching (13) believe that under standardized conditions alimentary lipemia curves may serve as an index of the rate of utilization of fat by the organism, but it should be emphasized in this connection that our uncertainty concerning the rate of intestinal absorption entails a fundamental weakness in such an interpretation. It is also important to point out that owing to the limitations of the methods at present employed by various investigators, the blood lipid curves can be of little, if any, value as a routine procedure for detecting alterations in the fat metabolism in pathological conditions.

An attempt to compare the foregoing results with those recorded by others presented difficulties due not only to the profusion of methods used in the estimation of blood lipids but also to the variety of the test meals, which have differed both in kind and in quantity of fat. The older nephelometric methods have been widely employed (14, 15, 16, 17). The use of nephelometric procedures in comparative studies of the blood fatty acids during the introduction of fat absorbed from the intestine has been criticized by Bloor (5), who points out that a sudden change in the composition of the lipids might readily alter their nephelometric properties. Recently, Man and Gildea (18) have employed a titrimetric method in their investigations of the influence of a fat meal upon serum fatty acids. As regards the present investigation, however, the results obtained with the more recently developed oxidative procedures, in which whole blood or plasma has been used, are of more significance. Variations in the response of the blood fatty acids to ingested fat have also been reported by investigators who have used these methods (7, 8, 19).

It seems paradoxical that the level of the blood fatty acids should drop below the fasting value during a 10-hour interval following the ingestion

of fat. Such an effect, however, was obtained in 2 normal subjects (C. E. H. and R. C.). In this respect, these results confirm similar observations made by Hiller et al. (14) and Page, Pasternack, and Burt (7).

The investigations dealing with the effect of a single feeding of fat upon the level of the blood cholesterol have yielded conflicting results. In 6 experiments of the present study no increase in the blood cholesterol was observed following the ingestion of olive oil, whereas in a single case a definite rise of a prolonged nature was found. That a single meal of fat is incapable of influencing to any appreciable extent the level of cholesterol has been reported previously by a number of workers (20, 14, 21, 22, 23). Page et al. (7) were led to the conclusion that the ingestion of 100 cc. of olive oil was followed by an increase in the blood cholesterol, but it should be noted in connection with the results of these investigators that, with the exception of a single case in which a rise of 35 per cent was recorded, the variations observed may be ascribed to diurnal fluctuations during the fasting state—a matter that has recently been investigated by Bruger and Somach (21).

In the present case of xanthomatosis the increase in the blood lipids was reflected in the fatty acid portion as well as in the cholesterol. The fatty acids, moreover, were responsible for the spectacular rise in the total lipids. Although a hypercholesterolemia has been shown by Bloor (24) and others to be an invariable accompaniment of pathological lipemias, the percentage increase in the cholesterol content of the blood is, as a rule, not as great as that in the fatty acids. This same relationship in the percentile increase in the fatty acids and cholesterol was found to hold in the fluctuations that occurred in the degree of lipemia in the present case of xanthomatosis.

Bloor (25) and others have called attention to the constant relationship between the different constituents of the blood lipids. In the 11 normal subjects examined by us in the postabsorptive state, cholesterol made up from 25 to 37 per cent of the total lipids, whereas, in the case of xanthomatosis, cholesterol was present in amounts varying from 21 to 28 per cent. A normal or low proportion of cholesterol in xanthomatosis has also been previously reported (1, 2, 26, 27). With regard to the cholesterol components, it is significant that a greater amount of the cholesterol was in the ester form in our case of xanthomatosis (Table III) than was found in normal subjects.

The fact that on repeated attempts the ingestion of a single meal of fat failed to raise materially the fatty acid or cholesterol content of the blood seems to rule out the possibility that there is any disturbance in the rate at which exogenous fat is removed by the tissues during its transport through the blood. Indeed, the results obtained in this experiment support the view that the removal of absorbed lipids of the tissues is as great as, or greater than, normal. Similar experiments by other observers have also failed to show that in xanthomatosis there is any impairment of the

capacity of the tissues to take up absorbed lipids (26, 27). From the foregoing experiments it appears to be a reasonable inference that the extra load of lipids in the blood in xanthomatosis is not derived from exogenous fat, but has as its source the fat that has been previously stored in the depots or has been synthesized *de novo* from non-fat precursors. The presence of increased amounts of cholesterol as well as fatty acids lends further support to this view, for it has been repeatedly shown that the ingestion of fat, although it may increase the fatty acid content of the blood, is without striking effect upon the blood cholesterol (Table IV; Bloor (22)).

Among the factors that determine the level of the blood lipids in xanthomatosis, the caloric intake may be of importance. After decreasing the diet from 3310 to 2510 calories, Curtis, Wile, and Eckstein (28) observed a fall in the total lipids of the blood in a diabetic patient suffering from xanthomatous tumors. It was not the ingested fat, however, that led to the changed lipid content of the blood, for the decrease in the calories was brought about by the elimination of the major portion of the carbohydrate from the diet, whereas the fat and protein content remained at the previous level. After reduction of the intake below the basal requirement in otherwise normal patients suffering from cutaneous xanthomata, these workers further found a reduction in the level of the blood lipids—which nevertheless was still more than twice the normal value—and simultaneously an involution of the lesions. Apparently the excess fat of blood and tumors is readily available for energy purposes.

SUMMARY

1. Whole blood lipids were determined by means of oxidative procedures in 12 normal subjects in the postabsorptive state.

2. The influence of the ingestion of 100 cc. of olive oil upon the blood lipids in normal subjects was determined. Marked variations in the response of the fatty acids in different individuals were observed. The maximum increase in the fatty acid content of the blood during a 10-hour period of observation was 35 per cent. In 6 out of the 7 normal subjects so studied the ingestion of fat had no appreciable effect upon the cholesterol level of the blood.

3. The limitations in the use of the curve of alimentary lipemia as an index of altered fat metabolism are discussed.

4. The level of the blood lipids in a patient with cutaneous xanthomata was followed for 14 weeks. During this period the total lipid values fluctuated from a minimum of 1160 mgm. to a maximum of 2180 mgm. per 100 cc. The main constituent affected in this rise was the fatty acid portion, which throughout the period of observation constituted from 72 to 79 per cent of the total lipids. The total cholesterol portion varied from 322 to 470 mgm. per 100 cc. of whole blood and composed from 21 to 28

per cent of the total lipids. On two occasions the cholesterol fraction in relation to total lipids was definitely below the lowest value found in the case of the normal subjects. The proportion of cholesterol in the esterified form was somewhat higher than that obtained in normals.

5. The response of the blood lipids to the ingestion of 100 cc. of olive oil was determined on four different occasions in the patient presenting xanthomatous tumors. No abnormality as compared with normal subjects was observed. In three experiments no appreciable rise in the blood fatty acids was noted, whereas in a single instance a delayed rise of a prolonged nature was obtained. The cholesterol level was not altered by the absorption of fat.

6. The nature of the lipemia in xanthomatosis is discussed.

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