Primary disorders of lipoprotein metabolism in childhood*

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Four major classes of lipid are found in human serum: cholesterol and its esters, triglyceride, phospholipids and non-esterified fatty acids. They exist in aqueous solution because they are combined with protein to form lipoprotein complexes. The non-esterified fatty acids are bound to albumin, and the other lipids are associated with certain serum globulins. The nomenclature of the lipoproteins derives from the methods used for their separation. The simplest method is paper electrophoresis (Salt & Wolff, 1957; Fredrickson, Levy & Lees, 1967a) and using this technique four lipoprotein fractions are identified (Fig. 1). Chylomicra remain at the point of application of the serum to the paper and are normally present only during fat absorption; \( \beta \)-lipoprotein and \( \alpha \)-lipoprotein have the mobility of \( \beta \)- and \( \alpha \)_1-globulins, respectively; pre-\( \beta \)-lipoprotein, which is not present in significant amounts in normal fasting serum, moves ahead of \( \beta \)-lipoprotein towards the position of \( \alpha \)_2-globulin. The chemical composition of the lipoproteins can be determined if they are separated in a preparative ultracentrifuge (Table 1). It will be appreciated that all lipoproteins contain some cholesterol, triglyceride and phospholipid, although in different proportions. Estimations, therefore, of the total serum triglyceride and cholesterol concentrations cannot alone identify a lipoprotein abnormality, but this becomes possible if electrophoresis is used in addition. Interpretation is facilitated if blood is taken in the fasting state (to avoid post-prandial chylomicronaemia), and the serum should not be stored or frozen, either of which procedures may alter the lipoprotein pattern.

**Classification**

Table 2 gives a classification of primary lipoprotein disorders according to the individual lipoprotein involved. Current terminology, however, is often based on the individual lipid which is most affected, and where appropriate this terminology is also given.

**Lipoprotein deficiency states**

Abetalipoproteinaemia

This rare condition is characterized by absence of \( \beta \)-lipoprotein from the serum, failure to form chylomicra from dietary fat (with consequent accumulation of triglyceride in the intestinal mucosal cell and malabsorption of fat), abnormally shaped red cells (acanthocytes), and the development of a pigmentary retinopathy and an ataxic neuropathy. The primary gene defect probably concerns the synthesis of the protein moiety of

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*An abridged version of a lecture given at the Institute of Child Health, 27 November 1966.*
α-lipoprotein, and the condition is inherited as an autosomal recessive. Heterozygote individuals show no clinical abnormality and usually have a normal lipoprotein pattern (Farquhar & Ways, 1966), although reduced levels of β-lipoprotein have been demonstrated in one family (Salt et al., 1960).

The disease usually presents with steatorrhoea, and symptoms appear during the first few months of life. Growth is retarded and secondary vitamin and mineral deficiencies may occur. The intestinal symptoms lessen in severity during later childhood and adolescence, but during this period the retinitis and ataxic neuropathy appear and result in progressive disability. Mental retardation has been present in a few patients but in the majority mental development is normal. Life expectancy is limited and cardiac arrhythmia resulting in death has been reported (Sobrevilla, Goodman & Kane, 1964).

The diagnosis is made on the lipoprotein pattern together with the typical red cell appearances. The total serum cholesterol concentration is very low, usually below 40 mg/100 ml, and on paper electrophoresis no β-lipoprotein can be detected; α-lipoprotein is reduced. The lipoprotein deficiency can be confirmed by immunochemical and ultracentrifugal techniques. Acanthocytosis of the red blood cells (acanthus = horn or sharp point) is always present but may be missed or misinterpreted unless a fresh wet undiluted blood film is examined. The misshapen cells and the failure of rouleaux formation are then obvious. The cells have a slightly shortened survival time but a haemolytic anaemia is uncommon. The phospholipid composition of the red cell membrane is abnormal, with an increase in the ratio of sphingomyelin to lecithin (Ways, Reed & Hanahan, 1963). Acanthocytes themselves are not pathognomonic of abetalipoproteinaemia and may occur in hepatic disease (Smith, Longergen & Sterling, 1964) and in patients with deficiency (as distinct from absence) of β-lipoprotein (Kuo & Bassett, 1962).

Treatment is symptomatic. The steatorrhoea usually responds to a low fat diet. Large doses of water-miscible preparations of vitamins A and E should be given together with supplements of vitamins D and K.

Familial alphalipoprotein deficiency (Tangier disease)

This condition was first described by Fredrickson in 1960 and named Tangier disease after the Chesapeake Island Bay home of the first two patients. A total of nine cases have so far been reported (Fredrickson, 1966; Kocen et al., 1967; Engel et al., 1967). The most striking abnormality is the deposition of cholesterol esters in the reticuloendothelial system which is manifest clinically by enlarged tonsils having a unique yellow-orange appearance. Lymphadenopathy and hepatosplenomegaly may be present and a peripheral neuropathy may develop in early adult life (Kocen et al., 1967; Engel et al., 1967).

The concentrations of cholesterol and phospholipid in the serum are reduced, but triglyceride is raised. α-Lipoprotein cannot be detected by paper electrophoresis, but more sensitive techniques reveal the presence of a small amount which, however, has an abnormal protein moiety (Levy & Fredrickson, 1966).

The disease is inherited as an autosomal recessive and the majority of heterozygote individuals can be shown to have reduced concentrations of α-lipoprotein.

Hyperlipoproteinaemias

Hyperchylomicronaemia (familial fat-induced hypertriglyceridaemia)

This condition is due to failure to clear chylomicra from the serum at a normal rate and is thought to be due to a deficiency of the enzyme lipoprotein lipase. The disease is inherited as an autosomal recessive. It is probably rare, only about thirty-five well-documented cases having been reported (Fredrickson & Lees, 1966). The incidence of the gene in the population is not known owing to the difficulty in identifying the heterozygote state.

The clinical manifestations include eruptive xanthomata which may appear at any age, attacks of abdominal pain, more common in childhood, hepatosplenomegaly, and lipoaemia retinalis. Occasionally symptoms are absent and the condition is discovered during examination of the serum for another purpose.

The serum is characteristically grossly turbid, even in the fasting state, and there is marked elevation of triglyceride (often to more than 3000 mg/100 ml) with only moderate elevation of cholesterol in keeping with the composition of chylomicra. Lipoprotein electrophoresis shows that most of the lipid remains at the origin; the amount of both β- and α-lipoprotein are reduced but there is usually some pre-β-lipoprotein present. Lipoprotein lipase activity in the plasma after intravenous heparin (Fredrickson, Ono & Davis, 1963) is low.

The response of the condition to reduction in dietary fat is rapid and confirms the diagnosis. Within a few days of starting a diet in which the daily fat intake is less than 5 g the fasting serum becomes clear and chylomicron material can no
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longer be detected on paper electrophoresis. Pre-
β-lipoproteinemia, however, persists and may
even increase owing to the high carbohydrate con-
tent of a low-fat diet (Lees & Fredrickson, 1965); 
thus even when chylomicronaemia has been cleared
the serum triglyceride concentration remains some-
what elevated. When the serum is clear the fat
intake can usually be increased to about 20 g a
day, although there is considerable individual
variation in the amount of fat that can be
tolerated. The clinical response is excellent; xan-
thomata disappear within a few weeks, the liver
and spleen return to normal size, and general
health and well-being improve (Lloyd & Wolff, 1967).
The palatability of a low-fat diet can be
greatly enhanced by the use of medium-chain
triglycerides, the fatty acids of which are absorbed
directly into the portal circulation and thus by-
pass the chylomicon route.

The natural history of the untreated condition
is not as benign as earlier observations have sug-
gested. The abnormality is persistent and xan-
thomata and abdominal crises can occur at any age.
There may also be problems due to increased
blood viscosity and impaired tissue oxygen uptake
from the lipaemic serum (Joyner, Horwitz &
Williams, 1960). There is as yet no definite evi-
dence that coronary artery atherosclerosis is
accelerated (Fredrickson et al., 1967a).

Hyperbetalipoproteinemia (familial hypercholes-
terolaemia)

Familial hyperbetalipoproteinemia is charac-
terized by elevated levels of β-lipoprotein in the
serum and the development of xanthomata and
accelerated atherosclerosis in a high proportion
of affected subjects. It is inherited as an auto-
sonal dominant. The gene frequency in the popu-
lation is not yet known.

In the homozygous form the clinical mani-
festations are usually severe and appear in child-
hood. Xanthomata are of the tendinous or tuber-
ose type and typically appear over the tendo-Achillis,
elbows, knuckles and backs of the knees. Sym-
toms of coronary artery disease may occur as
early as 7 years of age and death from cardiac
infarction in later childhood and adolescence is
not uncommon. The serum cholesterol is grossly
raised, usually above 700 mg/100 ml, and lipop-
protein electrophoresis shows a marked increase
in the β-lipoprotein fraction. The serum trig-
llyceride concentration is generally within the
normal range.

In the heterozygote form serum cholesterol
levels are usually between 300 and 500 mg/100 ml.
Although the lipoprotein abnormality is present
in childhood, clinical evidence of the disease is
rarely manifest until adult life when xanthomata
and coronary artery disease may develop at a
relatively early age.

Lowering serum cholesterol levels by diet and
drugs in heterozygous adults with established
coronary artery disease has not been found to
influence the prognosis (Oliver & Boyd, 1961;
Rose, Thomson & Williams, 1963), but no studies
have yet been made of the results of treatment
started before the onset of atherosclerosis, that is
in childhood. Until more evidence is available,
and especially in families in which there is a
history of the early development of coronary
artery disease, dietary treatment to lower β-lipo-
protein levels should be instituted in childhood
or early adult life (Lloyd & Wolff, 1967; Fred-
rickson, Levy & Lees, 1967b). A diet in which
at least 80% of the normal fat is replaced by
polyunsaturated fat is usually successful in lower-
ing cholesterol concentrations to near normal
levels. Drugs such as D-thyroxine, nicotinic acid,
cholestyramine and oestrogens have side effects
which limit their value in long-term therapy, and
have not proved superior to dietary treatment for
the heterozygous state. Unfortunately no therapy
has yet proved effective in the treatment of the
homozygous patient, but the prognosis for these
individuals is so poor that the combined use of
diet and drugs together with consideration of
more radical measures to interfere with cholesterol
metabolism, such as ileal bypass operations
(Buchwald, 1965; Davis et al., 1966) is probably
justified.

Prebetalipoproteinemia (carbohydrate-induced
hypertriglyceridaemia)

In 1961 Ahrens, Hirsch, Oette, Farquhar &
Stein described a group of hypertriglyceridaemic
patients who responded to a reduction in dietary
carbohydrate intake, and named this condition
carbohydrate-induced hypertriglyceridaemia. It is
now clear that pre-β-lipoproteinemia with ex-
cessive endogenous triglyceride synthesis is not
a single entity but represents a group of condi-
tions. Nevertheless, patients have certain features
in common: the development of atherosclerosis is
accelerated, obesity and abnormalities of carbo-
hydrate tolerance are frequently found and erupt-
ive xanthomata may occur if the hypertriglyceri-
daemia is severe. Serum cholesterol levels are
raised to a variable extent and lipoprotein electo-
phoresis shows a pre-β band, and reduction in α-
lipoprotein. The incidence of pre-β-lipoprotein-
aemia appears to increase with age (Fredrickson,
Levy & Lees, 1967a, b, c) but the condition has
been recognized in childhood (Segall, 1967).

Treatment is by reduction in the intake of
dietary carbohydrate. The type of carbohydrate eaten may be important as sucrose tends to produce higher levels of serum triglyceride than starch (Kuo & Bassett, 1965). In obese patients there will usually be a marked improvement after weight reduction (Fredrickson, Levy & Lees, 1967c). Clofibrate (chlorphenoxysobutrylate) is likely to be the most effective drug for the treatment of this type of hyperlipoproteinemia (Strisower & Strisower, 1964).

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Postgrad Med J 1967 43: 691-694
doi: 10.1136/pgmj.43.505.691

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