Invited article

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Hyperlipidaemia in children¹

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Hyperlipidaemia in children is most commonly expressed as hypercholesterolaemia. 'Normal values' for serum cholesterol, if defined statistically, vary between communities, and levels of cholesterol in childhood above which an increased risk of coronary heart disease in adult life may be expected have not been firmly established. It is suggested that serum cholesterol concentration over 250 mg/dl (6.47 mmol/l) in a child over 1 year of age merits detailed investigation, including full lipoprotein analysis, and levels of serum cholesterol between 230 and 250 mg/dl (5.95-6.47 mmol/l) should be repeated with further studies if indicated. Secondary hyperlipoproteinaemia rarely presents diagnostic problems but must always be excluded. The only primary hyperlipoproteinaemia likely to be encountered in childhood is familial hyperbetalipoproteinaemia in its common heterozygous form. The most effective means to date of lowering serum cholesterol in this condition is cholestyramine, but the long-term consequences of therapy are not known and treatment should at present be limited to children from high-risk families. Long-term follow-up is essential and until results of such studies are available population screening is unjustified.

Hyperlipidaemia, which includes hypercholesterolaemia and hypertriglyceridaemia, is now well established as a risk factor for the development of coronary heart disease in adults (Kannel *et al.*, 1971; Carlson and Böttiger, 1972). Because this hyperlipidaemia may have been present in childhood and because there is some evidence that atherosclerotic lesions may already be fairly advanced by the age of 20 years (Enos, Holmes, and Beyer, 1953; Mason, 1963; McNamara *et al.*, 1971), interest in the diagnosis and treatment of hyperlipidaemia in children is gathering momentum. This raises a number of problems: first, there is relatively little information available on the epidemiology of hyperlipidaemia at various ages throughout childhood; second, the methods of intervention are not fully evaluated in growing children; and third, there is as yet no real evidence that by maintaining lower serum lipid levels throughout childhood the development of atherosclerosis can be delayed or prevented. Long-term prospective studies need to be initiated and much more information obtained before dogmatic recommendations can be made. Nevertheless certain guidelines can be formulated, and this article gives a personal view of the current position regarding hyperlipidaemia in children.

Definition

Normal ranges for serum cholesterol and triglyceride are usually defined on a statistical basis by studies on groups of supposedly healthy children, the investigation of whom is often limited by ethical and practical considerations. The values obtained vary between communities and are likely to be influenced by environmental factors, such as diet, about which exact information may not be available. It must also be remembered that what is 'normal' in a community is not necessarily 'desirable' in terms of the development of atheroma, and precise information is lacking on which to base decisions regarding the upper cut-off limits for either cholesterol or triglyceride. At present it is not even clear whether serum lipid levels in adult life can be predicted from estimations made during infancy and childhood (*British Medical Journal*, 1973).

In a review of studies of serum cholesterol in the United States, Drash (1972) concluded that cholesterol concentration, which starts at around 65 mg/dl (1.68 mmol/l) in umbilical cord blood, normally rises after birth to reach a mean level of 165 mg/dl (4.27 mmol/l) by 2 years of age and that thereafter there is no further significant variation in cholesterol concentration with age, sex, rate of growth, or level of sexual maturation until approximately 20 years of age. In a cross-sectional investigation of normal

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individuals, Drash and Hengstenberg (1972) found 9 per cent of adolescents had values exceeding 200 mg/dl (5.18 mmol/l) and 2 per cent had levels over 235 mg/dl (6.08 mmol/l), all of the latter showing a heavy betalipoprotein band on electrophoresis (type II pattern, Beaumont *et al.*, 1970). The incidence of lipoprotein abnormalities and of vascular disease was greater in the families of the adolescents with cholesterols between 200–230 mg/dl (5.18–5.95 mmol/l) than in families of children with insulin-requiring diabetes mellitus. Drash suggested that upper cut-off limits might more prudently be set by epidemiological rather than statistical criteria, and that the value of 200 mg/dl (5.18 mmol/l) seemed reasonable until further studies had firmly established whether or not cholesterol was a risk factor in childhood. Some support for the use of this figure may be derived from the epidemiological study of Godfrey *et al.* (1972) in Western Australia; these workers suggested that a level of 200 mg/dl (5.18 mmol/l) in a 6-year-old boy may represent a risk equivalent to that predicted by a level of 238 mg/dl (6.16 mmol/l) in an adult. The latter value was chosen because it was the lower limit of the second highest quartile in the study of London busmen by Morris *et al.* (1966), and significantly more men in this group had coronary heart disease than in the groups with lower cholesterol concentrations.

Universal acceptance of values over 200 mg/dl (5.18 mmol/l) as 'abnormal' should be viewed with caution; it should be realized for example that one-third of the schoolchildren in Wisconsin (Golubjatnikov, Paskey, and Inhorn, 1972) would then be classified as hyperlipidaemic, as would a similar proportion of 1-year-old infants in London (Darmady, Fosbrooke, and Lloyd, 1972). Furthermore, there is evidence that cholesterol concentrations are not quite so stable during the childhood years as Drash has suggested. In the first year of life the values are much influenced by the type of dietary fat, and it is wiser to defer decision as to the normality or otherwise of serum lipids in individual babies until about the age of 1 year, when feeding with cow's milk and a mixed diet has been established (Darmady *et al.*, 1972). During later childhood variation is also likely in individual children, and the prospective study of Lee (1967) demonstrated the fluctuations that could occur; during the period of rapid growth at adolescence there was often a significant decrease in concentrations.

In the case of serum triglyceride there is even less data than for cholesterol on which to base recommendations, and the collection of information is further hindered by the need to standardize the timing of the blood specimen in relation to meals. Whereas there is little diurnal variation in serum

cholesterol concentration, triglyceride varies during fat absorption, and blood should, therefore, be taken in the fasting state; for older children a 12-hour fast is desirable but for younger children and babies an 8-hour period is probably adequate. In umbilical cord blood values are around 35 mg/dl (0.39 mmol/l) and levels rise rapidly with initiation of feeding. At 1 year of age fasting levels of between 37–111 mg/dl (0.41–1.25 mmol/l) have been found in a small group of London infants, and values for children between 2 and 13 years ranged from 31 to 87 mg/dl (0.35 mmol/l) (A. S. Fosbrooke and J. M. Darmady, unpublished data). The suggested upper limit of normal for American children aged 1 to 19 years is 140 mg/dl (1.58 mmol/l) (Fredrickson and Levy, 1972), and this figure is supported by more recent data from Cincinnati (Glueck *et al.*, 1973).

In addition to determinations of serum cholesterol and triglyceride, the serum lipoproteins may also require evaluation and this investigation is essential if either cholesterol or triglyceride concentrations are found to be abnormal. The lipoprotein typing system described for adults (Beaumont *et al.*, 1970) is equally applicable to children, but it must be emphasized that this system only describes an electrophoretic pattern and does not diagnose a disease. Family studies of serum lipids and lipoproteins should be undertaken if a primary disorder is suspected. The information thus obtained will often make the interpretation of data for individual children easier, bringing out the similarities between children and parents (Deutscher, Ostrander, and Epstein, 1970), and differentiating normals from abnormals in the same family.

No discussion of normal lipid levels in children (or adults) can be complete without mention of the methodological problems which still exist in the measurement of cholesterol and triglyceride concentrations. The use of standard methods and strict quality control is essential. The clinician who requests investigation of serum lipids and hopes to be able to interpret the results should always ascertain that the specimen has been obtained under appropriate conditions and analysed by reliable techniques. It is also helpful if a record is kept of the nutritional state and dietary habits of the patient as these may influence the lipid pattern.

To make a firm diagnosis of hyperlipidaemia in a child may thus present a problem, especially if the values are in the borderline range. My personal approach is as follows and is summarized in the Table. During the first year of life no final decision is taken unless there is obvious gross hyperlipidaemia. During the remainder of childhood up to puberty, children with serum cholesterol levels of

TABLE Suggested basis for diagnosis of hyperlipidaemia in children

Age	Cholesterol		Fasting triglyceride		Conclusion
	mg/dl	mmol/l	mg/dl	mmol/l	
Under 1 year					Defer diagnostic tests until about 1 year unless gross hyperlipidaemia present
1 year–puberty	< 200	< 5.18	< 120	< 1.35	Normal
	200–230	5.18–5.95	< 140	< 1.58	No action indicated at present; treat as 'normal'
	231–250	5.98–6.47	< 140	< 1.58	Repeat; normals will tend to be lower; for those still 'high' consider family studies
	> 250	> 6.47	> 140	< 1.58	Abnormal until proved otherwise; repeat with full lipoprotein studies, exclusion of other diseases, and probably family investigation
Puberty					Consider individuals empirically; insufficient data available for firm recommendations

less than 200 mg/dl (5.18 mmol/l) and fasting triglyceride of less than 120 mg/dl (1.35 mmol/l) are considered normal. Those with cholesterol between 200 and 230 mg/dl (5.18 and 5.95 mmol/l) and triglyceride below 140 mg/dl (1.58 mmol/l) are so unlikely to have primary hyperlipidaemia, and on present evidence are also unlikely to be subjected to dietary modifications, that they too are regarded as normal. Children with cholesterol between 230 and 250 mg/dl (5.95 and 6.47 mmol/l) and triglyceride below 140 mg/dl (1.58 mmol/l) have the estimations repeated; if the individual is normal the repeat values are likely to be lower (tendency to revert towards the mean), and if the values are higher family studies are done. Finally, cholesterol levels greater than 250 mg/dl (6.47 mmol/l) and/or fasting triglyceride greater than 140 mg/dl (1.58 mmol/l) are regarded as abnormal until proved otherwise, and the analyses are repeated with more detailed studies of lipoproteins, exclusion of other diseases, and if necessary family studies. For children passing through puberty insufficient data are available to make a firm basis for judgement and empirical decisions have to be made on each case.

Classification

Because all lipids in serum are incorporated into lipoproteins, and because the most widely accepted classification of hyperlipidaemic states is based on the lipoprotein pattern (Beaumont *et al.*, 1970), the term hyperlipoproteinaemia is preferable to hyperlipidaemia, and will be used in the description of the clinical disorders. A simplified classification of the main conditions in childhood in which hyperlipoproteinaemia occurs is given in the Figure, and this also indicates the relative magnitude of the rise in serum cholesterol and triglyceride. The major

division is into the primary and secondary disorders, the latter being at present more frequently recognized, at least in hospital practice.

Secondary hyperlipoproteinaemia

In children the cause of secondary hyperlipoproteinaemia is usually obvious and the diagnosis already established by the time the lipid abnormality is defined. Occasionally, however, hyperlipoproteinaemia may be the presenting feature and the possibility of a secondary disturbance should always be considered. The type of lipoprotein abnormality is seldom diagnostic for a specific disorder; indeed the pattern may differ between individuals with the same disease, and also in the same individual at different stages of the disease. As secondary hyperlipoproteinaemias tend to be reversed by the treatment of the basic disease process, serial observations of serum lipids and lipoproteins may sometimes be helpful in assessing progress. Only rarely is treatment of the hyperlipoproteinaemia indicated in its own right.

The diseases most commonly associated with hyperlipoproteinaemia in children are: poorly controlled diabetes mellitus, hypothyroidism, the nephrotic syndrome, the hepatic glycogenoses, and obstructive liver disease.

Poorly controlled diabetes mellitus

The most usual lipoprotein abnormality is the type IV pattern resulting in hypertriglyceridaemia with variable degrees of hypercholesterolaemia. With adequate insulin treatment even gross hyperlipidaemia will be corrected and the lipoprotein pattern returns to normal in the majority of children (Chance, Albutt, and Edkins, 1969a). In an attempt

ELECTROPHORETIC PATTERN	SERUM LIPIDS		TYPE*	PRIMARY	SECONDARY
	Chol.	Trig.
CHYLOMICRONS			I	HYPERCHYLOMICRONAEMIA (Fat-induced or exogenous hypertriglyceridaemia)	(DIABETES MELLITUS)
β			II	HYPER β LIPOPROTEINAEMIA (Familial hypercholesterolaemia)	HYPOTHYROIDISM NEPHROTIC SYNDROME OBSTRUCTIVE JAUNDICE
broad- β			III	BROAD- β DISEASE	(HYPOTHYROIDISM)
pre- β			IV	HYPER-PRE β LIPOPROTEINAEMIA (Endogenous or CHO-induced hypertriglyceridaemia)	DIABETES MELLITUS NEPHROTIC SYNDROME GLYCOGENOSIS (TYPE I) HYPERCALCAEMIA (HYPOTHYROIDISM)
CHY. pre- β			V	?	DIABETES MELLITUS NEPHROTIC SYNDROME PANCREATITIS

FIG. Classification of hyperlipoproteinaemia in childhood.

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to minimize the vascular complications which occur in adult life in the majority of diabetic children, modification of the dietary fat intake of childhood diabetics has been advocated (Lloyd, 1966). A 10-year follow-up, however, of children treated with diets low in ordinary fat and supplemented with corn oil showed no significant reduction in serum cholesterol concentrations (Chance, Albutt, and Edkins, 1969b). Adherence to the regimen was poor and some children developed excess prebetalipoprotein, possibly provoked by a relatively high-carbohydrate low-fat diet. At present, therefore, strict control of dietary fat cannot be recommended for diabetic children as a measure designed to lessen the development of large blood vessel disease.

Hypothyroidism

Hypercholesterolaemia with the type II lipoprotein pattern is commonly found in older children with hypothyroidism and this abnormality is corrected by adequate replacement therapy. In babies with hypothyroidism the lipoprotein pattern is often normal and serum cholesterol estimations are of little diagnostic help in this age group.

Renal disease

Most children with the nephrotic syndrome have hyperlipoproteinaemia. Increases in betalipoprotein and hypercholesterolaemia are common and there is a strong negative correlation between the concentrations of serum cholesterol and serum albumin. Increased levels of prebetalipoprotein and hence of serum triglyceride may also be found, but there is no correlation between the hypertriglyceridaemia and hypoalbuminaemia.

Hyperlipoproteinaemia in association with other forms of renal disease in children is not well documented, though it is recognized that children dying in renal failure may have extensive atheroma. The need to give children on renal dialysis high fat diets in order to provide sufficient calories for growth may conceivably result in secondary hyperlipoproteinaemia and acceleration of atherosclerotic lesions; this aspect of management requires further investigation.

Glycogen storage disease

Hyperlipoproteinaemia is usual in children suffering

from hepatic glycogenosis and the finding of hyperlipidaemia in a child with hepatic enlargement (who does not have obvious cirrhosis) should always arouse suspicion of this diagnosis. The lipidoses, which are often considered in the differential diagnosis in this situation, are in fact rarely accompanied by any significant serum lipid abnormality. Though the type of hyperlipoproteinaemia tends to vary with the nature of the glycogenosis (in glucose-6-phosphatase deficiency there is predominantly an increase in prebetalipoprotein, and in the debrancher and phosphorylase deficiencies the increase is mainly in betalipoprotein), the distinction is not absolute and the lipoprotein pattern cannot be used to aid the diagnosis of the type of glycogen storage disease. As there is no specific treatment for the glycogenoses, and as many affected children will probably survive into adult life, amelioration of the hyperlipoproteinaemia should be considered, and Fernandes and Pikaar (1969) have described the use of different dietary regimens for the different enzyme variants. Long-term evaluation of such therapeutic approaches in terms of the development of atheroma is not yet available.

Obstructive liver disease

Children with obstructive jaundice usually have hyperlipoproteinaemia unless they are in terminal liver failure when lipoprotein levels are often severely depressed. Various types of lipoprotein pattern may occur, but in intrahepatic biliary atresia a specific type of hyperlipidaemia is often present caused by accumulation of an abnormal lipoprotein termed lipoprotein X (Seidel, Agostini, and Muller, 1972). This lipoprotein has a high proportion of unesterified cholesterol and of phospholipid in its molecule and thus there is gross hypercholesterolaemia and even more marked hyperphospholipidaemia. Extensive xanthomatosis can give rise to considerable distress and treatment of the hyperlipoproteinaemia by diet and drugs is often successful in alleviating this aspect of the condition.

Primary hyperlipoproteinaemia

Of the 5 types of primary hyperlipoproteinaemia (Figure), only primary hyperchylomicronaemia (type I) and familial hyperbetalipoproteinaemia (type II) are at all likely to be encountered in children.

Broad-beta disease (type III), in which there is accumulation of betalipoprotein of abnormal composition and behaviour (both on electrophoresis and on ultracentrifugation), is rarely observed in childhood; Fuhrmann *et al.* (1971) reported one family

with affected children, but Fredrickson and Levy (1972) failed to find the disease under the age of 20 years in the course of extensive family studies of 36 kindreds.

Primary hyperprebetalipoproteinaemia (type IV) is also uncommon under the age of 21 (Glueck *et al.*, 1972). A few isolated cases have been reported around the age of puberty (Segall *et al.*, 1970a; Fredrickson and Levy, 1972). Glueck *et al.* (1973) investigated 33 families with type IV hyperlipoproteinaemia and found abnormal lipoprotein patterns in 32 of the 77 children under the age of 21; however, in only 9 was the type IV pattern present, 17 had hyperbetalipoproteinaemia (type IIA), and 6 had hyperbetalipoproteinaemia with only slight increase also in prebetalipoprotein (type IIB). These authors comment that it will be interesting to see how many of the children with the type II lipoprotein abnormality will eventually develop a type IV pattern.

Type V hyperlipoproteinaemia remains a confusing condition and there must be some doubt as to whether it is expressed as a primary disorder in childhood. The pattern (increase in chylomicrons and prebetalipoprotein) occurs in children with the type I disorder (especially after treatment) and accumulation of chylomicrons may also be found in familial type IV disorder (Segall *et al.*, 1970a). Fredrickson and Levy (1972) report one case of apparent familial type V in a child of 13 years.

Familial hyperchylomicronaemia (type I)

This disorder usually presents during childhood with eruptive xanthomata or attacks of abdominal pain. Some patients, however, remain asymptomatic and the diagnosis is made by the chance finding of turbid plasma, hepatosplenomegaly, or lipaemia retinalis.

The condition is rare and is inherited as an autosomal recessive, the basic defect being deficiency of lipoprotein lipase. The findings in heterozygotes are not consistent; in some individuals there may be evidence of some degree of lipoprotein lipase deficiency (Fredrickson and Levy, 1972), and moderate increase of serum triglyceride, increase in prebetalipoprotein, and/or delay in clearing dietary fat have all been observed.

In affected patients the serum is characteristically turbid, even in the fasting state, because of the increase in chylomicrons. In addition there is usually some increase in prebetalipoprotein, and concentrations of both beta- and alpha-lipoproteins are reduced. Analysis of the serum lipids reflects the composition of chylomicrons; there is a great increase in triglyceride (values of the order of 5 000

to 10 000 mg/dl (56.50 to 113.00 mmol/l), with lesser increases in total cholesterol and phospholipid. The enzyme defect can be demonstrated by the estimation of plasma post-heparin lipolytic activity, and a simple qualitative test has been described (Fredrickson and Levy, 1972). This investigation must be done within a few days of starting a low-fat diet because normal subjects fed low-fat diets for longer than 1 week may show abnormal responses (Fredrickson, Ono, and Davis, 1963). During episodes of abdominal pain there may be evidence of pancreatitis with raised plasma amylase levels.

There is no evidence that this disorder is associated with an increased incidence of premature atherosclerosis. Nevertheless the clinical manifestations are usually distressing enough to warrant treatment. Problems caused by increased blood viscosity, and the decreased tissue oxygen uptake which is associated with serum turbidity (Joyner, Hortwitz, and Williams, 1960) may be important, particularly if there is associated infection. Restriction of dietary fat reduces hyperchylomicronaemia and abolishes symptoms. The degree of fat restriction necessary to render the serum optically clear in the fasting state may be severe, perhaps as little as 3 to 5 g per day and it is doubtful if such severe restriction is necessary in the absence of symptoms. Nevertheless the dietary regimen required to maintain patients symptom free, with reasonable serum lipid levels, is often difficult to maintain on a life-long basis. The use of medium-chain triglycerides whose fatty acids are absorbed into the portal vein, thus bypassing the chylomicron route, can greatly improve the palatability and acceptability of the diet (Lloyd, 1968).

Familial hyperbetalipoproteinaemia (type II; familial hypercholesterolaemia)

This is the most common type of primary hyperlipoproteinaemia which can be detected during childhood. It is inherited as an autosomal dominant (Kwiterovich, Fredrickson, and Levy, 1974) and is associated with a high risk of the premature development of coronary heart disease (Slack, 1969). The basic defect is not yet firmly established, but recent work suggests it may involve deficiency of cell surface receptors for betalipoprotein (Brown and Goldstein, 1974). As long as the diagnosis has to be established (as at present) by measurement of serum cholesterol and/or betalipoprotein concentrations, the gene frequency is difficult to assess because it is impossible to define precise cut-off points. From an estimate of the number of homozygous individuals, Carter, Slack, and Myant (1971) have calculated the proportion of heterozygotes in the population of England and Wales to be about 1 in 280.

In the rare homozygous form of the disease xanthomata, both tendinous and tuberous, appear during early childhood and death from myocardial infarction often occurs during later childhood or adolescence.

In the heterozygous children clinical manifestations are uncommon though occasional patients may already have corneal arcus or xanthomata. The diagnosis is usually suspected because of a history of coronary heart disease at an early age in a near relative. Estimates of the size of the contribution of familial hypercholesterolaemia to the total problem of coronary heart disease vary; Patterson and Slack (1972) suggest that in London it is quite small, but in a study in Israel of 64 men under the age of 41 years who had survived a myocardial infarction for more than 6 months, Tamir *et al.* (1972) found 38 to have an abnormal lipoprotein pattern and 30 of the 85 children of these fathers had familial (type II) hyperbetalipoproteinaemia. It is, therefore, probably appropriate to investigate serum lipoproteins in children in families with a history of premature coronary heart disease. Many such children will be found to be normal and this knowledge is of considerable benefit to the whole family.

The diagnosis is established by finding raised serum cholesterol and betalipoprotein concentrations and the demonstration of a similar abnormality in at least one first-degree relative in the case of heterozygotes, and both parents in the case of homozygotes. Heterozygotes usually have cholesterol concentrations of the order of 270 to 400 mg/dl (6.99 to 10.36 mmol/l), and homozygotes have values very much higher around 700 to 1 000 mg/dl (18.13 to 25.90 mmol/l). In the majority of affected children prebetalipoprotein is not increased and serum triglyceride concentrations are normal. Kwiterovich *et al.* (1974) have estimated that about 10 per cent of heterozygous children may show some increase in prebetalipoprotein with mild hypertriglyceridaemia, the so-called type IIB pattern (Beaumont *et al.*, 1970). The earliest age at which the diagnosis can be made with certainty is still disputed; reports that it could be established at birth by estimation of cholesterol concentration in umbilical cord blood (Glueck *et al.*, 1971) have not been substantiated. Darmady *et al.* (1972) in a prospective study of 300 unselected normal infants found that serum cholesterol at birth did not predict cholesterol concentration at 1 year of age, and the only infant in their series who was subsequently shown to have familial hyperbetalipoproteinaemia would have been missed in a cord blood screening programme taking 100 mg/dl (2.59 mmol/l) as the cut-off point (Glueck *et al.*, 1971), because her cord serum value was only 87 mg/dl (2.25 mmol/l). If, however, one

parent is known to be heterozygous for the disorder, and betalipoprotein cholesterol rather than total serum cholesterol is estimated, then it may be possible to make a correct diagnosis in the infant at birth (Kwiterovich, Levy, and Fredrickson, 1973), but the practical advantage of this knowledge in terms of therapeutic intervention has not been established. Serum cholesterol concentrations in the early months of life are normally highest in infants fed on human milk, and the lowest levels are found in babies given artificial milks containing polyunsaturated fatty acids (Darmady *et al.*, 1972). These effects are, however, temporary and are abolished when mixed feeding is established. It is debatable whether it is wise to deny an infant the considerable advantages of breast feeding in order to lower serum cholesterol at this early age. In general, therefore, it may be wiser to wait until the infant is about 1 year of age and established on a mixed diet before embarking on diagnostic procedures.

Treatment of children with familial hyperbetalipoproteinaemia is carried out in the hope that by lowering betalipoprotein, and hence serum cholesterol concentrations, the development of atherosclerosis will be delayed and the premature occurrence of coronary heart disease prevented. No long-term studies have yet been made to show whether these expectations will be fulfilled. Arrangements should be made for the follow-up of all children currently being treated, and the treatment regimens themselves must undergo critical long-term evaluation. It is implicit that any therapy should be safe, acceptable, and effective, but studies to date indicate that none of the current regimens completely fulfils these criteria.

For the severely affected homozygous patients all forms of diet and drug therapy have proved disappointing. Diets low in saturated fat and supplemented with polyunsaturated fat, combined with at least two hypolipidaemic drugs (most often cholestyramine and nicotinic acid), usually result in lowering of serum cholesterol from around 1000 mg/dl (25.90 mmol/l) to around 600 mg/dl (15.54 mmol/l). Such reduction can lead to resolution of skin xanthomata (Segall *et al.*, 1970b; Moutafis *et al.*, 1971; Levy *et al.*, 1972), but there is no convincing evidence of retardation in the development of the arterial lesions. The operation of ileal bypass has also not been successful (Johnston *et al.*, 1967). More recently portacaval anastomosis has been performed (Starzl *et al.*, 1973) with immediately encouraging results in terms of lowered serum cholesterol levels; longer follow-up is required before this method of treatment can be fully assessed.

Heterozygous children, most of them asymptomatic, may be treated by diet or drugs or a combination of both approaches. The essential of dietary therapy is reduction in the amount of ordinary dietary fat (largely saturated). Segall *et al.* (1970b) found that strict reduction to about 18 g/day resulted in a fall in serum cholesterol of around 20 per cent of the pretreatment value. The addition of polyunsaturated fat (given as corn oil and corn oil products) had no further hypocholesterolaemic effect but did improve the palatability of the diet. Most dietary cholesterol consumed by children is in the form of eggs and a strict low fat diet effectively limits the intake of eggs so that formal instructions regarding cholesterol intake seem unnecessary, especially as dietary cholesterol is probably not a major factor in determining serum concentrations. Whether dietary treatment alone is likely to be effective depends to some extent on the initial serum cholesterol value; if this is over 350 mg/dl (9.06 mmol/l) it is less likely that sufficient reduction will be achieved to maintain acceptable levels of serum cholesterol (at least below 250 mg/dl (6.47 mmol/l)). Even for those children, who in the short-term do well on diet, long-term follow-up may give very different results. Recently West, Fosbrooke, and Lloyd (in press) showed that at the end of 1½ years, 14 out of 17 children were no longer adhering satisfactorily to a diet; the remaining 3 children, however, were still reasonably controlled 3 to 8 years later. In contemporary British society it does not seem practicable for most children to continue normal life eating restricted ordinary fat diets, even with supplementation with corn oil and corn oil products.

Clofibrate (chlorophenoxyisobutyrate; Atromid-S¹) has only a weak hypocholesterolaemic action. In combination with diet its administration may achieve a further 10 per cent lowering of serum cholesterol (Segall *et al.*, 1970b). Though this reduction is of immediate apparent benefit, long-term control of serum cholesterol has proved inadequate in children largely because of failure of adherence to the dietary component of the regimen (West *et al.*, in press). This drug is of limited value in the management of childhood hypercholesterolaemia and should probably no longer be used.

Cholestyramine (Questran² brand) is currently the treatment of choice for children with initial cholesterol concentrations greater than 350 mg/dl (9.06 mmol/l), or for those in whom a strict low-fat diet cannot be maintained. This drug has the advantage that its hypocholesterolaemic action appears equally effective without dietary fat restriction (West and Lloyd, 1973); furthermore it can be

¹ICI Ltd.

²Bristol Laboratories.

given twice daily which avoids the necessity of taking medicine at school. The degree of lowering of serum cholesterol is positively correlated with the size of the dose; the average effective dose for children is 0.6 g/kg body weight/day, which corresponds to about 30 to 40 g/day for an average adult. Using this dosage a reduction of about 36 per cent in serum cholesterol can be expected and in a 4-year period there appears to have been no escape from the hypocholesterolaemic action of the drug. Adherence to treatment is, however, far from perfect; by 3 years only 57 per cent remain on satisfactory dosage (West *et al.*, in press). The main reasons for non-adherence are the unpalatability of the drug, and less bulky, more palatable preparations are needed. Though the drug is not absorbed and therefore has no systemic toxicity, side effects from interference with absorption may be anticipated. It has now been shown that children develop steatorrhoea and folate deficiency, and that over a 2-year period serum concentrations of vitamin A and E and of serum phosphate fall significantly, though they have not yet reached abnormally low values (West and Lloyd, unpublished data). The folate deficiency can be corrected by administration of oral folic acid, 5 mg/day, and this should be given to all patients on long-term cholestyramine therapy. Steatorrhoea has not resulted in either diarrhoea or growth retardation in a 3-year follow-up period, but this aspect, as well as the serum levels of vitamin A, E, and phosphate needs continued surveillance.

No treatment regimen, therefore, can be said to be wholly acceptable, without side effects, and effective in lowering serum cholesterol to below 250 mg/dl (6.47 mmol/l) in all patients. In addition to the problems mentioned, the psychological implications of treatment on the child and his family have to be considered. It has been suggested that to administer an unpleasant diet or drug to an asymptomatic child and to check his progress with repeated blood examinations, while at the same time discussing prevention of 'heart attack' with his parents will engender fear which is unjustified, especially in view of the uncertain outcome. In our experience, families in whom there has been an early coronary event already have a high level of anxiety and many are asking about prevention for their children. In this situation an honest approach, with full explanations about the limitations of our current knowledge, has been well accepted and in the short term has generally allayed some measure of the family anxiety. Treatment of children in proven high risk families seems justified, but as long as failure of treatment is occurring at a fairly high rate even in these well-motivated groups, it does not appear appropriate to extend treatment to children

from families in whom early heart attack has not been a feature. Thus screening of the general population to detect children with familial hyperbetalipoproteinaemia is not at present, in my view, desirable.

The possibility that risk factors other than hypercholesterolaemia may present in the child and/or his family should not be overlooked, and appropriate action should be instituted if such factors are detected. In particular the disadvantages of smoking should be stressed.

Summary and conclusions

Hyperlipidaemia in children is for practical purposes most commonly expressed as hypercholesterolaemia. Levels of serum cholesterol in childhood above which an increased risk of coronary heart disease in adult life may be expected have not been precisely defined. Cholesterol values are influenced by many environmental factors such as diet, and concentrations vary between communities. Statistically defined 'normal' levels in a community may not necessarily be 'desirable' levels. It is suggested that at the present time the finding of a cholesterol concentration below 230 mg/dl (5.95 mmol/l) should not initiate any action, children with values over 250 mg/dl (6.47 mmol/l) should be fully investigated, and for those with levels between 230 and 250 mg/dl (5.95 and 6.47 mmol/l) the observations should be repeated and possibly further investigations carried out. Caution is needed in the interpretation of values throughout the first year of life, and during puberty.

Hyperlipoproteinaemia secondary to another disease rarely presents diagnostic or therapeutic problems during childhood. The possibility of hyperlipidaemia being secondary must, however, always be considered; the commonly associated disorders are diabetes mellitus, hypothyroidism, the nephrotic syndrome, the hepatic glycogenoses, and obstructive liver disease.

Familial hyperbetalipoproteinaemia (type II; familial hypercholesterolaemia) in its heterozygous form is the only primary disorder commonly found during childhood. It is associated with an increased risk of coronary heart disease in adult life but it is not certain whether treatment in childhood will lessen the risk. In only a minority of children is dietary treatment effective in maintaining acceptable levels of serum cholesterol in the long term. Cholestyramine is the drug of choice, but acceptance (though better than for diet) is only about 60 per cent after 3 years, and absorptive processes are interfered with. Because a satisfactory therapeutic regimen is not yet available, treatment should be

limited to children from families with demonstrable high risk. Population screening to detect the disorder is not at present justified.

The question of whether to attempt to lower serum cholesterol concentration in children whose cholesterol levels are above 230 mg/dl (5.95 mmol/l) and who do not have evidence of a primary or secondary lipoprotein disorder has been left unanswered. Drash (1972) suggested institution of dietary therapy for all children with serum cholesterol above 235 mg/dl (6.08 mmol/l) (and probably above 200 mg/dl (5.18 mmol/l)) but this recommendation has not been universally adopted. Prescribed dietary treatment is unlikely to be accepted for long, and to change eating habits is very difficult. If the recommendations of the Department of Health and Social Security (1974) that the amount of fat, especially saturated fat, in the United Kingdom diet be reduced, were put into practice, some reduction in serum cholesterol concentration in children (as well as in adults) might be achieved. For a physician to suggest to a family with 'borderline high' serum cholesterol that their consumption of fat be reduced, and that some of the saturated fat be replaced by polyunsaturated fat, is unlikely to do harm, but there is insufficient evidence to state that the children in the family will be thereby protected against atheroma. Likewise there is inadequate evidence on which to recommend lowering of serum cholesterol in early infancy by feeding formulas high in polyunsaturated fat, or by discouraging breast feeding. The latter has so many positive advantages that its temporary effect on serum cholesterol should be ignored.

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