Hypolipoproteinaemia

JUNE K. LLOYD

From the Institute of Child Health, University of London

Hypolipoproteinaemia, resulting from deficiency of one or more of the major serum lipoprotein fractions, may be due to a primary genetically determined condition or may occur as a secondary manifestation in another disease state (table I). This paper will be confined to a discussion of the primary disorders which, although rare, have contributed greatly to our understanding of the normal function of the serum lipoproteins.

Physiological Hypolipoproteinaemia of the Newborn

Concentrations of all serum lipoproteins are reduced in umbilical cord blood. β -Lipoprotein is present in a concentration of about one third of that in the adult and α -lipoprotein in about one half the adult concentration (Auerswald *et al*, 1963). The mean total cholesterol concentration is around 70 mg/100 ml, phospholipid 100 mg/100 ml, and triglyceride 20 mg/100 ml (Crowley, Ways, and Jones, 1965; Persson and Gentz, 1966). Values in the premature infant are similar to those in the full-term infant (Rafstedt, 1955). Concentrations of lipids and lipoproteins rise rapidly during the first week of life (Sweeney, Etteldorf, Organ, and Fisher, 1962) and values similar to those of later childhood are achieved by the age of about 4 months.

Abetalipoproteinaemia

This condition, which has now been described in about 40 patients, is inherited as an autosomal recessive. The basic defect probably concerns the synthesis of β -apoprotein, and it is likely that there

is complete suppression of synthesis of this apoprotein, which contains serine as its C-terminal amino acid, as none can be demonstrated in any lipoprotein fraction although all other apoproteins are present (Gotto, Levy, John, and Fredrickson, 1971). Heterozygotes have no clinical abnormalities and in most studies plasma lipids and lipoproteins have also been normal. In a few families, however (Lloyd and Wolff, 1972), reduced concentrations of β -lipoprotein have been observed in parents of patients and the genetic situation may be more complex than formerly supposed with the possible existence of more than one allele.

The clinical features comprise acanthocytosis of the red cells and malabsorption of fat which are both present from birth, and the development of a pigmentary retinopathy and an ataxic neuropathy which become manifest towards the end of the first decade and gradually progress throughout adolescence and adult life. With increasing age progressive crippling can be expected and the oldest living patient is probably not more than 40 years old. Death in two patients appears to have been due to unexplained cardiac arrhythmia.

SERUM LIPIDS AND LIPOPROTEINS

The serum is clear and even after a meal containing fat there is no turbidity. Absence of β -lipoproteins can be shown by electrophoresis, ultracentrifugation, or immunochemical studies. Furthermore, neither chylomicrons nor pre- β -lipoprotein can be demonstrated, and the concentration of α -lipoprotein is reduced to about one third of its normal value.

The serum lipids reflect the lipoprotein pattern

<i>Lipoprotein Primarily Affected</i>	<i>Primary Disorders</i>	<i>Secondary Disorders</i>
Chylomicron		Fat malabsorption
β -Lipoprotein	Physiological in newborn Abetalipoproteinaemia Familial hypo- β -lipoproteinaemia	Fat malabsorption Hyperthyroidism Hepatic failure Chronic anaemia
α -Lipoprotein	Familial α -lipoprotein deficiency (Tangier disease) Familial lecithin : cholesterol acyltransferase deficiency	Hepatic failure Non-specific in many acute and chronic illnesses

Table I *Classification of hypolipoproteinaemia*

and the range of values commonly found is given in table II. Cholesterol concentrations are greatly reduced owing to the absence of the main carrier protein, phospholipid levels are low because of the reduction in α -lipoprotein as well as the absence of β -lipoprotein, and triglyceride is found in only minute amounts owing to lack of all three triglyceride-carrying lipoproteins. Other substances normally transported by β -lipoprotein are also affected; carotenoids and vitamin E cannot be detected in the serum, and vitamin A levels are likely to be low unless large supplementary doses are being given.

PATHOGENESIS OF THE LESIONS

*Acanthocytosis*¹

The abnormal morphology of the red cells, known as acanthocytosis, can be seen on stained blood films, but is best shown on a fresh, wet, undiluted film when the failure to form rouleaux is also obvious. The latter is responsible for the low erythrocyte sedimentation rate (usually less than 1 mm in one hour). Although the cells have a slightly shortened half-life, clinical evidence of haemolytic anaemia is unusual. The reason for the unusual shape is not known. Analysis of the lipids in the red cell membrane show that concentrations of cholesterol and total phospholipid are usually within the normal range, although there may be some increase in the ratio of cholesterol to phospholipid (McBride and Jacob, 1970). The most striking abnormality is a relative increase in the proportion of sphingomyelin at the expense of phosphatidyl choline. The proportion of linoleic acid esterified with phospholipid is reduced.

The available evidence suggests that the red cell abnormality occurs as a result of exposure to the abnormal plasma environment. Red cell precursors in the bone marrow are of normal morphology, and younger red cells in the circulation show less structural or biochemical changes than do older cells. Cells morphologically indistinguishable from the acanthocytes of abetalipoproteinaemia may, however, be found in conditions in which the plasma lipoproteins show a completely different pattern, for example in alcoholic cirrhosis of the liver. Thus the red cell shape cannot be ascribed specifically to the lack of β -lipoprotein in the plasma.

Malabsorption of fat

The malabsorption of fat is due to an inability to form chylomicrons in the intestinal mucosal cell. The intraluminal phase of fat digestion and absorption is normal; fatty acids and monoglycerides pass into

the mucosa and triglyceride is resynthesized but, because it cannot be incorporated into chylomicrons, it accumulates within the cell. This accumulation results in a vacuolated appearance, especially prominent at the villous tips, and the presence of lipid can be demonstrated in frozen sections. After a meal containing fat no chylomicrons can be demonstrated in systemic blood but analysis of the fatty acid pattern of plasma lipids shows that some fatty acids present in the food are being absorbed (Barnard, Fosbrooke, and Lloyd, 1970) and it must be assumed that they are being transported via the portal vein. The exact reason for the failure of chylomicron formation is still not known; the most likely explanation is that β -apoprotein is an essential constituent of chylomicrons.

The degree of steatorrhoea is variable; faecal fat studies show that fat absorption ranges from 50 to 80% of the intake. Although with increasing age the symptoms due to fat malabsorption become less marked, this is probably due to avoidance of fat (voluntary or prescribed) as there is no evidence that the ability to absorb fat improves with age.

Retinopathy and neuropathy

The retinopathy of abetalipoproteinaemia differs from that in classical retinitis pigmentosa in that the macula as well as the periphery of the retina is involved. Abnormalities can be demonstrated in the electrooculogram and electroretinogram, and also in dark adaptation; eventually visual acuity may be expected to deteriorate. The earliest neurological symptom is unsteadiness in walking and the earliest sign is loss or diminution of the deep tendon reflexes. Ataxia, most marked in the trunk and lower limbs, is a later development and loss of vibration and position sense occur. The plantar responses become extensor. Musculoskeletal defects such as scoliosis and pes cavus develop. Athetoid movements, speech defects, and extraocular muscle imbalance have been reported, and in a few patients loss of pain and temperature sensation. Progressive disability results in many patients being unable to stand by the age of 30 years.

The pathogenesis of the retinal and neurological lesions is not known. Examination of neurological tissue from two patients at necropsy (Sobrevilla, Goodman, and Kane, 1964; Dische and Porro, 1970) showed extensive demyelination in the spinal cord and cerebellum, and in one patient large quantities of lipochrome pigment were present in the poles of the neurones in the cerebral cortex. The original suggestion of Singer, Fisher, and Perlstein (1952) that the neuro-ophthalmological condition be considered as an abiotrophic disorder (such as Friedreich's ataxia) does not advance our understanding of basic

¹A type of red cell with spiky projections.

mechanisms. The possibility of a structural and/or functional abnormality of nerve and retinal cell membranes consequent upon prolonged exposure to serum deficient in β -lipoprotein (Wolff, 1965), requires investigation; to date no chemical analyses of neurological tissue have been reported. It has also been postulated that lesions might result from the effects of prolonged deficiency of linoleic acid, vitamin A, or vitamin E. It seems unlikely that linoleic acid deficiency can be the sole explanation as low serum levels are found in other malabsorptive states. Vitamin A deficiency is likewise unlikely to be the primary or only cause. Although it has been reported (Fredrickson, Gotto, and Levy, 1972) that vitamin A administration appeared to reverse some part of the macular degeneration or retinal pigmentation, treatment which restored normal plasma levels from the age of 18 months did not prevent the patient of Wolff, Lloyd, and Tonks (1964) developing retinopathy at the age of 5 years. The role of prolonged vitamin E deficiency has recently been studied in more detail, and Lloyd and Muller (1972) suggest that administration of massive doses of tocopherol may have favourably influenced the neurological and retinal status of two of their patients.

DIAGNOSIS

The diagnosis should be suspected in all patients with unexplained malabsorption, in individuals found to have acanthocytes in the peripheral blood, and in patients with atypical retinitis pigmentosa, or an unusual Friedreich-like ataxic neuropathy. The demonstration of acanthocytes in a fresh wet undiluted blood film together with clear serum containing less than 50 mg cholesterol per 100 ml is virtually diagnostic. Neither acanthocytosis, hypocholesterolaemia, nor the appearance of the intestinal mucosa are, however, pathognomonic and the diagnosis should always be confirmed by showing the absence of β -lipoprotein by electrophoretic, ultracentrifugal, or immunochemical techniques.

TREATMENT

Treatment is symptomatic; steatorrhoea can be controlled by reducing fat intake and additional fat-soluble vitamins should be given orally. Very large doses of vitamins A and E are required (Lloyd, 1973).

Familial Hypo- β -lipoproteinaemia

It is now clear that familial hypo- β -lipoproteinaemia is distinct from abetalipoproteinaemia. It is inherited as an autosomal dominant and the basic defect is thought to be a reduction in the synthetic rate of

β -lipoprotein (Levy, Langer, Gotto, and Fredrickson, 1970). Studies in one family suggest that the lipoprotein is of abnormal composition (Fosbrooke, Choksey, and Wharton, 1973). α -Lipoprotein appears normal and both pre- β -lipoprotein and chylomicrons can be formed.

In some patients the lipoprotein disorder is not associated with any clinically detectable abnormality. In others, some but not all of the features which occur in abetalipoproteinaemia have been observed. One child presented with malabsorption of fat and had biopsy appearances of the intestinal mucosa identical with those seen in abetalipoproteinaemia (Anderson, Townley, Freeman, and Johansen, 1961). Irregularities of red cell shape have been reported in one patient (Mars, Lewis, Robertson, Butkus, and Williams, 1969), and neurological abnormalities have also occurred. Insufficient data are available for meaningful comment on the possible pathogenesis of the lesions.

Familial α -Lipoprotein Deficiency

This disorder has also been named Tangier disease after the island home of the first two patients. Only 13 patients have so far been described. Like abetalipoproteinaemia it is inherited as an autosomal recessive. The basic defect is probably a mutation in an allele regulating the synthesis of one of the major apoproteins of α -lipoprotein (apoLp-Gln-I) and as a result the concentration of α -lipoprotein is greatly reduced (Lux, Levy, Gotto, and Fredrickson, 1972).

Heterozygotes do not show any clinical manifestations but most of the individuals examined have had reduced concentrations of α -lipoprotein. This abnormality has been most marked in male subjects; α -lipoprotein concentrations have been variable in the females. Some heterozygotes have shown hypertriglyceridaemia with increase in pre- β -lipoprotein.

The clinical features are variable, but enlargement and a striking yellow/orange coloration of the tonsils appears to be a virtually constant feature and can be considered pathognomonic. Even if the tonsils have been removed, the appearance of the remaining lymphoid tissue in the pharynx is distinctive. Enlargement of the liver, spleen, and/or lymph nodes may be expected in most patients. Neurological abnormalities have been the presenting feature in four patients and have been present in eight of 12 patients who have been fully investigated (Fredrickson *et al*, 1972). Corneal opacities and xanthomas may also occur.

SERUM LIPIDS AND LIPOPROTEINS

Although α -lipoprotein cannot usually be visualized

	Plasma Lipids (mg/100 ml)		
	Total Cholesterol	Total Phospholipid	Triglyceride
Abetalipoproteinaemia ¹	19-72	33-96	1-12
Familial hypo- β -lipoproteinaemia ²	55-146	—	20-140
Familial α -lipoprotein deficiency ³	30-117	68-148	118-332
Normal range	120-250	160-310	40-125

Table II Plasma lipid concentrations in the primary hypolipoproteinaemias

¹Data from Fredrickson *et al* (1972) together with personal observations on eight patients²Data from Fredrickson *et al* (1972)³Data from first 10 cases reported in literature

after electrophoretic separation, ultracentrifugal and immunochemical studies show that a small amount, about 5% of the normal concentration, is present. This differs in its chemical composition from normal α -lipoprotein, containing different proportions of the two main apoproteins (Lux *et al*, 1972) and an increased proportion of triglyceride. β -Lipoprotein is reduced in concentration but pre- β -lipoprotein is increased, and chylomicrons may be present even in the fasting state. Thus the serum can be expected to be turbid.

The serum lipid pattern is unique (table II) in that total cholesterol and phospholipid levels are low but triglyceride is either normal or (more usually) high.

PATHOGENESIS OF THE LESIONS

The pathogenesis of all the lesions, with the possible exception of those in the nervous system where adequate studies have not yet been made, can be explained by the deposition of cholesterol esters. In addition to involvement of the reticuloendothelial system, deposition has been demonstrated in the rectal mucosa, bone marrow, skin, and cornea.

The relationship between the lipoprotein abnormality and the selective storage of cholesterol esters is not understood. Possible theories include instability of lipoproteins resulting in excessive deposition of lipid, and impaired activity of lecithin cholesterol acyltransferase causing decreased transfer of cholesterol from tissues to serum.

DIAGNOSIS

The diagnosis should be suspected in patients with abnormally coloured and enlarged tonsils, unexplained hepatic or splenic enlargement, lymphadenopathy, neuropathy, or corneal opacities. The finding of reduced concentrations of plasma cholesterol and phospholipid with normal or raised triglyceride is virtually diagnostic. Too much reliance should not be placed on failure to demonstrate α -lipoprotein by electrophoretic techniques, and the

diagnosis must always be confirmed by ultracentrifugation or immunochemical techniques. The lipoprotein pattern of first-degree relatives should be determined to confirm the familial nature of the disorder.

TREATMENT

No treatment to date has been effective in reducing the degree of storage of cholesterol ester in tissues.

Familial Lecithin: Cholesterol Acyltransferase Deficiency

Although this condition is not primarily a defect of lipoproteins, it is an inherited disorder of lipid metabolism in which there is a gross deficiency of normal α -lipoprotein. To date seven patients in three families (two from Norway and one from Sweden) have been described (Norum, Glomset, and Gjone, 1972) and the disorder appears to be inherited as an autosomal recessive. The basic defect is deficiency of the enzyme lecithin: cholesterol acyltransferase (LCAT) which is responsible for the esterification of cholesterol by promoting the transfer of an unsaturated fatty acid from phosphatidyl choline (lecithin) to free cholesterol. The enzyme is believed to form a specific complex with α -lipoprotein, and the lipids of α -lipoprotein form the preferred substrate for the action of the enzyme. Lack of the enzyme results in the major portion of the serum cholesterol being present in the free (or unesterified) form. Concentrations of total cholesterol have been increased to between 300 and 600 mg/100 ml in five of the six patients described. The concentration of total phospholipid is also increased and the proportion of phosphatidyl choline (lecithin) is raised whereas that of lysolecithin is reduced. Triglyceride levels have been raised (300-1800 mg/100 ml) in all but the youngest patient (who also had normal cholesterol and phospholipid concentrations). Electrophoresis of lipoproteins shows no pre- β -lipoprotein or α -lipoprotein bands although

Hypolipoproteinaemia

a small amount of α -lipoprotein which migrates in the α_2 -globulin region may be visualized.

The clinical features which have been present in all patients are proteinuria, anaemia, and corneal opacity.

Proteinuria has been the earliest sign noted and was discovered in one patient at the age of 3-4 years. The protein is mainly albumin and the concentration has been of the order of 500 to 1500 mg/100 ml; red cells and hyaline casts are present. Renal biopsy has shown foam cells in the glomerular tufts.

The anaemia is normochromic and normocytic. In most patients it was first discovered towards the end of the second decade, though it may well have been present earlier, with haemoglobin concentration reduced to about 10 g/100 ml and the presence of numerous target cells. The erythrocyte membrane contains a greatly increased concentration of cholesterol and a markedly raised proportion of phosphatidyl choline. The bone marrow may contain foam cells. Haematological investigations suggest that the anaemia is a combination of decreased erythropoiesis and moderately increased destruction.

The corneal opacity is due to infiltration of all layers of the stroma with minute greyish particles, presumably cholesterol. Infiltration has been noted from puberty. Other abnormalities have included very high non-specific antistreptolysin titres when sheep (but not rabbit) erythrocytes were used as the substrate, and elevated serum uric acid levels in three patients.

Functions of Lipoproteins

Studies of the primary lipoprotein deficiency disorders indicate that lipoproteins are important for normal functioning of many organs.

β -Lipoprotein, or more probably β -apoprotein, appears essential for the transport of triglyceride out of cells; thus in its absence triglyceride accumulates, particularly in the intestinal epithelial cell although also to some degree in the liver cell. Normal α -lipoprotein appears essential for cholesterol ester metabolism, and in its absence esterified cholesterol is stored in many tissues of the body but especially in the reticuloendothelial system. Both lipoproteins contribute to the maintenance of the normal composition of the erythrocyte membrane. The demonstration of widespread neurological lesions in abetalipoproteinaemia and in familial α -lipoprotein deficiency emphasizes the vital role of both the major plasma lipoproteins in preserving the integrity of the nervous system. β -Lipoprotein has an additional function as the major carrier of carotenoids and of vitamin E in the circulation.

The way in which the lipoproteins perform their

diverse functions and the mechanisms responsible for many of the clinical effects of the deficiency states are still poorly, if at all, understood. Further research into these rare disorders should help to improve our understanding of the role of lipoproteins in health and disease.

References

- Anderson, C. M., Townley, R. R. W., Freeman, M., and Johansen, P. (1961). Unusual causes of steatorrhoea in infancy and childhood. *Med. J. Aust.*, **2**, 617-622.
- Auerswald, W., Doleschel, W., and Müller-Hartburg, W. (1963). Flotationsanalytische Untersuchungen der Lipoproteinverteilung im mütterlichen und im Nabelschnurblut. *Klin. Wschr.*, **45**, 580-584.
- Barnard, G., Fosbrooke, A. S., and Lloyd, J. K. (1970). Neutral lipids of plasma and adipose tissue in α -betalipoproteinaemia. *Clin. chim. Acta*, **28**, 417-422.
- Crowley, J., Ways, P., and Jones, J. W. (1965). Human fetal erythrocyte and plasma lipids. *J. clin. Invest.*, **44**, 989-998.
- Dische, M. R., and Porro, R. S. (1970). The cardiac lesions in Bassen-Kornzweig syndrome. *Amer. J. Med.*, **49**, 568-571.
- Fosbrooke, A. S., Choksey, S., and Wharton, B. A. (1973). Familial hypobetalipoproteinaemia. (Abstr.) *Arch. Dis. Childh.*, **47**, 671.
- Fredrickson, D. S., Gotto, A. M., and Levy, R. I. (1972). Familial lipoprotein deficiency. In *The Metabolic Basis of Inherited Disease*, edited by J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, 3rd ed., pp. 493-530. McGraw-Hill, New York.
- Gotto, A. M., Levy, R. I., John, K., and Fredrickson, D. S. (1971). On the protein defect in abetalipoproteinaemia. *New Engl. J. Med.*, **284**, 813-818.
- Levy, R. I., Langer, T., Gotto, A. M., and Fredrickson, D. S. (1970). Familial hypobetalipoproteinaemia, a defect in lipoprotein synthesis. *Clin. Res.*, **18**, 539.
- Lloyd, J. K. (1973). Lipoprotein deficiency disorders. In *Clinics in Endocrinology and Metabolism*, edited by B. M. Rifkind. Saunders, London. In press.
- Lloyd, J. K., and Muller, D. P. R. (1972). Management of abetalipoproteinaemia in childhood. *Protides Biol. Fluids*, **19**, 331-335.
- Lloyd, J. K., and Wolff, O. H. (1972). Abetalipoproteinaemia and familial alphaslipoprotein deficiency. In *Handbuch der inneren Medizin*, Vol. VII/I edited by F. Linneweh. Springer, Berlin. In press.
- Lux, S. E., Levy, R. I., Gotto, A. M., and Fredrickson, D. S. (1972). Studies on the protein defect in Tangier disease: isolation and characterization of an abnormal high density lipoprotein. *J. clin. Invest.*, **51**, 2505-2519.
- McBride, J. A., and Jacob, H. S. (1970). Abnormal kinetics of red cell membrane cholesterol in acanthocytes; studies in genetic and experimental abetalipoproteinaemia and in spur cell anaemia. *Brit. J. Haemat.*, **18**, 383-397.
- Mars, H., Lewis, L. A., Robertson, A. L., Jr., Butkus, A., and Williams, G. H., Jr. (1969). Familial hypo-beta-lipoproteinaemia. A genetic disorder of lipid metabolism with nervous system involvement. *Amer. J. Med.*, **46**, 886-900.
- Norum, K. R., Glomset, J. A., and Gjone, E. (1972). Familial lecithin cholesterol acyl transferase deficiency. In *The Metabolic Basis of Inherited Disease*, edited by J. B. Stanbury, J. B. Wyngaarden and D. S. Fredrickson, 3rd ed., pp. 531-544. McGraw-Hill, New York.
- Persson, B., and Gentz, J. (1966). The pattern of blood lipids glycerol and ketone bodies during the neonatal period, infancy and childhood. *Acta paediat. scand.*, **55**, 353-362.
- Rafstedt, S. (1955). Studies on serum lipids and lipoproteins in infancy and childhood. *Acta paediat.* (Uppsala), Suppl. **102**.
- Singer, K., Fisher, B., and Perlstein, M. A. (1952). Acanthocytosis. A genetic erythrocytic malformation. *Blood*, **7**, 577-591.
- Sobrevilla, L. A., Goodman, M. L., and Kane, C. A. (1964). Demyelinating central nervous system disease, macular atrophy and acanthocytosis (Bassen-Kornzweig syndrome). *Amer. J. Med.*, **37**, 821-828.
- Sweeney, M. J., Etteldorf, J. N., Orban, P. M., and Fischer, R. (1962). Effect of diet during the first six to eight weeks of life on total concentrations of serum protein and on electrophoretic patterns of serum protein and lipoprotein. *Pediatrics*, **29**, 82-89.

Wolff, O. H. (1965). Abetalipoproteinaemia. In *Ergebnisse der inneren Medizin und Kinderheilkunde*, edited by L. Heilmeyer, R. Schoen, and A. Prader, pp. 190-201. Springer, Berlin.

Wolff, O. H., Lloyd, J. K., and Tonks, E. L. (1964). Abetalipoproteinaemia with special reference to the visual defect. *Exp. Eye Res.*, 3, 439-442.