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Recent Developments in the Management and Prognosis of some Inborn Errors of Metabolism

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Familial Hyperlipidæmias

Successful treatment now exists for certain of the diseases due to an inborn error of metabolism. In some of these conditions symptoms are already present in early infancy and treatment, if it is to achieve the maximum benefit, must be started during the early weeks, if not days, of life. Unfortunately the diagnosis is too often delayed and various screening tests are therefore being developed which can be applied to all newborn infants. In other conditions symptoms do not appear until the later years of childhood or adult life. Occasionally a chemical abnormality is detected in an as yet symptomless child who is examined either because of a family history of a genetically determined disorder or in the course of an unrelated condition.

Inborn Errors of Metabolism Involving the Serum Lipoproteins

The serum lipoproteins: All lipids exist in serum in association with proteins as lipoproteins and paper electrophoresis is a simple method for separating the various lipoproteins (Salt & Wolff 1957). In the fasting individual two lipoprotein bands are seen: the more prominent band is β-lipoprotein which has the mobility of β-globulin; the other band is α-lipoprotein which has the mobility of α_1-globulin. After a meal containing fat, a third band appears which is situated on the line of application of the serum to the paper; this fraction is chylomicron material and, because it is situated at the opposite end of the strip to α-lipoprotein, has been named ω-lipoprotein. A fourth fraction, prebetalipoprotein, is seen occasionally in apparently normal adults, but more often in adults with coronary disease. In children a prebetalipoprotein band is probably always an abnormal finding. This band extends forward from the β-lipoprotein band as far as the α_2-globulin fraction. Prebetalipoprotein contains triglyceride of endogenous origin.

Classification: The genetically determined disorders of the serum lipoproteins are conveniently classified according to these four lipoprotein species (Table 1). The two deficiency states, a-betalipoproteinæmia (Salt *et al.* 1960, Farquhar & Ways 1966) and Tangier disease (or familial high-density lipoprotein deficiency) (Fredrickson 1966) are rare conditions in both of which the mutant gene is transmitted as an autosomal recessive. The familial hyperlipidæmic conditions

Table 1
Primary disturbances of serum lipoproteins

Lipoprotein species	*Hypolipidæmia*	*Hyperlipidæmia*
Chylomicron		Fat-induced hypertriglyceridæmia
β-lipoprotein	A-betalipoproteinæmia	Familial hypercholesterolæmia
α-lipoprotein	Tangier disease	
Prebetalipoprotein		Endogenous hypertriglyceridæmia (carbohydrate-induced, mixed types)

are more frequent and at least two of them are associated with the early development of coronary disease. In fat-induced hypertriglyceridæmia chylomicron material accumulates; in familial hypercholesterolæmia β-lipoprotein accumulates and in carbohydrate-induced hypertriglyceridæmia, prebetalipoprotein. Occasional cases are encountered which do not fall into any of these three clearly defined categories. These 'mixed' cases accumulate prebetalipoprotein but in addition their serum also shows abnormalities of the other lipoprotein fractions. Fredrickson *et al.* (1967) classify the hyperlipidæmic states into five types.

Essential fat-induced hypertriglyceridæmia: This condition, first described by Bürger & Grütz in 1932, is the least common of the hyperlipidæmias. It is transmitted through an autosomal recessive gene. The primary abnormality responsible for the failure to clear ingested fat, and therefore for the accumulation of chylomicron material, is in most if not all cases a deficiency of the enzyme lipoprotein lipase (clearing factor). The typical skin lesion is the eruptive xanthoma which may be irritant. Hepatosplenomegaly and attacks of abdominal pain may occur. The serum is creamy. The chemical abnormality of the serum lipids reflects the composition of chylomicron material: there is a gross elevation of triglyceride and only a moderate one of cholesterol. Occasionally the diagnosis is first suspected because of the chance discovery of creamy serum. The failure to clear ingested fat is confirmed by estimating serum lipids after a fat-containing meal. In the normal child clearing is complete by five hours; in fat-induced hypertriglyceridæmia it may not be complete after twenty-four hours. Treatment consisting of a low fat diet is effective and the xanthomata and hepatosplenomegaly clear quickly. During the first few days of treatment the diet should contain no more than 3 g of fat per day. Once the serum lipid levels have become normal the dietary fat can usually be increased to 10–20 g without recurrence of lipæmia. Recently medium-chain triglyceride fat has become available. The shorter-chain fatty acids of this preparation are absorbed directly into the portal system, do not form chylomicra and therefore do not require lipoprotein lipase for their dispersal (Furman *et al.* 1965). Their addition makes the diet more palatable. It is not yet clear whether this type of hyperlipidæmia is associated with the early onset of atherosclerosis but Joyner *et al.* (1960) have shown that tissue oxygen uptake is decreased whenever the serum becomes turbid and deaths have been reported in infancy due to 'malignant hyperlipæmia' (Hagberg *et al.* 1964, Lusher & Farber 1964).

Essential familial hypercholesterolæmia: This condition is transmitted through an autosomal dominant gene of relatively high frequency. The exact incidence of the condition cannot at present be given and it is likely that previous estimates were too high because of the inclusion of cases which are now recognized to be due to endogenous or carbohydrate-induced hypertriglyceridæmia. The serum is clear and its chemical composition reflects the composition of β-lipoprotein. In the homozygous state serum cholesterol levels are markedly elevated, usually above 700 mg/100 ml, whereas in the heterozygote the elevation is only moderate, usually between 300 and 500 mg/100 ml. The typical skin eruptions are xanthomata of the tendinous and tuberous variety but in childhood these occur only in the homozygous state. Slack & Evans (1966) recently confirmed the high risk of ischæmic heart disease in these families.

For the homozygous condition, present-day treatment is disappointing and symptoms and signs of coronary insufficiency are frequent before adolescence, and death may occur before adult life is reached. The heterozygous child is usually free from symptoms and signs but we have seen a 12-year-old boy in whom arcus senilis was already present.

The diagnosis is usually made as a result of examination of serum lipids of a child, one of whose parents has developed coronary disease at an early age. In the course of such a family study we recently examined the serum cholesterol in the umbilical cord blood of a male infant whose 2-year-old sister had the heterozygous condition and whose father had had a coronary thrombosis at the age of 37. The mean normal level for serum cholesterol in umbilical cord blood is about 70 mg/100 ml and values over 100 mg are unusual. In this infant the value was 101 mg/100 ml and our suspicion that he too might have the heterozygous form of the disease was confirmed when at the age of 6 weeks the cholesterol level had risen to 264 mg and at 10 weeks to 319 mg. In the heterozygous form, treatment with a diet rich in polyunsaturated fat (Lloyd & Jukes 1961) is effective in maintaining nearly normal levels of serum cholesterol and β-lipoprotein. Such a diet is usually acceptable to children and with the advice of a dietician, whose help is essential in the treatment of all the hyperlipidæmic states, it can be made palatable. It has not yet been established whether lowering serum cholesterol and β-lipoprotein will delay or even prevent the onset of atherosclerosis, but in this condition the association between elevation of serum cholesterol and the premature development of atherosclerosis is so clearly established that for the heterozygous

form of familial hypercholesterolæmia it seems unjustifiable to withhold treatment which is chemically effective, at a stage of the disease when the arterial tree is still likely to be relatively normal.

Carbohydrate-induced hypertriglyceridæmia: This condition has only recently been defined (Ahrens *et al.* 1961, Fredrickson & Lees 1966). In adults it is more frequent than the fat-induced variety. The fasting serum is turbid and its chemical composition reflects the composition of pre-betalipoprotein, i.e. there is a marked elevation of serum levels of triglyceride and cholesterol. Xanthomata occur and the patients are prone to develop coronary disease in early adult life. There is also a strong association with diabetes mellitus and it is likely that patients with diabetes mellitus and an associated hyperlipidæmia which persists despite adequate diabetic control fall into this category.

Treatment consists of a low carbohydrate/high fat diet. In a 12-year-old boy serum lipids became normal within five days of starting such a diet. In adults treatment with chlorophenoxyisobutyrate (CPIB) has been used successfully (Strisower & Strisower 1964) but in children dietetic control seems preferable to long-continued drug therapy.

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The Prognosis and Management of Renal Tubular Disorders

Many of the disease entities classified as renal tubular disorders have only recently been described, and the details of their functional defects are still ill understood. It is, therefore, too early to give any clear and authoritative account of their prognosis and treatment, and in such a rapidly developing field dramatic future advances are to be expected. Most renal tubular defects involve abnormalities of reabsorption of water, electrolytes and organic compounds from the tubular lumen to the peritubular blood, and unfortunately knowledge of the basic mechanisms of these transport processes is either non-existent or rudimentary. Milne (1964) divided hereditary renal tubular defects into single, specific defects which are truly inborn, and disorders where there is generalized tubular damage possibly due to circulating renal toxins from an extrarenal metabolic defect. Cystinuria, Hartnup disease and hereditary nephrogenic diabetes insipidus are typical examples of the former type: the Fanconi syndrome, and the renal defects associated with Wilson's disease and hereditary galactosæmia of the latter variety. This division is of especial importance in relation to prognosis, as the basic abnormalities of inborn specific tubular defects remain unchanged throughout life, whereas nonspecific tubular damage is likely to be progressive unless the cause can be treated.

Specific Disorders of Amino-acid Transport

Cystinuria: In this disease there is defective transport of dibasic amino acids, i.e. lysine, ornithine, arginine and cystine, from the proximal tubular lumen, and also from the jejunum (Dent & Rose 1951, Milne *et al.* 1961). The condition would be a harmless metabolic anomaly were it not for the unusual insolubility of cystine causing renal or vesical calculi. Boström & Hambraeus (1964) have recently published a detailed study of the clinical aspects of the disease in 96 Swedish cystinuric patients. The disease was shown to reduce life expectancy to a mean of 51·7 years in males and 64·4 years in females. In addition, there was considerable disability from attacks of renal colic, urinary infections, and surgical operations. The average number of urological operations per individual patient was 1·6. Two methods of treatment are available, either separated or in combination: the high fluid regime of Dent & Senior (1955) and the use of penicillamine or its derivatives (Crawhall *et al.* 1963). Cystine precipitates in urine, particularly