CASE REPORTS

A CASE OF JUVENILE XANTHOMATOSIS

WITH ENLARGED LIVER AND SPLEEN AND GREATLY INCREASED PLASMA LIPOIDS

BY

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The present report describes an unusual syndrome in a girl aged seven years. The outstanding features of the case are extensive cutaneous xanthomatosis, enlargement of the liver and spleen, arrested growth and enormous increases in phospholipin, cholesterol, and cholesterol esters in the blood plasma, with little or no glycerol fat.

Case report

J. M., a girl aged seven years, came under the care of Dr. A. G. Ogilvie at the Royal Victoria Infirmary, Newcastle-upon-Tyne, in May, 1938. There was

mentally bright and her general condition fairly good. At this stage there was only a slight icteric tinge in the conjunctivae, and no frank clinical jaundice. There was extensive cutaneous xanthoma. The hands were the most affected, showing raised yellow nodules over the dorsal surfaces of the knuckles and on the palms, and flat linear yellow streaks along the flexures in the palmar surfaces of hands and fingers (fig. 1). In the region of both elbows there were aggregations of raised nodules over the olecranon process and flatter streaks along the skin folds on the flexor surface. On both feet, nodules were present over the ball of the big toe and the heel. Small patches occurred around the

FIG. 1

nothing of importance in the family history and there was no Jewish strain in the ancestry. At the age of two weeks the child had had a severe umbilical haemorrhage, and shortly afterwards developed jaundice. Repeated attacks of jaundice associated with bronchitis, continued up to the time when she came under observation, and had been more frequent during the period 1936-38. The skin lesions appeared in 1937, first on the fingers and elbows, and later increased in size and number and became generalized.

Examination showed an undersized child, but of normal proportions. (Weight 31 lb. 6 oz.) She was

knees, over the upper and outer edge of the patella on both sides, and in the popliteal fossae. There were none on the front of the trunk, a few over the scapulae and one on the vulva. The nodules were well marked over the face and neck, appearing on the back of the neck, in the skin flexures over the front of the neck, and at the corners of the mouth and eyes; there were large deposits in both ears. The child was constantly scratching.

The throat was normal; the teeth were badly formed and carious.

The systolic blood pressure was 140 mm. Hg

but otherwise the cardio-vascular system was normal.

The liver was enlarged two fingerbreadths below the costal margin and the spleen also moderately enlarged.

There were no abnormal physical signs in the central nervous system, but while in hospital the child showed occasional choreiform movements, twitching of muscles on the outer side of thigh, and involuntary movements of flexion of the knees. The optic fundi were examined by Mr. J. S. Arkle; he found some choroid atrophy and a 'pepper and salt' fundus, not regarded as of any special significance.

Radiological examination of the limbs, skull, pelvis, and chest showed no abnormality.

The Wassermann reaction was negative. The haematological examination showed: red cells, 3,580,000 per c.mm. (reticulocytes 2.6 per cent.), haemoglobin 65 per cent., colour index 0.91, leucocytes 8,600 per c.mm.

The urine showed heavy albuminuria and a gross excess of urobilin. Microscopic examination of the urinary deposit showed abundant leucocytes, some renal epithelial cells and a few 'fatty' casts. Under the polarizing microscope, anisotropic spherocrystals were seen, some in casts and in epithelial cells, and some as free droplets.

A glucose tolerance test, with a dose of 1 gm. glucose per kgm. body weight, gave the following blood sugar curve: Before, 0.105 per cent.; $\frac{1}{2}$ hr. after 0.140 per cent.; 1 hr. after, 0.122 per cent.; $1\frac{1}{2}$ hr. after, 0.107 per cent.

The total serum bilirubin was 0.8 mgm. per 100 c.c. of which 0.32 mgm. per 100 c.c. gave the direct Van den Bergh reaction. The blood urea was 52 mgm. per 100 c.c. The fragility of the red blood cells was normal.

The plasma lipoids, in the fasting state, showed an extraordinary picture (see table 1). The lipoid phosphorus, estimated in the first instance as the total phosphorus in a Bloor extract, was 203 mgm. per 100 c.c., corresponding to 5080 mgm. per 100 c.c. as phospholipin. This amazing result was confirmed by separation of the phospholipins from the lipoid extract, as will be described more fully later. It appears to be unprecedented.

Sphingomyelin and glycerophosphatide (lecithin and kephalin) contributed about equally to the plasma phospholipins.

The total plasma cholesterol was 2600 mgm. per cent., of which 610 mgm. per cent. was free cholesterol. Such figures, though rare, have been recorded in other types of severe lipaemia. In this case, as in other pathological lipaemias, the increase in cholesterol and phospholipin was confined to the plasma. On May 20, 1938, the corpuscles were analysed and showed 403 mgm. per 100 c.c. phospholipin and 120 mgm. per 100 c.c. cholesterol.

The total fatty acids of the plasma were completely accounted for by fatty acids in combination as phospholipin and cholesterol ester. There was therefore no measurable amount of fat as glycerol ester.

A biopsy specimen of a cutaneous nodule was examined by Dr. J. G. Thomson. Paraffin sections

TABLE 1
PLASMA LIPOIDS OF J.M. IN THE FASTING STATE

Plasma lipoids (mgm. per 100 c.c.)								
Date	Regime	Total lipoids	Phospho-lipin	Total cholesterol	Free cholesterol	Cholesterol ester		Glyceride
						Cholesterol	Fatty acid	
2.5.38	Full normal diet	9140	5080	2600	610	1990	1500	0
4.5.38		—	5270	—	—	—	—	—
20.5.38		6510 *	3970	1816	520	1296	613	0
June to October, 1938.	Light diet poor in fat							
20.10.38		3890 *	2185	979	521	458	364	227
23.10.38	Vegetable diet started							
8.11.38		—	1588	694	—	—	—	—
17.11.38		—	1880	750	—	—	—	—
24.11.38		—	1600	872	—	—	—	—
1.12.38		—	1860	757	—	—	—	—
1939	Light diet poor in fat							
10.2.40		5410	3350	1541	897	644	518	0
28.4.41		—	1783	1035	818	217	—	—

* The total lipid on these occasions included a little unsaponifiable matter other than cholesterol. This accounts for the fact that total lipoids are a little higher than the sum of phospholipin, free cholesterol, cholesterol ester, and fat.

showed the characteristic accumulation of xanthoma cells, with no inflammatory reaction. Frozen sections examined under the polarizing microscope showed the spherocrystals characteristic of cholesterol ester.

The child remained in hospital through May, 1938. Before her admission the diet had included much milk. On a diet of lower fat content all fractions of the plasma lipoids, though still extremely high, showed some reduction from the initial level. After this investigation in hospital the child was sent home and during the next five months was taking a diet low in animal fat. This was not a strictly quantitative diet, but the intake of animal fat was probably about 10 gm. per day. During this period she was generally better in health, free from jaundice, and free from itching of the skin.

She was admitted to hospital again in October, 1938, in order to try the effect of a diet entirely free of animal fat as recommended by Thannhauser (1935).

At this stage the liver and spleen were still enlarged and the xanthoma was just as extensive as in May. Her weight was now 33 lb. 10 oz. On admission a laevulose tolerance test was made after 15 gm. laevulose, with analysis of the blood laevulose by the writer's method (Herbert and Davison, 1938). The rises in blood laevulose above the fasting level were: at $\frac{1}{2}$ hr., 14.5 mgm. per 100 c.c.; at 1 hr, 13.0 mgm. per 100 c.c.; and at 2 hr., 12.0 mgm. per 100 c.c. This curve falls near the upper limit of normal, and shows no definite deficiency in laevulose tolerance (Herbert and Davison, 1938; Herbert, 1939).

The total serum bilirubin was at this time 0.56 mgm. per 100 c.c. and there was a positive direct Van den Bergh reaction. The blood urea was 39 mgm. per 100 c.c. The urine still contained albumin but no other abnormal constituent, and the deposit at this time was normal.

As a result of a suggestion made by Dr. Thannhauser in correspondence about the case, a test of the response of the blood sugar to adrenaline was made. It showed a normal rise of 0.038 per cent. above the fasting level, which was 0.08 per cent.

The plasma lipoids on admission were still very high, though the levels had fallen considerably from those observed in May (table 1).

A diet consisting entirely of vegetable foods was next instituted. The rationale of this treatment is that vegetable sterols are not absorbed, so that by a purely vegetable diet all exogenous cholesterol is eliminated. The daily diet gave 1430 calories (94 calories per kgm. body weight), 42 gm. protein (2.75 gm. per kg. body weight), 206 gm. carbohydrate and 41 gm. fat. The principal sources of protein were cereals (bread and oatmeal), lentils, and peanuts, and the fat was obtained chiefly from vegetable margarine and peanuts. Calcium and vitamin D were given as supplements. The only fluids given were water and lemonade. The child took the diet well and it was maintained for six weeks.

After a fortnight on this regime the plasma phospholipin had fallen from 2180 mgm. per 100 c.c. to 1590 mgm. per 100 c.c., and the total cholesterol from 979 mgm. per 100 c.c. to 694 mgm. per 100 c.c.; after this the levels fluctuated but fell no further.

This response to treatment was considered insufficient to justify the maintenance of a difficult

quantitative diet, and the child was discharged on the less stringent diet which she had previously taken at home. This was continued until February, 1940, when she came into hospital again for investigation.

Her age was now nine years and her weight 35 lb. The xanthoma showed the same distribution as before, but the lesions were larger. The liver and spleen remained enlarged but were rather smaller than before (liver one fingerbreadth below the costal margin, and the spleen palpable only on inspiration).

The albuminuria was still present, and the urine deposit showed numerous leucocytes, and a few renal epithelial cells, but no casts.

The total serum bilirubin was 1 mgm. per cent. and there was a faint direct Van den Bergh reaction. The blood urea was 50 mgm. per 100 c.c.

The laevulose tolerance test was repeated, and the rises in blood laevulose above the initial level were 5.7, 5.7, and 0 mgm. per 100 c.c. at $\frac{1}{2}$, 1, and 2 hr. respectively.

The plasma lipoids had risen during the period at home, but were not so high as when the child first came under observation. The characteristics of the lipoidaemia were the same as before; there was the same preponderance of phospholipin, with great rises also in free and combined cholesterol and absence of glycerol fat.

In April, 1941, the child had another spell in hospital. Her weight was now 39 lb. and her height 3 ft. 7 $\frac{1}{2}$ in. The xanthomatous lesions were as extensive as before and similarly distributed. In addition, lesions were noticed on the gums. The liver extended one fingerbreadth below the costal margin and the spleen was just palpable. The heart was enlarged and the blood pressure had increased to 165 mm. systolic, 100 mm. diastolic.

The eyes were examined again by Mr. Arkle, who reported an exaggerated form of 'tiger-striped' fundus.

The blood count showed: red cells, 3,590,000 per c.mm.; haemoglobin, 70 per cent.; colour index, 0.97.

In the laevulose tolerance test the rise of blood laevulose above the apparent fasting level was at $\frac{1}{2}$ hr. after the test dose, 10.9 mgm. per 100 c.c.; at 1 hr., 11.9 mgm. per 100 c.c.; and at 2 hr., 4.4 mgm. per 100 c.c.

The serum bilirubin was now normal (0.32 mgm. per cent.) and the direct Van den Bergh reaction was negative. The ordinary level of blood urea was 56 mgm. per 100 c.c.; it rose to 140 mgm. per 100 c.c. 1 $\frac{1}{2}$ hr. after a dose of 10 gm. urea. In the urea concentration test the maximum concentration of urea in the urine was 1.46 per 100 c.c. The standard blood urea clearance (corrected for body size) was 26 per cent. of normal.

The urine still contained a large amount of albumin and the deposit showed numerous leucocytes, occasional red blood cells, and some renal epithelial cells, but no casts. A catheter specimen gave a growth of *B. coli*.

The plasma lipoids remained at a level greatly above normal, though lower than they had been fourteen months earlier (see table 1).

At the end of March, 1942, the child's medical attendant reported that she was active and in good general condition, but had not grown.

The plasma lipoids

Analytical schemes. The volume of plasma used for the analysis on May 2, 1938, was 4 c.c. and for the later full analyses 6.5 to 7 c.c. The amounts of lipid present were so large that, even with these amounts of plasma, it was possible to employ methods depending on the separation and gravimetric estimation of the various fractions.* An analytical scheme suitable for lipaemic plasma has already been described (Herbert, 1937). The details will not be repeated here, but the scheme provided for analysis of three samples of a primary lipid extract, one being used for estimation of lipid phosphorus, one for the gravimetric estimation of free cholesterol, and the third, and largest, sample for the saponification of the total lipoids and the separation and gravimetric estimation of the total cholesterol and total fatty acid. The fat (triglyceride) was calculated indirectly from the fatty acid. The total fatty acid includes fatty acid originally in combination as phospholipin, cholesterol ester, and fat. Since phospholipin and combined cholesterol were known, the fatty acids in these fractions could be allowed for and the remaining fatty acid not thus accounted for was taken as the fatty acid combined as fat.

The first sample analysed in the investigation of the present case was dealt with by essentially the same scheme as the above, but as soon as the special

* For example, in the specimen of May 2, 1938, a sample of the lipid extract corresponding to 3 c.c. plasma yielded 78 mgm. of white crystalline unsaponifiable matter, which on analysis was found to be entirely cholesterol.

features of the case were known, a different scheme was adopted in which the phospholipins were precipitated with acetone and magnesium chloride and the acetone-insoluble and acetone-soluble fractions separately worked up. This allowed of the separate investigation of the phospholipin fraction; it also gave better conditions for the calculation of the glycerol fat fraction, as will be explained later.

The new scheme of analysis, in its most complete form, is summarized in table 2. The principal difference from the old scheme is in the separation of the acetone-soluble and acetone-insoluble lipoids. (When an estimate of the total acetone-insoluble lipoids was required, it was obtained from the difference between the total ether-soluble lipoids and the acetone-soluble lipoids, as indicated in the table; it was only for this purpose that the weights of these extracts were needed, and they were not taken on every occasion.) There are two other differences from the earlier published scheme. The first is the removal of the alcohol and ether from the original Bloor extract at a temperature below 40° C. in order to avoid loss of phospholipin (Herbert, 1937; Ellis and Maynard, 1937). The second difference is that in dealing with the acetone-soluble fraction, the digitonide precipitation of the free cholesterol is first performed, and the lipoids not precipitated (cholesterol ester and fat) are collected quantitatively and used for saponification and separation of unsaponifiable matter and fatty acids. This was done for the sake of economy of material.

The phospholipin precipitate. Observations were

TABLE 2

PRIMARY EXTRACTION OF PLASMA LIPOIDS BY BLOOR'S METHOD (7 c.c. PLASMA TO 250 c.c. TOTAL VOLUME)

Sample for phosphorus	MAIN FRACTIONATION (200–225 c.c. Bloor extract)		
	<ol style="list-style-type: none">1. Solvent removed in vacuo below 40° C. Residue extracted with ether.2. Solvent removed from ether extract. Weight of total lipoids obtained.3. Lipoids re-dissolved in ether. Phospholipins precipitated with acetone and MgCl₂. Quantitative separation of acetone-insoluble and acetone-soluble fractions.		
	PHOSPHOLIPIN PRECIPITATE	ACETONE SOLUBLE FRACTION	
	Weight calculated by difference between total and acetone-soluble lipoids	<ol style="list-style-type: none">1. The lipoids were freed from the MgCl₂ as follows: Acetone solution diluted with water. Lipoids extracted with mixed ether and petroleum. Extract washed with water.2. Solvent removed and lipoids weighed.3. Lipoids dissolved in alcohol and treated with digitonin for precipitation of free cholesterol.	
	Precipitate used for one or more of the following analyses:		
	<ol style="list-style-type: none">1. Phosphorus2. Phospholipin fatty acids3. Sphingomyelin by reineckate method	DIGITONIDE PRECIPITATE	LIPOIDS NOT PRECIPITATED BY DIGITONIN.
		Gravimetric estimation of free cholesterol	Collected quantitatively in ether solution, and saponified with sodium ethylate. Unsaponifiable matter and fatty acids separated and purified.
			UNSAPONIFIABLE FRACTION
			<ol style="list-style-type: none">1. Weight of unsaponifiable matter obtained2. Estimation of cholesterol
			FATTY ACIDS
			Weight obtained

made on the precipitated phospholipins firstly, to confirm the extraordinarily high figures obtained in estimations of lipid phosphorus, and secondly, to get information on the proportions of glycerophosphatides and sphingomyelin in the phospholipin mixture.

On two occasions, the total acetone-insoluble lipoids were estimated, as well as the phosphorus in the phospholipin precipitate. On May 20, 1938, the total phospholipin, estimated from the acetone-insoluble lipoids, was 3970 mgm. per 100 c.c. plasma, and the phosphorus in the precipitate 141 mgm. per 100 c.c. plasma; on February 10, 1940, the total phospholipin precipitated was 3970 mgm. per 100 c.c. plasma, and the phosphorus 136 mgm. per 100 c.c. plasma. The phosphorus, expressed as a percentage of the phospholipin, was 3.55 per cent. and 3.43 per cent. on these occasions.

The proportion of phosphorus to total phospholipin varies somewhat for different phospholipins, but the following are theoretical values for some typical compounds: Palmityl-oleyl lecithin, 3.99 per cent.; stearyl-arachidonyl lecithin, 3.75 per cent.; stearyl-linoyl cephalin, 4.17 per cent.; stearyl arachidonyl cephalin, 4.04 per cent.; lignoceryl sphingomyelin, 3.72 per cent. It has been usual, in calculating phospholipin from lipid phosphorus, to assume the factor 4 per cent. as the phosphorus content of phospholipin. Ellis and Maynard (1937) determined the factor for the phospholipins of bovine plasma and found 3.57 per cent., a value close to that obtained in the present work. Possible analytical errors in these determinations are the over-estimation of the total acetone-insoluble material due to slight contamination with non-lipoid material, and the under-estimation of the phosphorus of the precipitated phospholipin due to slight losses in manipulation. Both would have the effect of lowering the percentage of phosphorus found. For convenience the conventional value of 4 per cent. has been used in calculating phospholipin from phosphorus in the present work, and the figures given in table 1 were obtained in this way. Any error due to the use of this factor would result in figures slightly lower than the true values.

The behaviour of the phosphorus at different stages of the analytical scheme has also been followed. Comparisons between the phosphorus of the original Bloor extract, of the ether extract obtained from it (after removal of the solvent and extraction of the residue) and of the phospholipin precipitate are shown in table 3. The phosphorus of the Bloor extract is completely recovered in the ether extract, and there is either a slight loss, or none, during precipitation and re-solution of the phospholipin.

TABLE 3

Date	Lipoid phosphorus, mgm. per 100 c.c. plasma, found in:		
	Original Bloor extract	Ether extract	Phospholipin precipitate
4.5.38	211	208	189
20.5.38	157	154	141
20.10.38	87.7	—	87.4
10.2.40	134	—	136

These results confirm that the high phosphorus of the Bloor extract is all, or almost all, true lipid phosphorus.

Plasma phospholipins consist of a mixture of glycerophosphatides (lecithins and cephalins) and sphingomyelins. The glycerophosphatides have one atom of phosphorus and two fatty acid radicles in the molecule, and the sphingomyelins one atom of phosphorus and one fatty acid radicle. The ratio of phosphorus to fatty acid can therefore be used as a measure of the proportion of glycerophosphatide and sphingomyelin.

Estimates of the phospholipin fatty acids were made on two occasions (May 4, 1938 and February 10, 1940). On the first occasion, the separated phospholipins were saponified with sodium ethylate, the fatty acids were liberated from the soaps obtained, purified, and estimated both by direct weighing and titration. The ratio found was one atom of phosphorus to 1.55 molecules of fatty acid. As the amount handled was small, this is an approximate figure. It corresponds to a mixture of 45 per cent. sphingomyelin and 55 per cent. glycerophosphatide. Further experience with this procedure showed that alkaline hydrolysis of phospholipin under these conditions might involve difficulties in quantitative handling, probably due to the presence of magnesium, as noted by Stewart and Hendry (1935). Therefore, on February 10, 1940, the phospholipins were subjected to acid hydrolysis. The phospholipins in methyl alcohol solution were hydrolysed with hydrochloric acid, the resulting methyl esters of the fatty acids were extracted, purified, and weighed, and the fatty acids calculated from the weight of the methyl esters. The ratio obtained was one atom of phosphorus to 1.61 molecules of fatty acid. This corresponds to a mixture of 39 per cent. sphingomyelin and 61 per cent. glycerophosphatide.

On another occasion (October 20, 1938) sphingomyelin was directly estimated by the method of Thannhauser and Setz (1936). The phospholipin precipitate was dissolved in methyl alcohol and the sphingomyelin precipitated as the reineckate and estimated gravimetrically.* The sphingomyelin amounted to 692 mgm. per 100 c.c. plasma, and the total phospholipin 2185 mgm. per 100 c.c. plasma; or, of the phospholipin mixture, 32 per cent. was sphingomyelin and 68 per cent. glycerophosphatide.

These results show that both the glycerophosphatide fraction and the sphingomyelin are enormously increased in this case, and that the proportions of the two fractions are not greatly different from those occurring normally. Stewart and Hendry (1935) found that for the phospholipins of whole blood the ratio of phosphorus to fatty acids was one atom of phosphorus to 1.5 molecules of fatty acid, indicating equal parts of glycerophosphatide and sphingomyelin. Thannhauser and Setz (1936), using the reineckate method, found varying proportions in normal human plasma, the sphingomyelin usually constituting from 44 to 64

* In calculating the sphingomyelin from the weight of its reineckate the factor of Thannhauser and Setz has been used (sphingomyelin = reineckate $\times 0.877$). The sphingomyelin complex in serum gives two reineckates, one soluble and the other insoluble in cold acetone. The acetone-insoluble fraction is regarded by the authors as a reineckate of a trimeric sphingomyelin, and it is to this compound that the factor 0.877 applies. The other reineckate may be formed from a monomeric sphingomyelin. The effect of using the factor 0.877 for the total reineckate, as has been done in the present work, will probably be a slight overestimate of the sphingomyelin.

per cent. of the total phospholipin, with occasional higher values.

The calculation of fat (glyceride). In the older scheme of analysis (Herbert, 1937) the total fatty acids of plasma were estimated. The fatty acids of phospholipin and cholesterol ester were calculated, and the remainder of the fatty acid not accounted for as phospholipin and cholesterol ester represented the fatty acid in combination as glycerol fat. This method involves an uncertain assumption as to the fatty acid obtained from phospholipin, since the fatty acid corresponding to the total phospholipin varies according to the proportions of glycerophosphatide and sphingomyelin in the mixture. No serious error is introduced when phospholipin forms a small proportion of the total lipoids, but in the present case, with the large proportion of phospholipin, the fat could only be calculated by the above method if the proportion of fatty acid in the phospholipin mixture was known.

In the analysis of May 2, 1938, in which the acetone-insoluble and acetone-soluble lipoids were not separated, the calculation was made on the basis of the determination of phospholipin fatty acids two days later. The total fatty acids were completely accounted for as phospholipin and cholesterol ester.

In the analyses of May 20, 1938, October 20, 1938, and February 10, 1940, the acetone-insoluble and acetone-soluble fractions were separated. The fatty acids of the acetone-soluble lipoids can only be derived from cholesterol ester and fat, so that if fat is present, there will be an excess of fatty acids relative to combined cholesterol. On May 20, 1938, the amount of fatty acid obtained was actually less than would have been expected from the combined cholesterol. It was shown that this was not due to incomplete saponification. It might be explained if some of the cholesterol was in combination with short-chain fatty acids which would be lost during the washing of the fatty acids. On October 20, 1938, there was a definite fat fraction, though it was a small amount compared with the other lipoids. On February 10, 1940, the fatty acid of the acetone-soluble fraction was exactly equivalent to the combined cholesterol.

Discussion

The mechanisms involved in the metabolism and transport of lipoids, and the physiological relations between the different lipoids, are by no means fully understood, and it is therefore impossible to give an adequate account of the derangements which lead to abnormal accumulations of lipid in the blood and tissues in pathological conditions. In general, rises in blood lipoids may occur as a result of excessive mobilization, or diminished excretion, or over-production in endogenous metabolism. Abnormal accumulations of cholesterol in tissues (excluding purely local conditions) may be the result of gross increases in the plasma cholesterol, or may occur as a lipoidosis involving the reticulo-endothelial system without abnormalities in the blood.

The lipidaemia of diabetes, and of renal disease (lipoid nephrosis and subacute nephritis) are

probably due to increased mobilization of lipoids from the tissues. The hypercholesterolaemia of diabetes may be of extreme degree and may lead to cutaneous xanthoma and to deposits of cholesterol ester in the reticulo-endothelial system. The hypercholesterolaemia of the 'nephrotic syndrome,' though often considerable, does not ordinarily reach the levels met with in diabetic xanthomatosis, and does not lead to cutaneous xanthoma. Cholesterol ester is deposited in the kidneys, but the relation between the plasma lipoids and kidney deposits is obscure.

In biliary obstruction the plasma cholesterol is increased as a result of retention of cholesterol which would normally be excreted in the bile. The association of xanthomatosis with jaundice is well known, but, as will be indicated later, it is not possible to attribute this association to biliary obstruction alone.

There remain a number of conditions in which generalized xanthomatosis occurs, with or without hypercholesterolaemia, in which the primary cause is unknown, and which must be classed as 'idiopathic.' A classification of these conditions has been put forward by Thannhauser and Magendantz (1938). These authors regard all these types of 'primary essential xanthomatosis' as due to a cellular metabolic disorder of the reticulo-endothelial system with overproduction of cholesterol. The group of diseases is, however, heterogeneous, and may well include conditions of different etiology. The chief interest in the classification of Thannhauser and Magendantz is their analysis of the different conditions in relation to plasma cholesterol, the type of skin lesions found, and the liability of different internal organs to involvement in the lipoidosis. It is used here as an empirical classification without accepting the authors' etiological theory as applying throughout the group.

There are two main divisions, the 'hypercholesterolaemic' and the 'normocholesterolaemic' type.

In the 'hypercholesterolaemic' type the rises in plasma cholesterol are of varying degree but often are not very great, so the xanthomatosis is probably not simply the result of the high blood cholesterol. In this type the skin lesions have the form of 'xanthoma tuberosa' and 'xanthoma plana.' Associated lesions are xanthomata of tendons and tendon sheaths, and of the endocardium and blood vessels, and the syndrome of 'xanthomatous biliary cirrhosis' of the liver. The authors' analysis of cases seems to indicate two subdivisions in the hypercholesterolaemic group. In the first are grouped cases with tendon xanthoma, skin lesions, and cardiovascular lesions, occurring separately or together. In the second subdivision comes the syndrome of xanthomatous biliary cirrhosis with jaundice and skin lesions.

In 'primary essential xanthomatosis of the normocholesterolaemic type' the plasma cholesterol is normal; the skin lesions, when present, are of the form 'xanthoma disseminata,' and the

other organs which may be involved, separately or together, are the bones (Schüller-Christian syndrome), the pituitary, tuber cinereum, and other parts of the brain, and the lungs and pleurae.

Thannhauser and Magendantz regard 'primary essential xanthomatosis' as analogous to the other primary lipidoses, Niemann-Pick's disease and Gaucher's disease. All are conditions in which lipoids accumulate in the cells of the reticulo-endothelial system. In the xanthomatoses the lipid is cholesterol ester. In Niemann-Pick's disease phospholipin, and to a less extent cholesterol, are involved (Epstein and Lorentz, 1930, 1932; Baumann, Klenk and Scheidegger, 1936; Sobotka et al., 1933; Tenuissen, 1937; Tropp and Eckardt, 1936, 1937), and it has been shown by Klenk (1934, 1935) that the phospholipin which accumulates in the tissues is sphingomyelin. There may be a rise in blood cholesterol, but when this occurs it is not usually very great (Baumann, Klenk and Scheidegger, 1936). The plasma phospholipin in Niemann-Pick's disease has not been adequately studied. In Gaucher's disease the lipid is a cerebroside, kersin, a compound of glucose, sphingosine and lignoceric acid, and this is found in the tissues without any accumulation in the plasma. This condition is excluded from the present discussion, which is concerned only with phospholipins and cholesterol.

In all the conditions in which plasma cholesterol and cholesterol esters are increased, there is also a rise in the plasma phospholipin. This is true of diabetic lipaemia, and the lipaemia of the nephrotic syndrome. Biliary obstruction also leads to increases in plasma phospholipin as well as cholesterol (Chanutin and Ludewig, 1936; Stroebel, 1935). In various types of xanthoma associated with hypercholesterolaemia, with or without jaundice, rises in phospholipin have also been recorded. (Buerger and Grutz, 1932; Chanutin and Ludewig, 1937; Herbert, 1937; Montgomery and Osterberg, 1938; Thannhauser and Magendantz, 1938). There is therefore some relation between phospholipin and cholesterol, common to all conditions in which cholesterol is increased in the plasma, in spite of the great variety in the etiology. Yet the lipoidaemia in the case here reported has special features. In most pathological lipaemias the greatest increase is in the fat; cholesterol and cholesterol esters come next in order, and the phospholipins show less increase (see Herbert, 1937, and other literature there cited). In the present case the order was reversed; there was little or no fat, an enormous rise in cholesterol and cholesterol ester, and an even greater rise in phospholipin.

In the case here reported, there was intermittent jaundice for many years, followed by the appearance of cutaneous xanthomatosis. The jaundice was slight or absent during the period of observation (1938 to 1941) when the features of the case were gross increases in plasma phospholipin, cholesterol, and cholesterol ester, cutaneous xanthoma taking the form of 'xanthoma tuberosa' and 'xanthoma

plana,' enlargement of the liver and spleen, and renal disease with azotaemia and hypertension. There was no oedema at any stage of the disease, and diabetes was excluded.

The rise in plasma lipoids was so extreme that it is reasonable to suppose that the lipid deposits in the tissues were secondary to the lipoidaemia, but the cause of the lipoidaemia is quite obscure. Possible primary causes suggested by the clinical picture are renal disease and jaundice. The renal disease ran its course without oedema and with azotaemia and hypertension, so that the picture bore no resemblance to lipid nephrosis. At one time the urine deposit showed spherocrystals under the polarizing microscope, indicating that the kidney was involved in the lipoidosis, but later examinations were negative. Moreover, the increases in plasma phospholipin and cholesterol were far greater than would be expected if the renal disease were the primary abnormality. It seems that the involvement of the kidney was incidental to the general disorder of lipid metabolism rather than the primary condition.

The next question that arises is the association of jaundice and xanthoma. This association is well known, and in the majority of cases reported the jaundice has been present for months or years before the development of cutaneous xanthomatosis. Some authors have considered that biliary obstruction, with consequent retention of cholesterol, accounts for the syndrome. It is difficult to accept this interpretation, because chronic biliary obstruction is a common condition and does not usually lead to cutaneous xanthomatosis even when the obstruction is of long standing. In the case reported in the present paper, biliary obstruction cannot account for the syndrome, as there was no indication of extrahepatic biliary obstruction, and the lipoidaemia and xanthomatosis persisted for a long period after the jaundice had almost disappeared.

Thannhauser and Magendantz (1938) have drawn attention to the syndrome of 'xanthomatous biliary cirrhosis.' The clinical picture is of chronic enlargement of the liver and spleen with jaundice and hypercholesterolaemia, and cutaneous xanthoma. They believe that the primary abnormality is a disorder of cholesterol metabolism, leading to xanthomatosis of the larger bile ducts, followed by scarring and partial obstruction, which in turn initiates biliary cirrhosis of the liver. It certainly seems that a large proportion of the recorded cases of chronic jaundice with cutaneous xanthoma have shown biliary cirrhosis, but it is not easy to determine whether the xanthomatous diathesis precedes the liver disease or follows it. The chronic jaundice precedes the cutaneous lesions, and at the time when cutaneous xanthomata occur the hypercholesterolaemia is sometimes extreme. For example Dyke (1928) reported a case of this type with a total plasma cholesterol of 1250 mgm. per 100 c.c. and free cholesterol 1030 mgm. per 100 c.c. Chanutin and Ludewig (1937) recorded one with total plasma cholesterol ranging from 632 to 1480 mgm. per 100 c.c., with low

cholesterol ester, and with plasma phospholipins 1280 to 2480 mgm. per 100 c.c. (Figures re-calculated and expressed as phospholipin. In the original they are given as lipid phosphorus.) The second case of Buerger and Grutz (1932) is similar, with total plasma cholesterol 2575 mgm. per 100 c.c., free cholesterol 1440 mgm. per 100 c.c., and phospholipin 3045 mgm. per cent., and Weidman and Boston (1937) described another case with blood cholesterol 1020 mgm. per 100 c.c. The syndrome may occur with more moderate degrees of hypercholesterolaemia, but on the whole it would seem that the skin lesions are secondary to the increase in blood lipoids, and it is very doubtful whether such cases should be classed as 'primary essential xanthomatosis' in the sense in which Thannhauser and Magendantz use the term, as a disorder originating in the cells which become xanthoma cells.

It seems unlikely that the case reported in the present paper is one of xanthomatous biliary cirrhosis. The subsidence of the jaundice is strongly against the diagnosis of biliary cirrhosis. Also there was never any evidence of deficient hepatic function in the laevulose tolerance test based on analysis of blood laevulose, though this was repeated at intervals during three-and-a-half years. Another point against damage to the liver parenchyma is the high level of cholesterol ester in the plasma. Liver damage is characteristically associated with deficient formation of cholesterol ester and a decreased ratio of combined cholesterol to free cholesterol in the plasma. In the present case, the first observation showed that the cholesterol ester was very high, being increased in about the same proportion as the free cholesterol. Later, with diminution of the lipidaemia, the cholesterol ester showed a greater fall than the free cholesterol and phospholipin, but still remained abnormally high in absolute amount. Therefore, although the possibility of an early cirrhosis cannot be excluded, the evidence is against any gross disorganization of the liver.

It is probable that the enlargement of the liver and spleen was due to lipid deposits. So far as the period of investigation is concerned, the high blood lipoids would account for it. It is more difficult to interpret the jaundice of the preceding years, but it may have been due to early involvement of the liver in a lipoidosis which later became more generalized. It is of interest to consider other cases in which the liver was involved, but probably without cirrhosis.

Montgomery (1938) records the case of a girl aged nineteen years. She had an attack of jaundice at the age of ten, lasting three weeks, and immediately followed by cutaneous xanthoma tuberosum. The liver function was normal at the time when she came under observation, though the xanthomata were still present and the plasma cholesterol was 641 mgm. per 100 c.c.

Another case with involvement of the liver and spleen without jaundice is the first case of Buerger and Grutz (1932). This was a boy aged twelve. He had cutaneous xanthomatosis dating from the first

year of life, and a history of 'disease of the spleen and nephritis' at the age of eleven. The liver and spleen were enlarged. The analysis of the plasma at the first observation showed: phospholipin 1740 mgm. per 100 c.c., total cholesterol 686 mgm. per 100 c.c., free cholesterol 310 mgm. per 100 c.c., combined cholesterol 376 mgm. per 100 c.c., and total lipoids 9476 mgm. per 100 c.c. On a fat-free diet, the blood lipoids fell in a striking manner, though not quite to normal; the liver and spleen returned to normal size, and the xanthomatosis regressed, so that at the end of eight months only the remains of old lesions were to be seen.

This case of Buerger and Grutz is similar to that reported in the present paper. Both are instances of juvenile xanthoma with enlargement of the liver and spleen and with great increases in plasma phospholipin and cholesterol. The most important difference is in the response to a fat-free diet, which was good in the case of Buerger and Grutz and unsatisfactory in the present case.

This case, and others already mentioned, showed greatly increased plasma phospholipin as well as increased cholesterol. Not many authors have considered the plasma phospholipins in xanthomatosis, but wherever analyses have been made hypercholesterolaemia has been associated with high plasma phospholipin. In the work of Thannhauser and Magendantz (1938) and in the present study, rises in both sphingomyelin and glycerophosphatides have been found. The question therefore arises whether the primary metabolic disorder affects all these lipoids or whether their association in the blood is connected with the mechanisms regulating transport. It is noteworthy that in the present case, the two cases of Buerger and Grutz (1932), and the case of Chanutin and Ludewig (1937), all of which are instances of xanthomatous disease with involvement of the liver, the increases in plasma phospholipin are even more striking than the increases in cholesterol, high as these are. On the other hand in diabetic lipaemia with a comparable degree of hypercholesterolaemia the increase in phospholipin is relatively less (Herbert, 1935, 1937). Therefore it seems probable that the gross increase in plasma phospholipin found in some xanthomatous diseases is an expression of some fundamental disturbance of phospholipin metabolism, and not a secondary result of hypercholesterolaemia.

For this reason it is of interest to consider whether there is any relation between these cases of xanthoma and the Niemann-Pick syndrome. The typical picture of Niemann-Pick's disease is quite different, as it is a rapidly fatal disease of infancy, and in general hypercholesterolaemia, when it occurs, is of moderate degree.

Yet there is one reported case of a child aged five-and-a-half (Chevrel et al., 1937) which should probably be regarded as Niemann-Pick's disease running an unusually chronic course. The liver and spleen were grossly enlarged, and both histologically and chemically the lipoidosis was of the Niemann-Pick type. The blood cholesterol was 250 mgm. per cent., and there was no cutaneous xanthomatosis.

There may therefore be some relation between this syndrome and idiopathic xanthomatosis, since phospholipins and cholesterol are concerned in both. On the other hand the preponderance of sphingomyelin in the tissues is characteristic of the Niemann-Pick syndrome, whereas in the xanthomatosis the main deposit in the tissues is cholesterol ester, and in the plasma sphingomyelin and glycerophosphatide are both increased.

In conclusion, it may be said that although little is known of the true nature of the metabolic disorders in idiopathic xanthomatosis, the unusual case here reported should probably be classified as idiopathic xanthomatosis of the hypercholesterolaemic type with involvement of the liver, spleen, and kidneys, and is especially remarkable in showing

enormously raised plasma phospholipins as well as cholesterol.

Summary

A case of juvenile xanthomatosis is reported, with arrested growth, enlargement of the liver and spleen, renal disease with hypertension, and enormous increases in plasma phospholipins and cholesterol.

The abnormalities in plasma and tissue lipoids in various pathological syndromes, and the classification of xanthomatous diseases, are discussed, and the case compared with others reported in the literature.

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