SESSION III

HYPERLIPIDAEMIA, SMOKING AND HYPERTENSION

Chairman: PROFESSOR A. S. TRUSWELL

The place of the hyperlipidaemias

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Summary

Of the primary hyperlipidaemias, familial hypercholesterolaemia (hyperbetalipoproteinaemia, type II) is always expressed in childhood and carries a high risk for the early development of coronary heart disease. The diagnosis can be established with a high degree of certainty by estimating the serum cholesterol concentration in selected children in whom the genetic risk is known to be great, e.g. if a parent or other first-degree relative is known to have the disease, or if a parent has had an attack of ischaemic heart disease at a young age. Screening of the general population in order to detect this disorder is not advocated. Treatment by either diet or drugs will lower serum cholesterol but long-term compliance is poor and the effect of treatment on the atherosclerotic process has not been evaluated. Follow-up studies must be maintained.

Familial hypertriglyceridaemic states are rarely fully expressed during childhood, and screening for them at this age is not practicable. Control of co-existent obesity and dietary treatment are usually successful in lowering serum lipids but long-term results have not yet been evaluated.

In a childhood population, single estimations of serum cholesterol or triglyceride should be interpreted with caution. Percentile rank correlations for serum cholesterol are of the order of 0.61 and for triglyceride of 0.31. Prediction of adult values cannot therefore be assured in childhood and the place of hyperlipidaemia in the childhood population as a risk factor for coronary heart disease in adult life is not established. Thus population screening of serum lipids in children cannot be justified. Evidence that a change in the diet of

children which would be expected to lower serum lipids will also delay the development of atherosclerosis in general and coronary heart disease in particular is lacking. Nevertheless the dietary changes which have been recommended for adults can safely be followed by children, and changes in eating habits are perhaps more likely to succeed if promoted on a family basis rather than for individual sections of the population.

In considering the place of the hyperlipidaemias in the prevention of coronary heart disease in childhood, three aspects will be discussed; first, the definition of hyperlipidaemia, second, the extent to which hyperlipidaemia in adult life can be predicted during childhood, and third, the measures available for the control of hyperlipidaemia in children. Because cardiovascular risk in adults has in the main been quantified in terms of hypercholesterolaemia and hypertriglyceridaemia these terms will be used, but it must be remembered that all lipids exist in serum in combination with each other and with proteins as lipoproteins, and the type of lipoprotein disturbance is also relevant in considering risk (Stanhope, Sampson and Clarkson, 1977).

What is hyperlipidaemia?

Hypercholesterolaemia and hypertriglyceridaemia are usually defined by statistical analysis of the values obtained in groups of supposedly healthy children. Values thus obtained vary between communities and are influenced by environmental factors such as diet, about which exact information may not be available, age, sex and puberty. To these

variables must be added differences in analytical methods and it is thus hardly surprising that there is no general agreement about upper limits of normality for either serum cholesterol or triglyceride in children. Even if statistically defined norms for serum lipid concentrations were agreed, values within such a 'normal range' could still be associated with an increased risk of atherosclerosis, and Drash (1972) has suggested that hyperlipidaemia should be defined in terms of what is desirable rather than what is apparent.

In reviewing studies of serum cholesterol in children in the United States he came to the conclusion that values above 5.12 mmol/l (200 mg/100 ml) should be regarded as abnormal. If hypercholesterolaemia were to be defined in this way, then between 8 and 25% of children in industrialized societies would be diagnosed as hypercholesterolaemic (Glueck, Fallat and Tsang, 1974). If, however, a statistical approach were adopted and if two standard deviations above the mean were used as the cut-off point, hypercholesterolaemia would be diagnosed in Cincinnati at levels above 5.74 mmol/l (224 mg/100 ml) (Glueck *et al.*, 1973a) and in London at levels above 6.74 mmol/l (260 mg/100 ml) (Darmady, Fosbrooke and Lloyd, 1972) or 6.32 mmol/l (246 mg/100 ml) (Leonard *et al.*, 1976). Such examples serve to illustrate the complexity of the problem. In the case of serum triglyceride concentration, for which there are less data, the situation is even worse.

At the present time it would therefore seem wise not to adopt too rigid definitions for hyperlipidaemia in children until more evidence is available regarding the subsequent risk for the development of atherosclerosis in adult life, and until it is clear that hyperlipidaemia can be modified.

Prediction of adult hyperlipidaemia in childhood

For simplicity, hypercholesterolaemia and hypertriglyceridaemia will be considered separately, although in most instances hypertriglyceridaemia will also be accompanied by some elevation of serum cholesterol.

Hypercholesterolaemia

Epidemiological studies of serum cholesterol concentrations in populations of adults have clearly established that individuals with levels in the upper quintile have a significantly increased risk of coronary heart disease (Carlson and Böttiger, 1972; Stamler and Epstein, 1972). Some of these individuals will be heterozygous for the inherited disorder of familial hypercholesterolaemia (familial hyperbeta-lipoproteinaemia, type II) and for men the risk has been estimated to be about ten times that of men in the general population whose serum cholesterol

levels are above the 95th centile of the normal distribution (Slack, 1974). The reasons for hypercholesterolaemia in the latter category are multifactorial and the two groups will be considered separately.

Familial hypercholesterolaemia. Individuals with this disorder have a high risk of coronary heart disease in early adult life. In the very rare homozygous form, clinical evidence of ischaemic heart disease is usually apparent in most patients by the second decade, and death generally occurs before the age of 30 years. In the more common heterozygous form, 50% of males will have had their first heart attack by the age of 50 years (Slack, 1969); for females the risk is much less, the comparable figure being 12%, but nevertheless it is considerably greater than for women who do not have the disorder.

Biochemical evidence of familial hypercholesterolaemia is always present during childhood, although if serum cholesterol alone is used for identification, the diagnosis cannot be made reliably at birth, and may be very difficult during the first year of life (Darmady *et al.*, 1972). If, however, one parent is already known to be heterozygous and if β -lipoprotein cholesterol is measured (rather than total cholesterol), then the diagnosis can be made at birth by examination of umbilical cord blood (Kwiterovich, Levy and Fredrickson, 1973). After the first year of life, the diagnosis can usually be established relatively easily if a first-degree relative is known to be affected, and if the level of serum cholesterol is unequivocally high, say >7.69 mmol/l (300 mg/100 ml).

In order to assess the degree of confidence with which serum cholesterol estimation could be used to make the diagnosis, Leonard *et al.* (1977) examined the distribution of serum cholesterol concentration in 134 children aged 1–16 years who had at least one first-degree relative with familial hypercholesterolaemia. They found that if a cholesterol concentration of 6.77 mmol/l (264 mg/100 ml) were used as the cut-off point, only 4.25% of the children would be misdiagnosed. This figure is, however, only valid for a population in which the genetic risk is 1 in 2, that is in the first-degree relatives of known heterozygous individuals. In the general population, in whom the risk of familial hypercholesterolaemia is about 1 : 500, Leonard (personal communication) has shown that even at a cut-off point of 7.5 mmol/l, the probability of making a correct diagnosis would be only about 10%. He suggests that if screening of the childhood population were to be attempted in order to diagnose this disorder, it should be confined to the children of individuals who have had a myocardial infarction; in this population of children the genetic risk might be of the order of 1 in 8 (Paterson and Slack, 1972) and the probability of making

a correct diagnosis would be correspondingly higher.

Hypercholesterolaemia of affluence. The term 'hypercholesterolaemia of affluence' has been used (Lloyd, 1976) to describe the hypercholesterolaemia in children in the rich countries of the world, which is presumably related to their dietary patterns. Studies of serum cholesterol at birth show relatively little difference between infants of different races and in different societies; in childhood, however, mean values vary considerably between populations, and children in countries where there is a high rate of coronary heart disease in adults have the highest values (Uppal, 1974). Nevertheless, whereas it may be possible to conclude that *populations* of children with relatively high serum cholesterol concentrations will retain their 'hypercholesterolaemia' in adult life, and thus increase their risk of coronary heart disease, there is less information on which to judge the risks for *individual* children.

The degree to which serum cholesterol concentrations in children remain in the same centile rank (tracking) over the years is being investigated in a number of longitudinal studies, and in the Muscatine Study in Iowa, U.S.A., a four-year follow-up of 1953 children aged 5–18 years showed a rank correlation for cholesterol of 0.61 (Clarke *et al.*, 1976). Very few of the children with cholesterol concentrations in the upper fifth centile stayed in this centile 4 years later. The practical difficulties of selecting cholesterol levels for intervention purposes was highlighted in the study of Uppal (1974). He re-screened one hundred and eleven 9–12-year-old children who at their initial examination had serum cholesterol greater than 6.15 mmol/l (240 mg/100 ml), and found that in only 40% were the values still above this cut-off point. The interval to re-screening was only 6 months, and the statistical phenomenon of regression towards the mean could not entirely explain the magnitude of the difference.

The evidence, therefore, that in populations of children serum cholesterol concentrations can be used to determine individuals at risk for developing coronary heart disease, is not strong, and mass screening of serum cholesterol in children cannot be advocated.

Hypertriglyceridaemia

Hypertriglyceridaemia (which is of course usually associated with some degree of hypercholesterolaemia), has also been shown to be a risk factor for coronary heart disease in adults (Carlson and Böttiger, 1972). Of the primary lipoprotein disorders in which hypertriglyceridaemia is a constant feature, only the rare condition of familial hyperchylomicronaemia (type I) is invariably expressed during childhood, but evidence that this disorder is asso-

ciated with premature atherosclerosis is lacking and this disease will therefore not be considered further. There are three other main types of primary hypertriglyceridaemia which are associated with premature atherosclerosis; familial hypertriglyceridaemia (type IV), familial combined hyperlipidaemia (with a type IIb pattern), and broad beta disease (remnant hyperlipoproteinaemia, type III). All of these are thought to be dominantly inherited and attempts have been made to detect them early in life in affected families.

Familial hypertriglyceridaemia (type IV). Because there have been only sporadic case reports of this type of hyperlipidaemia in children it has generally been concluded that the disorder is rarely expressed during the childhood years. In a study of 113 children under the age of 20 years from 36 families Glueck *et al.* (1973b) found 23 to have type IV hyperlipoproteinaemia; this was present in 7 of the 52 children who were under the age of 13 years, i.e. in only 13%. For a dominantly inherited disorder, 50% would be expected to be affected, and thus it is clear that expression is indeed delayed in childhood.

Familial combined hyperlipidaemia (type IIb). This disorder has only been delineated as a separate condition relatively recently, and there is still some dispute about its mode of inheritance. In a study of the offspring of 33 families, Glueck *et al.* (1973a) investigated 35 children under 13 years of age, of whom 16 (45%) were found to have some form of lipid abnormality. However, only three had a type IIb pattern and the remainder had either a type II pattern (10) or a type IV pattern (3). Further follow-up studies are needed before the situation regarding the expression of this type of hyperlipidaemia in children can be clarified.

Primary broad-beta disease (type III). It is generally accepted that this disorder is also only rarely expressed during the childhood years. Probably it is even less often manifest in children than the other hypertriglyceridaemic states; Morganroth, Levy and Fredrickson (1975) in an analysis of 29 kindreds found only 2 of 55 children had hyperlipidaemia, and both of these had a type IV pattern.

Investigation of children in families with primary hypertriglyceridaemia, of whatever type, is likely to result in very few clear-cut diagnoses, and follow-up will be essential because of the low rate of expression. In the general childhood population the degree to which serum triglyceride was found to track was only 0.31 in the Muscatine Study (Clarke *et al.*, 1976). Mass screening of serum triglyceride in children would therefore appear to be unjustified.

Control of hyperlipidaemia in children

Measures to control hyperlipidaemia in children

may be divided into those used to reduce serum lipid concentrations in the childhood population as a whole, and those used to treat specific disorders in individual children. As far as *population control* is concerned a number of countries have recommended that children over the age of one year should participate in any measures advocated for population control in adults; broadly these recommendations comprise some reduction in saturated fat intake, the possible substitution of polyunsaturated fat for some of the saturated fat, and some limitation of cholesterol intake (Lloyd, 1976). Radical change in the diets of infants under the age of one year is probably both unnecessary and undesirable. Breast feeding, although known to be associated with somewhat higher serum cholesterol concentrations than artificial feeding (Darmady *et al.*, 1972), should certainly not be discouraged on this account. Whether population control measures will be acceptable and effective is still not certain. A recent study from Belgium suggests that reduction in dietary fat in a population is practicable, that it is associated with a fall in mean serum cholesterol concentration, and that it may result in a reduction in cardiovascular mortality and morbidity (Joossens *et al.*, 1977). Nevertheless scepticism persists (McMichael, 1977), and the subject is likely to remain controversial.

Treatment of *individual children* found to have one of the inherited forms of hyperlipidaemia is probably justified in the present state of knowledge, and this is particularly so for those children in whom the diagnosis can be established with certainty and in whom the risk is known to be high because of a family history of early ischaemic heart disease. Thus children with the heterozygous form of familial hypercholesterolaemia and a positive family history of coronary heart disease form the major group requiring urgent attention. Whether therapeutic regimes should be confined to the boys in these families is a matter for debate. Although the risk for girls is appreciably less than for the boys, it has not in fact been the authors' practice to differentiate between the sexes in their approach to the treatment of children with familial hypercholesterolaemia.

Treatment of familial hypercholesterolaemia

A number of studies of diets which all have restricted saturated fat, and usually contained additional polyunsaturated fat, but have varied in their emphasis on cholesterol restriction, have shown a fall in serum cholesterol concentration of between 6–23% in the short-term (<one year) (Segall *et al.*, 1970; Glueck *et al.*, 1976, 1977b; Farah, Kwiterovich and Neill, 1977). It has been stated that in children aged 1–5 years dietary treatment will result in 'normal' serum cholesterol concentration in 60–

80% of affected children, but that in older children (aged 6–12 years), only about 40% will have 'normal' levels with diet alone (Larsen, Glueck and Tsang, 1974). Whether or not acceptable serum cholesterol concentrations are achieved will of course depend to some extent upon the initial concentration, although this is not an invariable guide to the success of dietary treatment. Very few studies of the long-term efficacy of diet appear to have been made; West, Fosbrooke and Lloyd (1975) reported that only 20% of a small group of children continued to have satisfactory control of serum cholesterol after 18–24 months, but those who were effectively controlled, remained so for 5 years or longer, and their initial serum cholesterol was not significantly different from the group as a whole. The authors suggest that it is probably worth-while starting with dietary modifications in all cases even though in general initial results and long-term compliance may be poor.

Of the drugs available for treatment of familial hypercholesterolaemia, only the ion-exchange resin cholestyramine has been extensively investigated in childhood (West and Lloyd, 1973; Glueck *et al.*, 1976, 1977b; Farah *et al.*, 1977). Reduction in serum cholesterol of between 17 and 35% has been reported and there is general agreement that the drug is effective in twice-daily dosage. West and Lloyd (1973) found efficacy to be equally good with a normal as with a low fat diet, but other workers have all advocated combining drug administration with some form of dietary restriction. The dose required to produce the maximum effect varies in individual children; West and Lloyd found a positive correlation with the weight of the child and reported a mean dosage of 0.6 g/kg/day in their patients. Farah *et al.* (1977) and Glueck *et al.* (1977b) have questioned the need to use such relatively large doses; Farah *et al.* found no correlation with weight but claim that the dose can be predicted by the initial serum cholesterol concentration. In practice the authors suggest that all children should be started on a small dose (4 g twice daily) and that this is then increased until the desired effect is achieved, or the child cannot tolerate any further increase.

Side effects of cholestyramine have been evaluated in a 2–3 year follow-up by West and Lloyd (1975), and it is recommended that all children should receive additional oral folic acid (5 mg/day), and regular monitoring should be undertaken of levels of fat soluble vitamins, growth, and general well-being.

Long-term compliance with cholestyramine is undoubtedly better than for diet alone, at least in England. In a 3-year follow-up of 36 children West *et al.* (1975) found 57% were still satisfactorily

controlled, and after 6 years the proportion was still 56% (West, unpublished data). Glueck *et al.* (1977b) followed seven children for 3 years, of whom five (71%) remained satisfactorily controlled; however, five of their original group had 'dropped out' before this time because of poor palatability and acceptance of the drug, and thus overall compliance in twelve children over a 3-year period showed that only 41% were adequately treated at the end of this time. It is clear therefore that a substantial number of children is likely to find cholestyramine unpalatable and unacceptable for what is probably going to be life-long therapy, and alternative regimes are obviously needed. Other resins such as colestipol have been shown to be effective, and probably to have better short-term acceptability than cholestyramine (Glueck *et al.*, 1976), but results of long-term compliance are not yet available.

Current management of familial hypercholesterolaemia in children is therefore far from satisfactory, even in terms of simply maintaining lowered levels of serum cholesterol. To date there is no evidence that lowering serum cholesterol in this disorder delays the atherosclerotic process, although resolution of skin xanthomata in homozygous children (Levy, Fredrickson and Shulman, 1972) at least indicates that tissue deposition of lipids can be influenced. If progress is to be made in devising more acceptable therapy and in evaluating its effect on the prevention of coronary heart disease it is essential that children are treated in collaboration with centres capable of maintaining long-term follow-up.

Treatment of familial hypertriglyceridaemic states

Although familial hypertriglyceridaemic states (with the exception of type I which is not being considered further) are rarely expressed during childhood, treatment is probably worth-while if they are detected and is likely to be easier than for familial hypercholesterolaemia. Many of the children are obese (Fredrickson and Levy, 1972; Glueck *et al.*, 1973a) and in these weight reduction with a low energy diet is indicated as an initial measure irrespective of the type of lipoprotein abnormality. In some patients serum lipids will revert to normal on this measure alone. In 40 children (mean age 13 years) with familial hypertriglyceridaemia (type IV) Glueck *et al.* (1977a) report that a diet in which 20% of energy was derived from protein, 40% from carbohydrate and 40% from fat, with a polyunsaturated to saturated fat ratio of 1.5 resulted in normalization of serum triglyceride (below 1.58 mmol/l, 140 mg/100 ml) in twenty-nine of the children during the first 6 months of treatment. In thirteen children treated for 8–12 months, mean triglyceride concentration fell from 3.2 mmol/l (290 mg/100 ml) to 1.68 mmol/l (149 mg/100 ml). A

similar regime will probably be effective for some children with combined hyperlipidaemia and broad-beta disease. For the latter disorder, clofibrate is the drug of choice if any drug therapy is required.

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