

THE RELATIONSHIP BETWEEN SERUM LIPIDS AND SKIN XANTHOMATA IN EIGHTEEN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

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Since 1938 several reports have appeared in the literature establishing xanthomatous biliary cirrhosis as a specific disease (1-5). Thannhauser, while supporting this concept, has altered his original contention regarding the primary role of essential xanthomatosis in the causation of biliary obstruction and secondary biliary cirrhosis (3, 5). It is now generally agreed that the xanthomatosis of this disease is secondary to a type of biliary cirrhosis. Observations on 18 female patients to be discussed in this paper support this conclusion. In addition, evidence is presented for the existence in the development of the full-blown disease of a pre-xanthomatous stage which is characterized by a lesser degree of biliary obstruction and a less impressive elevation of the lipids of the serum. Xanthomata appear only when the total lipid elevation is extreme and prolonged, and the disease frequently arrests itself prior to the development of xanthomata. Thus, a level of total serum lipids critical for the appearance of xanthomata can be demonstrated. Data concerning the typical lipid pattern of the disease based on a newly available method of total lipid estimation are presented (6).

MATERIAL

Sera which form the basis of this study were obtained from 18 female patients with chronic partial intrahepatic biliary obstruction and cirrhosis (hereafter termed "primary biliary cirrhosis"). Fifteen of these patients had xanthomatous skin lesions; in seven the lesions were generalized large tuberous and flat xanthomata; in eight the distribution was localized to the eyelids (hereafter called xanthelasma). Three of the 18 patients have not yet developed xanthomata. Thannhauser's classification (2) of these various types of xanthomata has been used in this report.

Clinical and laboratory data relevant to the singleness of the disease entity suffered by these 18 patients will be presented separately (7). Briefly, diagnostic criteria of primary biliary cirrhosis included the following: pruritus and prolonged painless jaundice without history, signs, symptoms, or operative findings of extrahepatic

biliary obstruction or infection; sudden or insidious onset without known nutritional, toxic, or infectious hepatitis background; excellent physical condition and strength on a complete diet; appearance of xanthomata after months or years of jaundice and itching; pronounced liver enlargement but variable splenomegaly; no ascites, edema or evidence of portal hypertension except as late signs; rare spiders and liver palms; melanosis and thick dry skin. Laboratory data included: signs of biliary obstruction (severe steatorrhea; elevated bilirubin, alkaline phosphatase and serum lipids; clear serum; decreased fecal urobilinogen, increased urine bile and urobilinogen); adequate protein synthesis (minor depression of serum albumin, normal prothrombin, normal or elevated fibrinogen, normal or slightly decreased serum esterase); elevated gamma globulin; cephalin flocculation 0 to 4+; moderate normochromic-normocytic anemia.

METHODS

Total serum lipids were determined by the manometric lipid carbon method of Ahrens, Eder and Van Slyke (6). Analysis is made of lipid carbon in the alcohol-ether extract of a tungstic acid precipitate of serum, a procedure which has been found to avoid contamination of the final extract by non-lipid impurities and which measures 95% or more of the lipid. Lipid P was measured by a modification of the Fiske and SubbaRow (8) method, and converted to phospholipid by the factor of 25. Total and free cholesterol were determined by the Schoenheimer-Sperry method (9). Neutral fat was calculated by difference between the total lipid carbon and that of cholesterol and phospholipid as described in (6). In the last three years more than 300 serum lipid patterns have been carried out at frequent intervals in the present series of patients. In addition, a turbidimetric procedure (10, 11) for rapid estimation of total serum lipids has been extremely useful as a screening procedure and as a means of following the course of serum lipids in patients examined at frequent intervals.

Serum cephalin was calculated from the lipid P unhydrolyzed by *Cl. welchii* lecithinase, since MacFarlane (12) and Zamecnik, Brewster and Lipmann (13) have shown that phosphatidylserine and phosphatidylethanolamine (the two known serum cephalins) are not affected by that enzyme. One-half cc. of serum was incubated at 37° C. for 24 hours with an excess of buffered enzyme, at which time the remaining lipid P was measured in an alcohol-ether extract of the trichloroacetic-acid-precipitated serum, as described in (14). Lipid P was converted to

cephalin by a factor of 23.5, assuming equal concentrations of phosphatidylserine and -ethanolamine. The "cephalin" values given below are recognized to be approximate and on the high side, since no effort was made to maintain pH at optimal levels to compensate for increasing acidity with hydrolysis, nor has it been conclusively proven that sphingomyelin is entirely hydrolyzed under these conditions. It can be stated with assurance, however, that cephalin levels were not higher than those listed.

RESULTS

Typical patterns of the serum lipids in eight different patients with primary biliary cirrhosis are presented in Figure 1 along with the duration in each of jaundice, xanthelasmic streaks in eyelids, or severe generalized xanthomata (tuberous or flat types). These eight patterns show a marked similarity irrespective of total lipid concentration or of the presence or absence of xanthomata. Preponderance of phospholipids is noted at all levels of total lipid concentration. The rise in free cholesterol concentration is also evident, although not as marked as the phospholipid increase. Cholesterol ester concentration has been normal or slightly elevated in all sera tested, except terminally when the esterifying ability of the liver fails along with many other functions. However, the ratio of free to total cholesterol has been markedly elevated because of the characteristic increase in the free form. Neutral fat levels

have been moderately elevated in all patients except during periods of malnourishment on low fat diets or terminally. Every fasting serum encountered in the present series of patients has been clear.

Figure 2 shows typical lipid patterns in other hyperlipemic conditions in order to demonstrate the uniqueness of the pattern in primary biliary cirrhosis. All high-lipid sera, with the exception of that found in biliary obstruction, are lipemic.

Table I lists the total phospholipid and cephalin concentrations in 19 sera of patients with unexplained biliary cirrhosis as compared to five normals. Since it is seen that the cephalin fraction is very little increased in this disease, either lecithin or sphingomyelin or both must make up the characteristically elevated phospholipid fraction. Using other methods MacMahon and Thannhauser (5) report that in two of their patients, where individual phospholipids were determined, the phospholipid increase was mainly lecithin.

Figure 3 charts 150 separate serum lipid patterns determined in the present series at various stages of disease. Concentrations of the major lipid components are charted on the ordinate against the total lipid concentration of each serum on the abscissa, and for comparative purposes a line has been drawn through the phospholipid and cholesterol points. The range of normal, as

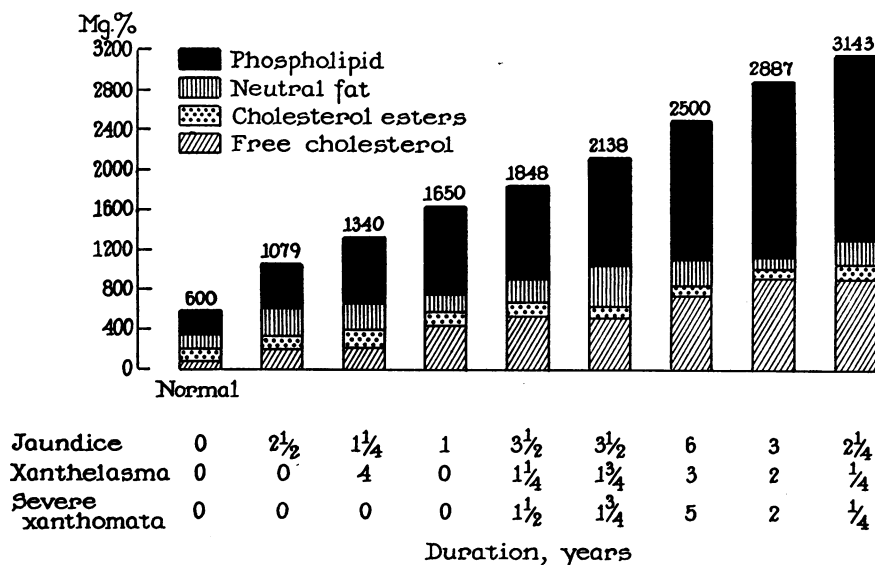


FIG. 1. SERUM LIPID PATTERNS IN EIGHT PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

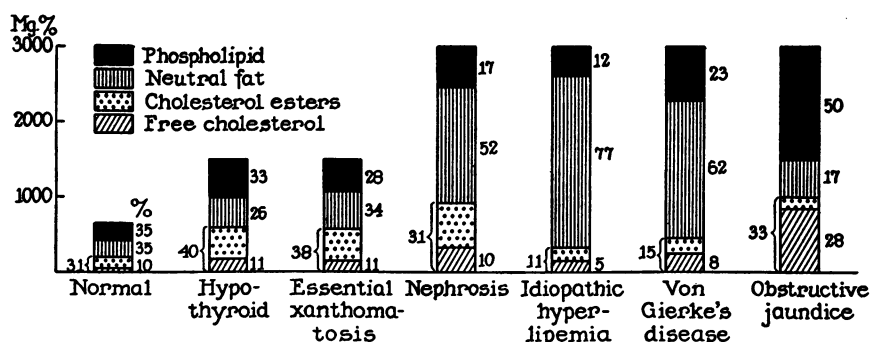


FIG. 2. REPRESENTATIVE LIPID PATTERNS IN VARIOUS HYPERLIPEMIC CONDITIONS

All high-lipid sera are lipemic (milky) except that of obstructive jaundice (intra- or extrahepatic in origin). Hypothyroid pattern calculated from data of Gildea, Man, and Peters (26).

determined in this laboratory in 20 sera, is shown in the hatched areas on the left. Patients who have not yet developed xanthomata or who have xanthelasma without other xanthomata are represented by open circles, whereas those who have or have had tuberous or flat xanthomata are shown by closed circles.

Several points are apparent from inspection of Figure 3. 1) With increasing total lipid levels the predominant component is phospholipid rather than cholesterol or neutral fat. 2) Free chole-

sterol is elevated in all sera but rises with increasing total lipids less sharply than phospholipids. 3) Neutral fat is elevated in almost all sera, but less so than phospholipids and free cholesterol. 4) All patients with total lipids of 1800 mg.% or more had severe xanthomata. 5) Serum lipid patterns of pre-xanthomatous patients were indistinguishable from many of the patterns found in xanthomatous patients, as noted in the zone below 1800 mg.% total lipid.

Certain additional information could not be included in Figure 3. 1) Patients with minor degrees of skin xanthomata (xanthelasma) had total lipid levels of about 1300–1800 mg.%. 2) Patients without any xanthomata had total lipid levels of about 900–1300 mg.%. 3) Elevated total lipid levels were found in all patients at some time in their course. The patient with the least elevation had total lipids in the normal range at certain intervals. 4) The disappearance or diminution of xanthomata in four cases was preceded in all by dramatic spontaneous decrease in total lipid concentration. Patterns made periodically during these decreases account for the presence of closed symbols in Figure 3 below 1800 mg.% total lipid. They conformed in all respects to the patterns of patients in the pre-xanthomatous group.

The length of time required for the deposition of skin xanthomata in the presence of elevated serum lipids cannot be accurately stated, since in none of the patients could the initial rise in lipids be dated. In one pre-xanthomatous patient with total lipids of more than 2000 mg.%, severe generalized skin xanthomatosis was predicted and

TABLE I

	Serum no.	Total lipid	Total phospholipid	"Cephalin"	Total cholesterol	Free cholesterol	Free total cholesterol	Neutral fat
		mg. %	mg. %	mg. %	mg. %	mg. %		mg. %
Normals	1	591	185	43	217	54	.25	88
	2	640	190	29	212	64	.30	116
	3	650	190	27	200	62	.31	174
	4	700	210	29	205	60	.29	201
	5	720	215	41	207	64	.31	209
Primary biliary cirrhosis	1	758	238	32	208	66	.32	224
	2	1000	386	55	325	129	.40	167
	3	1193	406	53	463	161	.35	126
	4	1230	363	53	432	138	.32	242
	5	1269	494	53	425	146	.35	177
	6	1355	425	80	387	164	.42	404
	7	1385	581	56	442	275	.62	258
	8	1615	844	75	583	443	.76	102
	9	1641	706	58	416	276	.66	432
	10	1678	900	59	608	443	.73	68
	11	1754	769	47	571	311	.54	253
	12	1927	912	65	675	536	.79	253
	13	1933	963	52	800	630	.78	64
	14	1943	995	53	566	450	.79	355
	15	2173	1110	93	691	528	.76	271
	16	2346	1350	82	650	524	.81	268
	17	2693	1525	94	866	756	.88	224
	18	3017	1688	108	1070	880	.82	141
	19	3027	1538	112	883	821	.93	568

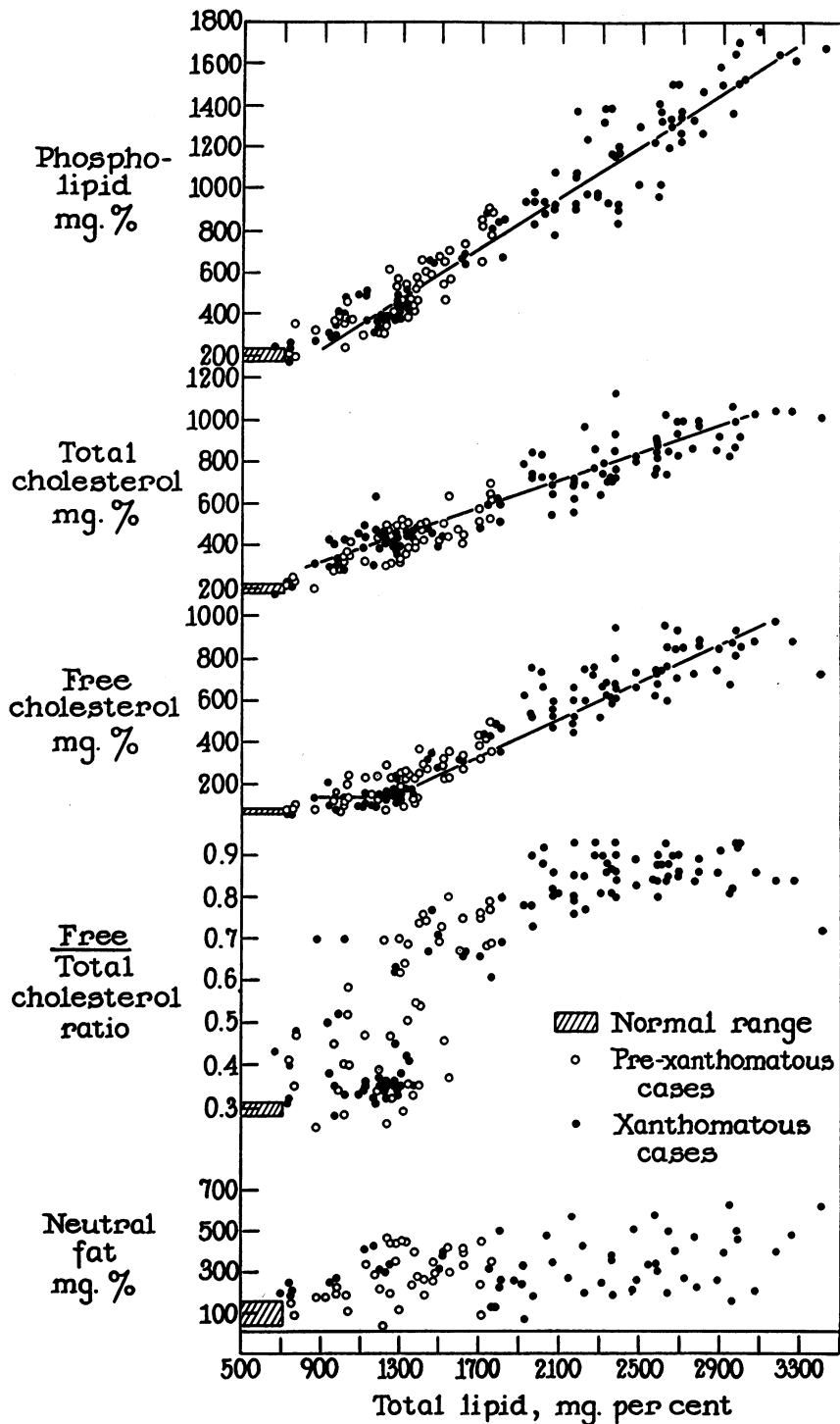


FIG. 3. SERUM LIPID FRACTIONS REPEATEDLY DETERMINED IN 18 PATIENTS WITH PRIMARY BILIARY CIRRHOSIS, PLOTTED AGAINST TOTAL LIPID CONCENTRATION FOR EACH SERUM, AS COMPARED TO NORMAL RANGE

Xanthomatous cases (closed circles) = severe generalized flat or tuberous xanthomata. Pre-xanthomatous cases (open circles) = all others, including those with xanthelasma only.

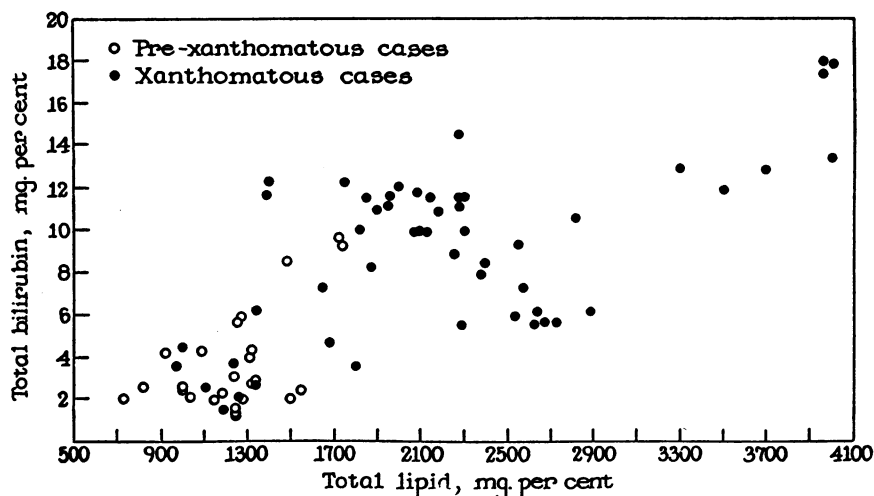


FIG. 4. CORRELATION BETWEEN TOTAL SERUM LIPID AND TOTAL SERUM BILIRUBIN CONCENTRATIONS REPEATEDLY DETERMINED IN 18 PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

Symbols as in Figure 3.

indeed developed floridly four months later (Figure 6). In another patient generalized flat xanthomata developed nine months after elevated serum lipids were recognized, and were similarly predicted in the pre-xanthomatous phase of her illness. A third patient developed flat xanthomata of the palms within three months of the onset of her illness, but only after nine months with total lipids consistently above 2000 mg. % did generalized tuberous xanthomata appear (Figure 5). Thus, it seems that severe xanthomata appear only after prolonged periods with marked serum lipid elevation, and in this there is considerable individual variation.

Figure 4 represents the rough correlation in this series of patients between total lipid and total serum bilirubin levels, both of which are regarded in this Hospital as indications of biliary obstruction (whether mechanical or purely functional retention cannot be stated with the evidence at hand). It is seen again that xanthomata are absent in the patients who are the least jaundiced and who show the least elevation of total lipids. Two of the four patients whose xanthomata regressed had parallel decreases in bilirubin and lipid levels. However, in a third, where the decrease in serum lipids coincided with disappearance of xanthomata in the terminal year, there was a steady rise in bilirubin levels. Independent

variation of serum bilirubin, serum lipids, and alkaline phosphatase activity has been noted repeatedly in this group, although, as Figure 4 shows, there is a general tendency for correlation in the group as a whole.

Laboratory evidence of the degree of biliary obstruction in these patients, when sought at monthly or more frequent intervals, has shown striking spontaneous variability. Complete obstruction has not been seen in a single patient in this series, as measured by urine and feces urobilinogen and urine bile, but when measured frequently over prolonged periods these indices of partial biliary obstruction have showed significant periodic rises and falls. Over longer intervals there have also been significant variations in serum bilirubin and serum lipid levels, as illustrated by the following two cases. In Figure 5 are charted the levels of total lipids and total bilirubin in a patient followed since 1943. This patient developed flat xanthomata of the hands in January, 1943, three months after the onset of jaundice and pruritus, and in April, 1945, generalized tuberous xanthomata appeared which rapidly became more extensive and disabling than any encountered in this series of patients. Four major spontaneous rises and falls in lipid levels occurred between 1943 and 1948. In 1948, when for the first time total lipids returned to normal limits,

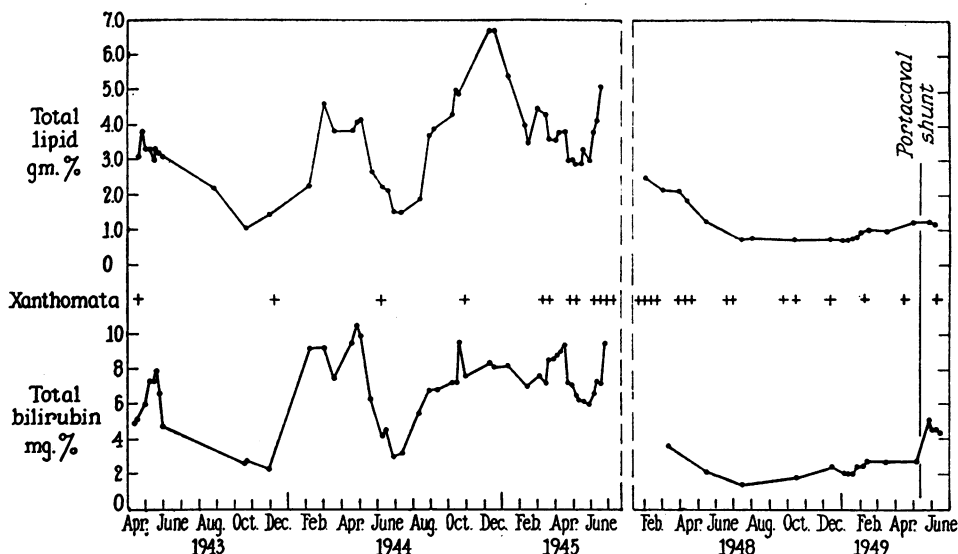


FIG. 5. VARIATIONS IN TOTAL SERUM LIPID AND TOTAL SERUM BILIRUBIN CONCENTRATION IN A 35 YEAR OLD FEMALE WITH ONSET OF PRIMARY BILIARY CIRRHOSIS IN OCTOBER, 1942; RESOLUTION OF XANTHOMATA WITH FALL IN LIPIDS

Portacaval shunt in May, 1949, for relief of portal hypertension and hemorrhage; at present in excellent general condition.

her xanthomata rapidly diminished in size and at present have almost completely disappeared. The soybean lecithin administered by mouth during this last period of alleviation of biliary obstruction might have received credit for the improvement,

had it not also been given to five other patients in this series without effect. The changes in bilirubin and lipid levels in this patient are more strikingly parallel than have been observed in others in this series.

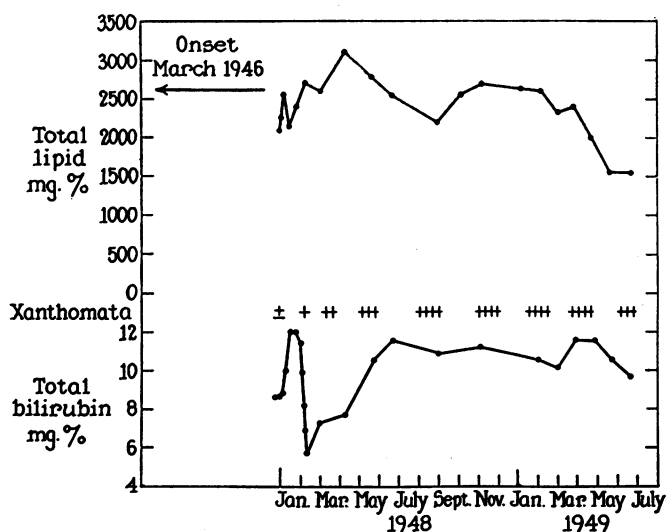


FIG. 6. PREDICTED APPEARANCE OF SEVERE GENERALIZED XANTHOMATA IN A 48 YEAR OLD FEMALE WITH PRIMARY BILIARY CIRRHOSIS FOR TWO YEARS

In April, 1949, a fall in total lipids preceded a beginning resolution of xanthomata.

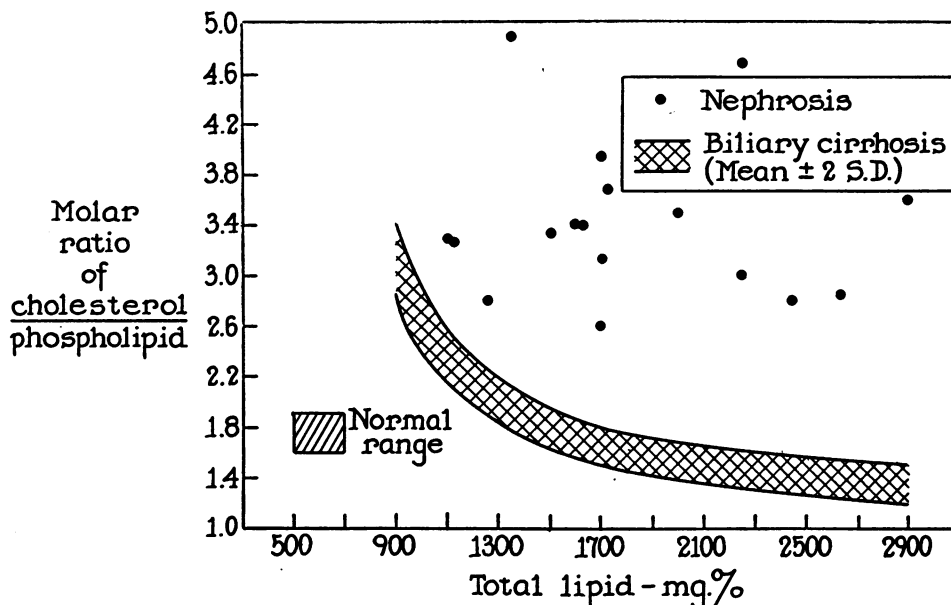


FIG. 7. RANGE OF MOLAR RATIOS OF FREE PLUS ESTERIFIED CHOLESTEROL TO TOTAL PHOSPHOLIPID IN NORMAL SERA AND IN 95% OF DATA OF FIGURE 3, PLOTTED AGAINST TOTAL SERUM LIPID CONCENTRATION

Nephrotic sera plotted individually. (Total phospholipid calculated as lecithin, and esterified cholesterol as cholesterol palmitate.)

Figure 6 illustrates the appearance of generalized tuberos and flat xanthomata in a patient two years after the onset of her illness. When first seen in January, 1948, she was found to have a pinpoint yellow deposit in one eyelid. On the basis of the finding of total serum lipids of more than 2000 mg.%, it was predicted that this patient would progress from her current pre-xanthomatous condition to that of florid xanthomatosis. This occurred three months later. Coincident with the administration of desoxycholic acid orally (3 gm. per day) she experienced marked relief from abdominal bloating, nausea, anorexia and bowel frequency, and shortly thereafter showed a dramatic fall in total serum lipids. She now shows softening and decrease in size of her xanthomata. Figure 6 also illustrates a dramatic change in bilirubin levels produced by nitrogen mustard in January, 1948, with red blood cell destruction and rise in bilirubin followed by anemia and secondary fall in bilirubin. Despite these variations there was no essential change in her intrahepatic "obstruction," and no significant change in serum lipids. By October, 1949, her total lipids had fallen to 600 mg.%, serum bilirubin to 4 mg.%,

and her xanthomata continued to show dramatic resolution.

The possibility of a relationship between the ratio of hydrophobic/hydrophilic serum lipids and atheromatosis has been suggested (14, 15). In Figure 7 the molar ratio of cholesterol/phospholipid at various levels of total lipid has been calculated from the 150 lipid patterns of Figure 3 within limits including 95% of the data. This range is compared with individual determinations in patients with the nephrotic syndrome. In biliary cirrhosis it is seen that the higher the total lipid, the lower the cholesterol/phospholipid ratio, while in nephrosis this ratio is increased over normal at all total lipid levels.

DISCUSSION

Only seven of the 18 patients in this series showed the full-blown picture of xanthomatous biliary cirrhosis (5). The other 11 patients showed various stages in the development of this picture, some with xanthelasma alone and others with no xanthomata. Determination of total lipid levels at frequent intervals permitted the prediction of generalized xanthomatosis in two patients

and the resolution of xanthomata in four. Thus, a definite pre-xanthomatous stage in this disease can be characterized, and the transition into and out of the full-blown xanthomatous stage is seen to depend upon the degree of elevation of the serum lipid level. Patients whose lipid levels never exceed 1800 mg.% remain arrested in the pre-xanthomatous phase of the disease. These patients are more numerous than those with the full-blown disease.

The characteristic serum lipid picture in this group of patients affords an objective measure by which the efficacy of various therapeutic agents may be judged. The use of a rapid turbidimetric method (10, 11) for determination of total serum lipid concentration has been of great assistance in this regard. Agents which have been administered in this series without significant alterations in lipid or bilirubin levels in the serum include: cholesterol-free diet, low fat diet, high protein diet, thyroid, soybean lecithin, intravenous serum albumin, tocopherol, nitrogen mustard, intravenous and intramuscular liver extract, and lipocaic. Desoxycholic acid appeared to have a lowering effect on the serum lipids in two of the patients. A full diet including fat with supplemental doses of fat-soluble vitamins was found necessary for adequate supportive treatment. The marked spontaneous variation in lipid and bilirubin levels which has been demonstrated in these patients necessitates prolonged observation for proper evaluation of therapeutic measures. Evaluation of therapy also is complicated by the fact that late in the disease, along with the development of signs of portal hypertension, there is a pronounced fall in serum lipid levels which may be accompanied by decreases in bilirubin and alkaline phosphatase activity, along with beginning resolution of xanthomata. This natural course of the disease must be differentiated from therapeutic success. Lacking knowledge of the exact means by which biliary obstruction (be it functional or mechanical) leads to elevation of serum lipids, it is evident that the mechanism by which the amelioration of obstruction is followed by a fall in lipids and disappearance of xanthomata also remains entirely conjectural.

The serum lipid values reported by MacMahon and Thannhauser (5) in their six patients with "xanthomatous biliary cirrhosis" differ in two

respects from the values given in the present report. Three of their cases showed major elevations of cholesterol esters, whereas in the present series there has been a consistently major elevation of free cholesterol. Since the Schoenheimer-Sperry (9) method has been used in both laboratories, this discrepancy is difficult to explain. Secondly, although MacMahon and Thannhauser report extremely low figures for neutral fats, recalculation of their data by the formula of Thannhauser and Reinstein (16) shows significant elevations of neutral fats in some cases. In the present series manometric estimation of total lipid carbon gives clearcut evidence of increased amounts of neutral fats in the sera of xanthomatous and pre-xanthomatous patients.

The importance of serum phospholipids as stabilizers of the serum lipid emulsion has recently been stressed in a study (14) in which the particle size of lipid droplets in serum has been related to the ratio between hydrophilic and hydrophobic lipid concentrations. The implications of this thesis for studies on the pathogenesis of atheromatosis have received support in the recent work of Ladd, Kellner and Correll (15, 17) which demonstrated a reduced incidence of experimental atherosclerosis in rabbits in the presence of a reduced ratio of cholesterol to phospholipid in the serum. The relatively normal cholesterol/phospholipid ratios in the present patients despite total lipids greater than 1800 mg.% is thus of interest, since it has been shown that with these greatly elevated total lipid levels skin xanthomata occur regularly. In contrast to the well-known incidence of premature atherosclerosis in nephrosis, in the present series of patients with biliary cirrhosis and skin xanthomatosis there has been no clinical, electrocardiographic or radiographic evidence of atherosclerosis or coronary disease, and in four autopsied cases the degree of atherosclerosis was entirely commensurate with the age of the patient. The factors leading to xanthomatosis of the skin appear, therefore, to differ strikingly from those which determine the presence of arterial atheromatosis.

The serum lipid pattern which is characteristic of "primary biliary cirrhosis" has also been found in this Hospital in obstructive jaundice of other types: in extrahepatic biliary obstruction (two cases), occasionally in congenital bile duct

atresia (two cases), and in severely jaundiced patients with infectious hepatitis (five cases), and has elsewhere been reported in these conditions (18-21) and in arsenical liver injury (22, 23). Moreover, it has been noted in experimental bile duct ligation in rats (24, 25). Thus, the occurrence of elevated serum lipids in a clear serum, with predominant proportions of phospholipids, free cholesterol, and neutral fat, in decreasing order, appears to be pathognomonic of chronic partial biliary obstruction, either intra- or extra-hepatic in origin. If serum lipids remain sufficiently elevated for a sufficient length of time, skin xanthomata can be predicted, and, if for any reason the obstruction is relieved, it can be expected that the serum lipids will fall to normal levels and xanthomata will resolve.

CONCLUSIONS

1. In 18 patients with primary biliary cirrhosis, the occurrence of skin xanthomata has been directly related to the degree of elevation of the total serum lipids.

2. All patients with prolonged elevation of total serum lipids above 2000 mg.% have developed severe generalized skin xanthomata. Patients with total lipids below 1300 mg.% have shown no xanthomata, while in the intermediate range xanthelasma has occurred.

3. The typical lipid pattern of this disease, both in its pre-xanthomatous and its xanthomatous phases, is characterized by significant elevations of phospholipids (lecithin), free cholesterol, and neutral fat, in order of decreasing magnitude, with clear non-lipemic serum.

4. Disappearance of skin xanthomata coincident with fall in total serum lipids is described for the first time, and occurred in four out of seven patients with severe xanthomata.

5. The development of skin xanthomata without significant arterial atheromata in these patients is discussed.

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