Disorders of the Serum Lipoproteins

II: Hyperlipoproteinaemic States*

JUNE K. LLOYD

From the Institute of Child Health, University of London, and The Hospital for Sick Children, Great Ormond Street, London W.C.1

A classification of hyperlipoproteinaemia, based on the major lipoprotein species involved, is given in the Table.

**Primary Hyperlipoproteinaemias**

*Hyperchylomicronaemia* (familial fat-induced hypertriglyceridaemia). This condition, which is characterized by gross accumulation of chylomicrons in the serum due to defective clearing of dietary fat, was first described by Bürger and Grütz in 1932. Cases have since been recorded under a variety of names, the most common being ‘idiopathic familial hyperlipaemia’ and ‘essential hyperlipaemia’. The basic defect in most, though possibly not all, cases is a deficiency in the enzyme lipoprotein lipase (Fredrickson and Lees, 1966). The disease is inherited as an autosomal recessive and the gene frequency is not known. The severe homozygous form is probably rare, as Fredrickson and Lees (1966), using strict criteria for the definition of the syndrome, found only about 35 certain examples in a recent review of the published reports. An estimated incidence of 2-3% for the heterozygous state in a Swedish population (Hirschhorn et al., 1959) was based only on the demonstration of impaired clearing of absorbed fat and may have included cases of pre-β-lipoproteinemia.

**Clinical features and laboratory findings.** Eruptive xanthomata may appear at any age and are found especially on extensor surfaces (Fig. 1); the yellow papules may be surrounded by a small red halo and are often intensely irritant. Enlargement of the liver and spleen is common, and attacks of abdominal pain, often associated with vomiting, may occur in childhood and adolescence. The causal mechanism of the pain is not understood. The ocular fundi show lipaemia retinalis (Fig. 2).

<table>
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<th>Lipoprotein Species Involved</th>
<th>Primary Disorders</th>
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<tr>
<td>Chylomicron</td>
<td>Hyperchylomicronaemia (familial fat-induced hypertriglyceridaemia; familial hyperlipaemia)</td>
<td>Primary and secondary increase in pre-β-lipoprotein</td>
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<td>β</td>
<td>Hyper-β-lipoproteinaemia (familial hypercholesterolaemia)</td>
<td>Hypothyroidism; obstructive jaundice</td>
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<td>Pre-β</td>
<td>Pre-β-lipoproteinaemia (CHO-induced hypertriglyceridaemia; endogenous hypertriglyceridaemia; some 'mixed' hyperlipaemias)</td>
<td>Conditions in which CHO is not freely available: diabetes mellitus; glycogen storage disease; starvation; glucose/galactose malabsorption; Nephrotic syndrome; infantile hypercalcaemia; progeria</td>
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<td>α</td>
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<td>Liver disease; ? steroid therapy; pregnancy</td>
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* Part I was published in the August issue (*Arch. Dis. Child.*, 43, 393).
Non-specific symptoms such as pallor, irritability, and poor appetite may occur especially in young children. Symptoms in the individual child are variable and may be absent altogether, in which case the condition can only be detected by the chance finding of turbid serum or lipaemia retinalis. The outstanding feature on examination of the serum is the gross turbidity which is present even

Fig. 1.—Eruptive xanthomata in hyperchylomicronaemia. (a) Before treatment (serum triglyceride 3500 mg./100 ml.) (b) Two weeks after start of low-fat diet. (Serum triglyceride 400 mg./100 ml.)

Fig. 2.—Lipaemia retinalis in hyperchylomicronaemia. (a) Fundus photograph of patient with serum triglyceride 10,000 mg./100 ml. (b) Normal appearance.
in the fasting state. Lipoprotein electrophoresis shows a great increase in the chylomicron fraction, with reduction in the β- and α-fractions (Fig. 3). Chemical analysis reflects the composition of chylomicrons with a great increase in triglycerides, and a lesser increase in cholesterol and phospholipid. The proportion of unesterified cholesterol is greater than normal owing to the fact that about 50% of chylomicron cholesterol is unesterified. The clearing defect can be demonstrated by estimation of the plasma post-heparin lipolytic activity (PHLA) which is very low (Fredrickson, Ono, and Davis, 1963), and by measurements of the serum lipids after a fat meal (Fig. 4); compared with the normal there is an increase in the degree of chylomicronaemia, a delay in reaching peak values, and a failure to return to basal levels for as long as 24-48 hours. It is important that neither of these investigations should be done when the patient has been on a low fat diet for longer than

Fig. 3.—Paper electrophoretic patterns of serum lipoproteins in primary hyperlipoproteinaemic states. Tg, triglyceride; TC, cholesterol.
7 days, as under such circumstances even normal subjects may show abnormal responses (Fredrickson et al., 1963).

In the heterozygote there are no clinical manifestations, and the serum lipids and lipoprotein pattern do not show any consistent abnormalities. Fasting levels of triglyceride may be raised and pre-β-lipoprotein increased. Low levels of plasma PHLA have been reported (Fredrickson et al., 1963), as has delayed clearing of dietary fat (Bialkin et al., 1962). On the other hand, the serum lipoprotein patterns of both parents of an affected child may be completely normal and the clearing of fat unimpaired (Fredrickson, Levy, and Lees, 1967a).

**Treatment and prognosis.** A virtually fat-free diet renders the serum optically clear and greatly reduces the triglyceride level within 4–5 days (Fig. 5), though it may not reach its lowest level for 2 to 3 weeks. Normal triglyceride levels, however, are seldom achieved, as pre-β-lipoprotein may be increased owing to the relatively high carbohydrate content of a low fat diet, which promotes endogenous synthesis of triglyceride (Fredrickson et al., 1967a).

Concomitant with the reduction in chylomicrons, the total serum cholesterol and phospholipid concentrations fall, and in the treated patient are usually somewhat lower than normal owing to persistence of the reduced levels of β- and α-lipoproteins. Once the serum is clear, dietary fat should be increased up to the amount that will maintain a clear fasting serum with normal total lipid content. About 10–20 g daily can usually be given and should be distributed evenly between the main meals. Individual variations, however, are considerable, and there is no evidence that the quantity tolerated increases with the age of the child. Though a low-fat diet can be successfully maintained over the years (Lloyd and Wolff, 1968), it tends to be unpalatable, and the recent introduction of medium chain triglycerides (MCT) has greatly increased palatability as well as providing additional calories. The C₈ and C₁₀ fatty acids of MCT are absorbed directly into the portal bloodstream, and this type of fat does not therefore result in chylomicron accumulation (Furman et al., 1965).

The clinical response to dietary treatment is excellent; xanthomata disappear (Fig. 1), the liver and spleen return to normal size, attacks of abdominal pain cease, and general health and well-being improve. The ultimate prognosis is uncertain but is probably good, and recent work suggests that the accelerated development of atherosclerosis is not a feature of this type of hyperlipoproteinaemia (Fredrickson et al., 1967a; Kuo, 1967). Problems
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due to increased blood viscosity and the decreased tissue oxygen uptake which is associated with serum turbidity (Joyner, Horwitz, and Williams, 1960) may be important, particularly if there is an associated infection. In two babies who had gross hypertriglyceridaemia and septicemia, death occurred (Baba and Volk, 1964; D. Cottom, 1968, personal communication), and we have treated one infant at the age of 5 weeks who had a serum triglyceride level of 10,000 mg./100ml. and was very ill with *Salmonella typhimurium* septicemia. Deaths occurring in infancy due to so-called 'malignant hyperlipaemia' have also been reported (Hagberg *et al.*, 1964; Lusher and Farber, 1964), as has the association of hyperlipaemia with the haemolytic uraemic syndrome (Campbell and Carré, 1965). In 'malignant hyperlipaemia' additional haematological abnormalities (anaemia and thrombocytopenia) were present, and it is possible that this may be a different disease entity.

**Hyper-β-lipoproteinaemia** (familial hypercholesterolaemia). This condition is characterized by raised levels of β-lipoprotein and therefore by hypercholesterolaemia, and is inherited as an autosomal dominant with incomplete penetrance. The gene frequency is unknown; estimates in the United States of America and in Europe that the incidence of the heterozygous state may be as high as 5% are based on serum cholesterol levels, and as some people with hypercholesterolaemia undoubtedly have pre-β-lipoproteinaemia the true incidence cannot be assessed from these data.

The mechanism responsible for the accumulation of β-lipoprotein is not known. On present evidence it seems most likely that the genetic defect concerns the control of β-lipoprotein synthesis (Frederickson, Levy, and Lees, 1967b). Studies of cholesterol turnover (Lewis and Myant, 1967) are normal, as is the biological half-life of β-lipoprotein (Walton *et al.*, 1963).

**Clinical features and laboratory findings.** The homozygous form of the disease is rare and is characterized by the occurrence of tendon and tuberose xanthomata during childhood (Fig. 6). These usually appear at the age of 2-3 years but have been recorded at birth (McCleary, Brunsting, and Kennedy, 1959); they are most common over areas of friction such as the heels, elbows, and backs of the knees. Symptoms and signs of coronary insufficiency may occur as early as 7 years of age and become increasingly frequent in later childhood and adolescence. The serum is characteristically clear and has a very prominent β-lipoprotein band on electrophoresis (Fig. 3). Total cholesterol concentrations are over 700 mg./100 ml. and often of the order of 1000 mg./100 ml.; serum phospholipid levels are also raised, but triglyceride levels are normal or only slightly increased.

In the heterozygote there are often no clinical signs of the disease during childhood; occasionally, however, arcus senilis is present, indicating deposition of lipid in the cornea (Tschetter, 1966), and we have observed a well-marked arcus in 2 out of 12 children with heterozygous hypercholesterolaemia. Splenomegaly may also occur and was present in 4 of our patients; the pathogenesis of the enlarged spleen is not known. In adult life xanthomata and coronary artery disease frequently develop. Serum electrophoresis shows a marked β-lipoprotein band though it is less prominent than in the homozygous state (Fig. 3). Total cholesterol concentrations are usually between 300-500 mg./100ml.; phospholipid levels are moderately raised and triglyceride levels are usually normal.

The diagnosis depends upon (1) the finding of clear fasting serum, with raised concentrations of β-lipoprotein and cholesterol, and normal or only slightly raised levels of triglyceride; (2) the exclusion of other causes of hyper-β-lipoproteinaemia such as hypothyroidism and obstructive jaundice; and (3) the demonstration of hyper-β-lipoproteinaemia in other members of the family. The earliest age at which the diagnosis can be established with certainty is not known; in two children the finding of a high cholesterol level in umbilical cord blood has subsequently enabled the diagnosis to be made (Kaplan *et al.*, 1957; Wolff, 1967a), but normal cord blood cholesterol levels may not preclude the heterozygous state (Lewis, Brown, and Green, 1967).

**Treatment and prognosis.** In the heterozygous condition treatment with a polyunsaturated fat diet (Lloyd and Jukes, 1961) is successful in lowering serum cholesterol and β-lipoprotein levels to normal or near normal (Lloyd and Wolff, 1968). Reduction in the intake of saturated fat is an important part of the dietary regimen (M. M. Segall, unpublished observations), and the amount of ordinary dietary fat (which is largely saturated) should not exceed 10-15 g. daily. The remainder of the fat intake should consist of fats containing a high proportion of polyunsaturated fatty acids (corn oil, safflower oil), but there is no advantage in giving excessive amounts. The mechanism of the cholesterol lowering effect of such a diet is not fully understood. The feeding of polyunsaturated fat has been shown to be associated with an increase in the faecal excretion of sterols (Wood, Shioda, and Kinsell, 1966), and Spritz (1966) has postulated that
June K. Lloyd

Fig. 6.—(a) Hands, (b) knees, showing tendon and tuberose xanthomata in the homozygous form of primary hyper-β-lipoproteinaemia.

the incorporation of unsaturated fatty acids into the structure of lipoproteins reduces their cholesterol carrying capacity. The reduction in cholesterol intake consequent upon restricting saturated fats (especially if egg yolk is eliminated) undoubtedly also plays a part (Connor, Stone, and Hodges, 1964).

The association between familial hyper-β-lipoproteinaemia and the accelerated development of atherosclerosis is clearly established, but it is still not known whether treatment designed to lower serum choleserol levels will prevent this accelerated development of atherosclerosis in the heterozygote. In adult patients with established atherosclerosis the effect of such treatment is controversial; in some studies no improvement in the prognosis has been recorded (Rose, Thompson, and Williams, 1965; Oliver and Boyd, 1961), whereas in others the incidence of fresh cardiac infarction has been shown to be significantly reduced (Christakis et al., 1966). Prevention of
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atherosclerosis is most likely to be successful if treatment is instituted early in life, that is during childhood, and though prospective controlled studies are needed to evaluate the effect of preventive measures, it seems unjustifiable to withhold dietary treatment that is chemically effective from any child with familial hyper-β-lipoproteinaemia (Wolf, 1967b; Fredrickson et al., 1967b).

Treatment of the homozygous form of the disease is unsatisfactory; dietary measures result in only moderate reduction in serum lipid levels, and for these children other methods of therapy have to be considered. Many drugs have been used to lower serum cholesterol levels. Cholestyramine (Horan, DiLuizio, and Ettledorf, 1964; Hashim and Van Itallie, 1965) binds bile acids and prevents their reabsorption; it has to be given in large doses (15-25 g. daily), is unpleasant to take, and may cause nausea, vomiting, and constipation. Thyroxine lowers serum cholesterol by increasing the katabolism of β-lipoprotein (Walton et al., 1965b); the use of D-thyroxine diminishes the general metabolic effects of the drug. Despite initial lowering of serum cholesterol levels, however, later "escape" is common and long-term treatment is unsatisfactory. Nicotinic acid in large doses probably interferes with cholesterol biosynthesis (Parsons, 1961); side-effects (flushing, pruritus, and gastro-intestinal discomfort) are frequent and usually preclude its use. Clofibrate (chlorphenoxysobutyrate) is more effective in reducing levels of pre-β-lipoprotein than of β-lipoprotein and probably has little place in the treatment of familial hyper-β-lipoproteinaemia (Oliver, 1967).

Nevertheless, it has been shown to inhibit cholesterol biosynthesis in experimental animals (Avoy, Swyryd, and Gould, 1965), and clinically its use is associated with regression of xanthomata even in the absence of consistent reduction in serum cholesterol levels (Oliver, 1967). Though transient nausea and vomiting may occur, no toxic effects have been reported. Oestrogen therapy, which has been used in adults (Oliver and Boyd, 1961), is contraindicated in children. Operative treatment designed to interfere with the regulatory mechanisms for cholesterol metabolism has been advocated in the form of ileal bypass (Buchwald and Varco, 1966; Lee, Frantz, and Buchwald, 1967).

Though the short-term effect in terms of lowering serum cholesterol levels appears to have been good, long-term results are less certain and the poorest results have been achieved in familial hypercholesterolaemia.

In spite of the lack of satisfactory therapy for the homozygous subject, the prognosis is so bad, with death commonly occurring before or during adolescence, that combined dietary and drug treatment should probably be given. We have recently studied a child of 10 years in whom serum cholesterol levels were only lowered to 600 mg./100 ml. (from 1000 mg./100 ml.) on treatment with a polyunsaturated fat diet together with clofibrate and large doses of cholestyramine, but nevertheless after 8 months there was significant reduction in the size of her xanthomata (Fig. 7), and no fresh skin lesions appeared during this time. Thus, even moderate lowering of serum cholesterol levels, if maintained, may be beneficial to these children. In the patient reported by Davis et al. (1966) ileal bypass with exclusion of about one-third of the small intestine resulted in only a temporary fall in serum cholesterol levels, but, as these authors point out, more extensive bypass may have been indicated. In the present state of knowledge, it is not possible to define the role of such operative treatment in the management of the severely affected homozygous child.

Pre-β-lipoproteinaemia (endogenous hypertriglyceridaemia; carbohydrate-induced hypertriglyceridaemia). Pre-β-lipoprotein cannot usually be detected by paper electrophoresis of fasting sera from healthy children (Pantelakis et al., 1964b). The presence of a marked pre-β band in the fasting state in children eating a normal diet indicates a defect in the turnover of endogenously synthesized triglyceride, and the various mechanisms that may be involved have been reviewed by Fredrickson and Lees (1966). Because the hypertriglyceridaemia responds to a reduction in dietary carbohydrate the name ‘carbohydrate-induced hypertriglyceridaemia’ has been used to distinguish endogenous hypertriglyceridaemia from the exogenous or fat-induced variety (Ahrens et al., 1961). It has recently become apparent, however, that hypertriglyceridaemia can be induced in healthy adults by high carbohydrate feeding (Lees and Fredrickson, 1965), and we have shown a similar response in children with familial hypercholesterolaemia but with normal serum triglyceride levels (Segall, Tamir, and Lloyd, 1968). Though the degree of hypertriglyceridaemia induced in normal subjects is less than that found in pathological states, it is probably best to discontinue the use of the term ‘carbohydrate-induced’ to signify a disease state. Furthermore, it is now clear that the endogenous hypertriglyceridaemia manifest in pre-β-lipoproteinaemia is not a single entity but represents a group of conditions with differing causal mechanisms and modes of inheritance.
The incidence of primary pre- β-lipoproteinaemia in childhood is not known. It is probably a common cause of hypertriglyceridaemia in adults (Kuo, 1967), but seems to be much less frequent in children (Fredrickson, Levy, and Lees, 1967c).

Clinical features and laboratory findings. In children clinical features are probably lacking, but in adults eruptive xanthomata occur, and obesity and atherosclerosis are commonly found. The serum is turbid in the fasting state and pre- β-lipoprotein can be demonstrated by electrophoresis (Fig. 3) and ultracentrifugation. Serum triglyceride levels are raised and serum cholesterol concentrations are increased if much pre- β-lipoprotein is present. The clearing of dietary fat is impaired in the presence of increased amounts of endogenous triglyceride (Fredrickson and Lees, 1965), and thus a small accumulation of chylomicron material may occur though post-heparin lipolytic activity is normal (Fredrickson et al., 1963): α-lipoprotein concentrations are always depleted (Levy, Lees, and Fredrickson, 1966). Tests of carbohydrate tolerance are usually abnormal; oral glucose tolerance and the response to intravenous tolbutamide may be impaired, and plasma insulin levels may be raised (Knittle and Ahrens, 1964). We have shown an increase in serum triglyceride and pre- β-lipoprotein during the course of an oral glucose tolerance test in one patient (Segall, 1967).
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The diagnosis is established by the exclusion of other causes of pre-β-lipoproteinemia (Table) and by the response to dietary manipulations.

Treatment and prognosis. We have treated a 12-year-old boy with a low carbohydrate, high fat diet, and have succeeded in abolishing the pre-β band and restoring serum triglyceride levels to normal (Segall, 1967). Ahrens and Spritz (1963) have suggested that the best results are obtained if about 50% of the dietary fat is polyunsaturated. The type of carbohydrate may also be important; Kuo and Bassett (1965) and Kaufmann et al. (1967) showed that starch resulted in lower serum triglyceride levels than sugar in some patients, and Macdonald (1967) considered that glucose was less lipogenic than sucrose. In our patient we were unable to demonstrate any difference between the effects of glucose and sucrose. Reduction in pre-β-lipoprotein and serum triglyceride levels can also be achieved by the administration of clofibrate (Strisower and Strisower, 1964) which has been extensively used in the treatment of adult patients (Brown and Doyle, 1967). For the treatment of children we do not consider that drugs should be used if dietary control can be achieved; in our experience, however, a low carbohydrate diet is more difficult to maintain over prolonged periods than a low fat diet, and treatment with clofibrate, which fortunately has few side effects, may be indicated.

The ultimate prognosis relates to the development of atherosclerosis and cardiac infarction. An increase in pre-β-lipoprotein is commonly found in patients with coronary artery disease (Smith, 1957), and in a large series of hyperlipidaemic patients with coronary artery disease Kuo (1967) found 91% with the carbohydrate-induced type of hypertriglyceridaemia.

Secondary Hyperlipoproteinaemias

Excess of chylomicrons. The clearing of absorbed dietary fat is delayed in any condition in which levels of endogenous triglyceride are raised (Fredrickson and Lees, 1965). Thus, excessive accumulation of chylomicrons may be found in association with pre-β-lipoproteinemia whether this be the primary abnormality or secondary to such disorders as diabetes mellitus, glycogen storage disease, or the nephrotic syndrome.

Excess of β-lipoprotein. Increased levels of β-lipoprotein are commonly found in hypothyroidism and obstructive jaundice. In hypothyroidism there is a decreased rate of katabolism of β-lipoprotein (Walton et al., 1965b); in addition to hypercholesterolaemia, levels of serum carotene (which is carried by β-lipoprotein) are often also raised (Walton, Campbell, and Tonks, 1965a). Treatment with thyroid hormone rapidly corrects the lipoprotein abnormality. Occasionally hypertriglyceridaemia may occur in hypothyroidism due to an increase in very low-density lipoprotein material (O'Hara, Porte, and Williams, 1966); this lipoprotein may have pre-β mobility on paper electrophoresis (Fredrickson et al., 1967c) or β mobility as was the case in a boy who presented to us with xanthomata, gross hypercholesterolaemia, and moderate increase of serum triglyceride.

In biliary cirrhosis gross increase in β-lipoprotein can occur and may be associated with xanthomatosis. Hypercholesterolaemia is largely due to an increase in unesterified cholesterol, phospholipid is often increased to a proportionally greater degree than that of cholesterol, and serum triglyceride is usually normal (Russ, Raymunt, and Barr, 1956; Fredrickson et al., 1967c). The fact that the major increase in serum lipids is due to unesterified cholesterol and phospholipid may give rise to difficulties in the interpretation of the electrophoretic pattern, as the dye uptake of these lipids is relatively poor and therefore β-lipoprotein, as visualized on the stained paper strip, may not appear to be unduly increased: α-lipoprotein is usually severely reduced and may even appear to be absent on electrophoresis though small amounts can be detected by ultracentrifugation. The mechanism responsible for the lipoprotein abnormalities is not certain: failure of the liver to excrete cholesterol into the bile (Phillips, 1960), altered stability of serum lipoproteins due to bile salt retention (Kunkel and Ahrens, 1949), and interference in the negative feedback mechanism due to lack of bile in the intestinal tract (Dietschy and Siperstein, 1965) have all been postulated. Treatment with cholestyramine may be successful in lowering hyperlipoproteinaemia in some cases (Kecskes, Goldberg, and Fergusson, 1964).

Hypercholesterolaemia due to increase in β-lipoprotein may occasionally occur in hypopituitary patients in the absence of hypothyroidism, and in such subjects the administration of human growth hormone has been shown to lower serum cholesterol levels (Hubble, 1966).

Excess of pre-β-lipoprotein. Excessive amounts of pre-β-lipoprotein are found when carbohydrate is not freely available and plasma levels of non-esterified fatty acids are high (thus promoting triglyceride synthesis in the liver), as in diabetes.
hepatic synthesis and release, of non-esterified triglyceride (Pantelakis et al., 1965). The hyperlipidaemia usually responds rapidly to insulin treatment, though it may be several weeks before normal levels are reached. If hyperlipidaemia persists in spite of adequate insulin control the possibility of an associated disorder of lipoprotein metabolism should be considered (Lloyd, Fosbrooke, and Wolff, 1964). In glycogen storage disease considerable elevation of pre-β-lipoprotein may result in a turbid serum with high triglyceride and cholesterol concentrations. Treatment with a high protein high carbohydrate diet often abolishes the hyperlipidaemia. In starvation pre-β-lipoproteinaemia occurs and is presumably due to the mobilization of adipose tissue stores of lipid.

The mechanisms responsible for the hyperlipidaemia in progeria, in infantile hypercalcaemia, and in generalized lipodystrophy are not known; in the latter condition abnormalities of carbohydrate metabolism are also present.

In the nephrotic syndrome marked pre-β-lipoproteinaemia with considerable increases in serum cholesterol and triglyceride concentrations frequently occur (Baxter, 1962; Scanu, 1965). The magnitude of the lipoprotein disturbance is related to the degree of hypalbuminaemia, and treatment, which restores serum albumin levels to normal, also results in restoration of a normal lipoprotein pattern. The mechanisms responsible for the hyperlipoproteinaemia are not, however, fully understood. Lack of albumin-binding sites for non-esterified fatty acids, with consequent increased triglyceride synthesis and incorporation into pre-β-lipoprotein by the liver, may be one of the factors; other possibilities include a block in the ‘conversion’ of pre-β- to β-lipoproteins, increased hepatic synthesis of lipoproteins provoked by proteinuria, and decreased removal, or increased release, of triglyceride by adipose tissue.

Excess of α-lipoprotein. Increase in a α-lipoprotein in childhood is uncommon; we have observed it in a few children with liver disease of unknown aetiology ('hepatitis'), and it has been reported in some cases of biliary cirrhosis (Fredrickson et al., 1967c); it may occur in some children receiving high dosage of corticosteroids. In adults raised levels of α-lipoprotein are normal during pregnancy (Pantelakis et al., 1964a).

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