Childhood Nutrition and Adult Cardiovascular Disease
Henry C. McGill

Childhood Origin of Atherosclerosis

The aortas of children as young as 3–4 years often contain intimal lipid deposits, commonly called “fatty streaks” (Figure 1).1,2 These aortic fatty streaks increase in extent rapidly during the second decade of life, and similar lesions begin to appear in the coronary arteries in the latter part of the second decade. The early fatty streaks are formed by clusters of macrophages containing lipid inclusions that are predominantly cholesterol and its esters.3 In older children, lipid particles also accumulate in smooth muscle cells and in extracellular spaces.

At some anatomic sites, fatty streaks are converted into fibrous plaques, which have a core of lipid-rich debris overlaid by endothelium and a capsule of fibrous and muscular tissue.4 During middle age, fibrous plaques accumulate more lipid and undergo vascularization and calcification. Fibrous plaques may rupture, expose the blood to thrombogenic materials, and precipitate the formation of an occlusive thrombus, which occludes the flow of blood and causes ischemic necrosis of the heart (myocardial infarction), brain (stroke), or extremity (peripheral arterial disease).

The past two decades of research in atherosclerosis have yielded a wealth of information about the cellular and molecular processes involved in the pathogenesis of these lesions. Endothelium provides an antithrombotic barrier between circulating blood and the underlying tissue, controls adhesion and migration of leukocytes, regulates permeability, and secretes the arterial vasodilator nitric oxide.5 Low density lipoprotein (LDL), long known as the major culprit in atherogenesis, is converted to an oxidized form by arterial wall cells and becomes cytotoxic, attracts monocytes, and stimulates secretion of cytokines.6 Monocytes accumulate lipid through scavenger receptors with an affinity for oxidized LDL particles,7 process the ingested lipid,8 and secrete a variety of growth factors.9 Smooth muscle cells accumulate lipid, proliferate, and secrete collagen.10 These observations have transformed our concept of the fibrous plaque from that of a slowly progressing irreversible structure to a metabolically active lesion subject to episodes of rapid change. The observations have also suggested many different strategies by which the process can be controlled.

There is little question about the central role of the fibrous plaque in the pathogenesis of occlusive thrombosis and clinical disease. However, the relationship of fatty streaks in children and young adults to the fibrous plaques of middle age has been more difficult to establish and remains more controversial. The present consensus is that only some fatty streaks in selected sites progress to fi-

Figure 1. Natural history of atherosclerosis. Fatty streaks begin to appear in the aorta in the first decade of life and in the coronary arteries in the second decade. In the third and fourth decades, some fatty streaks become thicker and accumulate macrophages, smooth muscle, necrotic lipid-rich debris, and a fibromuscular cap to become fibrous plaques. Fibrous plaques undergo a number of changes, some of which lead to rupture of the endothelial surface and cap and precipitate the formation of an occlusive thrombus. Arterial occlusion produces several clinical syndromes, the manifestations of which vary with the target organ involved. Redrawn from McGill et al.1

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brous plaques and other more advanced lesions and that this conversion is accelerated under certain conditions in some, but not all, persons. Identifying the conditions that accelerate progression from fatty streaks to fibrous plaques and the conditions that destabilize the intimal covering of the fibrous plaque is a major objective of current research in atherosclerosis.

The Risk Factors for Atherosclerotic Disease

In the 1950s and 1960s, epidemiologic studies identified a number of characteristics that predicted the probability that an individual would develop one of the clinical manifestations of atherosclerosis. These conditions, which became known as the "risk factors" for atherosclerotic disease, included markers for subclinical disease, such as electrocardiographic abnormalities; intervening variables, such as serum cholesterol concentrations; causative agents, such as tobacco smoke; other disease conditions, such as hypertension or diabetes; and genetically determined characteristics, such as sex or polymorphisms in candidate genes for atherosclerosis. The number and heterogeneity of risk factors indicate that they affect atherosclerosis and its clinical sequelae by a variety of different mechanisms. Elevated plasma cholesterol concentrations, which result from an interaction between genetically controlled metabolic processes and a high dietary intake of cholesterol and saturated fatty acids, increase the rate of deposition of lipids in the arterial intima. Cigarette smoking accelerates atherogenesis and also increases the coagulability of blood by unknown mechanisms. Hypertension and diabetes accelerate the conversion of fatty streaks to fibrous plaques, again by unknown mechanisms.

Some risk factors can be controlled; others cannot. The concept that modification of risk factors by changes in diet and lifestyle or by drugs could reduce the incidence of atherosclerotic disease was proposed many years ago, but the proposition has been extraordinarily difficult to prove. However, a number of experimental human trials have now demonstrated conclusively the validity of this concept, and the results have led to many recommendations for clinical medical practice and for public health designed to prevent the initial occurrence of coronary heart disease and to reduce the probability of recurrence.

Initially, risk factors were considered important only in adults. During the 1970s and 1980s, epidemiologic studies of children demonstrated that they, too, varied in serum cholesterol concentrations, lipoprotein profiles, blood pressure, adiposity, and smoking, although within lower ranges than adults.

Plasma cholesterol concentrations in children in the United States between 5 and 20 years of age average about 160 mg/dL, with the 95th percentile at about 200 mg/dL. The average remains fairly constant throughout this age range, but a redistribution of cholesterol from high density lipoprotein (HDL) to LDL occurs in adolescent boys, probably because of an increase in testosterone at puberty. Data from other countries are limited, but averages range from 100 to 190 mg/dL in a continuous distribution. In contrast, the average concentration among adults in the United States is about 210 mg/dL; the 95th percentile is about 270 mg/dL. The lower averages and lower ranges of values in youth should not lead one to conclude that plasma cholesterol concentrations are not of concern to persons under 20 years of age. Among adults, the risk of coronary heart disease increases continuously from the lowest to the highest concentrations, even below 200 mg/dL. Consequently, there is reason to suspect that plasma cholesterol concentrations in children might also be associated with the extent and severity of the early stages of atherosclerosis. Obesity was also determined to be quite prevalent in children in the United States, and its prevalence has been increasing. Smoking also is prevalent among young people.

The question is whether these characteristics are associated with atherosclerotic lesions in children and young adults and whether modifying them is beneficial. Some critics have expressed concern about the safety of modifying dietary fat intake or restricting the caloric intake of children, who, it is speculated, may need the additional calories or cholesterol provided by a high-fat diet or suffer from deficiencies of vitamins or other essential elements. A comprehensive review concluded that dietary fat restriction may have a small, but measurable, effect on growth but also concluded that height and weight were not necessarily the best indications of health.

The Risk Factors and Atherosclerosis

The risk factors identified because they predict the occurrence of coronary heart disease in adults are also associated with fibrous plaques and other advanced lesions in persons beyond early middle age. However, until recently, there was no direct evidence that linked plasma cholesterol, blood pressure, smoking, or other risk factors to atherosclerotic lesions in children, and it was not feasible to conduct a clinical trial of risk-factor modification in children or young adults with clinical disease events as endpoints.

One of the programs surveying cardiovascular risk factors in children examined the arteries of a few subjects who died and were autopsied and whose risk factors had been measured during life. There was an association of serum cholesterol concentrations with fatty streaks. In 1985, a group of pathologists organized a multicenter cooperative study (Pathobiological Determinants of Atherosclerosis in Youth, PDAY) of the relationship of cardiovascular risk factors to atherosclerosis in about 3000 15- to 34-year-old victims of accidental and traumatic death. Serum and lipoprotein cholesterol concentrations were mea-
sured in postmortem serum. Smoking was detected by measuring thiocyanate in postmortem serum. Elevated blood pressure was assessed by measuring the intimal thickness of small renal arteries. Elevated blood glucose, an indicator of preclinical diabetes, was detected by measuring glycohemoglobin in red blood cells. Adiposity was assessed by computing the body mass index and measuring the thickness of the panniculus adiposus. Genetic polymorphisms were identified in DNA from liver samples. Atherosclerotic lesions were measured by visual estimation of the percentage of intimal surface of the aorta and right coronary artery involved with fatty streaks or raised lesions (the sum of fibrous plaques and other advanced lesions).

Results from this study have shown that the very low density lipoprotein (VLDL) plus LDL cholesterol concentrations and smoking are positively associated, and HDL cholesterol concentrations are negatively associated with both fatty streaks and raised lesions throughout this age group (Figure 2)27; that adiposity and glycosylated hemoglobin are positively associated with raised lesions28; that blood pressure is positively associated with raised lesions29, and that polymorphisms in apolipoprotein (apo)E30 and apoB31 are also associated with lesions.

Another extrapolation is required to conclude that modification of these risk factors in children and young adults would retard the progression of atherosclerosis, particularly the conversion of fatty streaks to raised lesions, and eventually reduce the incidence of coronary heart disease and other syndromes related to atherosclerosis in middle age and later.

**Dietary Effects on Plasma Lipoprotein Concentrations in Youth**

In 1957, the American Heart Association first advocated modification of the fat content of adult diets in order to reduce plasma cholesterol concentrations and thereby reduce the risk of coronary heart disease.32 This recommendation was repeated periodically in subsequent years by the American Heart Association and by other expert panels in the United States and other countries.

In 1978, the American Heart Association recommended fat-modified diets for children over 2 years of age who were in the top decile of plasma cholesterol concentration.33 Five years later, the recommendation was extended to all children over 2 years of age.34 A National Institutes of Health Consensus Conference in 1985 focused mainly on the need for dietary modifications in adults but added that fat-modified diets would be desirable for all children beyond the age of 2 years.35 An expert panel, focused on blood cholesterol concentrations in children and adolescents, recommended limitation of fat, saturated fatty acid, and cholesterol intake for all children over the age of 2 years.36

In 1972, an experiment conducted in a New England boarding school showed that adolescent boys responded to restriction of dietary saturated fat and cholesterol intake with a reduction in plasma cholesterol concentrations.37 In a number of observational studies, dietary saturated fat and cholesterol intakes were associated with plasma cholesterol concentrations in children.38

A more recent and more broadly based experiment addressed the issue of safety as well as efficacy. A multicenter controlled clinical trial compared the effects of intervention promoting adherence to a fat-modified diet with the effects of a normal diet for 3 years in 663 hyperlipidemic children between 8 and 10 years of age.39 The intervention diet provided 28% of energy from total fat and less than 75 mg of cholesterol per 1000 kcal. There were no deleterious effects on growth, serum ferritin concentrations, a number of other hematologic or blood chemical concentrations, and behavioral characteristics. The LDL cholesterol concentrations were lowered in the control group by 11.9 mg/dL (as often happens in such trials) and in the treatment group by 15.4 mg/dL. After adjustment for baseline values, the treatment group was 3.2 mg/dL lower (p = 0.02) than the intervention group. No data are available as a basis to predict the effect of this intervention on subsequent adult LDL cholesterol concentrations or the effect of this modest reduction in LDL cholesterol throughout a lifetime on coronary heart disease morbidity and mortality. Over many years, all indications are that a mod-
est reduction of LDL cholesterol in childhood would have a cumulative favorable effect. The emerging results of controlled clinical trials indicate that lowering of LDL cholesterol by diet and drugs rapidly and dramatically lowers risk of coronary heart disease in adults.

There are also genetic causes of hyperlipidemia, and there is genetically programmed variability in lipidemic responses to dietary fat and cholesterol. These genetic influences are manifested in children as well as in adults. A family history of precocious heart attacks or of hyperlipidemia is useful in clinical medicine as an aid in detecting children likely to be hyperlipidemic. A positive family history combined with a quantity of plasma cholesterol in the highest decile are widely considered an indication to prescribe fat-modified diets. However, this information is of little use in formulating recommendations applicable to entire populations.

Until a noninvasive method is available to measure early and intermediate preclinical atherosclerotic lesions, efficacy of dietary modification can be measured only in terms of lowering plasma cholesterol concentrations, particularly LDL cholesterol. The evidence relating LDL cholesterol to atherosclerotic lesions in young persons from the PDAY study strongly suggests that lowering LDL cholesterol will retard the progression of atherosclerosis. It is not feasible to maintain an experimental diet study in humans for the 30-40 years that would be required to test its effect on clinically manifest coronary heart disease or other atherosclerotic diseases.

**Infant (Preweaning) Nutrition Effects on Lipoprotein Metabolism**

More controversial and more difficult to resolve is whether preweaning nutrition has a long-term deferred effect on lipid and lipoprotein metabolism in adulthood and thereby affects atherosclerotic disease. This concept was first advanced by Hahn and Koldovsky in 1966 as a result of their work with premature weaning of rat pups. Subsequently, Reiser and his associates reported that premature weaning and a high intake of cholesterol in infancy made adult rats and pigs more resistant to dietary cholesterol.

Mott and his associates reported that feeding formulas with various concentrations of cholesterol to infant baboons had a minimal effect on cholesterol metabolism in adults up to 8 years of age. However, adult baboons that had been breast-fed as infants and consumed a human-like cholesterol- and fat-enriched diet as adults had lower HDL cholesterol concentrations and higher LDL-to-HDL cholesterol ratios—more atherogenic lipoprotein profiles—than those that had been fed formula. The adults that had been breast-fed had more extensive atherosclerotic lesions but the difference was not statistically significant.

In a later experiment, also comparing effects of infant feeding regimens, a lower HDL cholesterol concentration and more extensive experimental atherosclerosis were again found among adult baboons that were previously breast-fed than among those that had been formula-fed. The effect of breast versus formula feeding on adult lipoprotein profiles was not the result of differences in types of fat in breast milk and formula.

The mechanism by which breast and formula feeding during infancy permanently imprint lipoprotein and cholesterol metabolism for life is not known. The major metabolic difference associated with the lower HDL cholesterol concentrations in adult baboons that had been breast-fed was a lower rate of bile acid synthesis and excretion. Subsequent studies have shown that formula feeding produces higher plasma triiodothyronine concentrations than breast-feeding by the end of the preweaning period, and thyroid hormones are known to affect lipid metabolism.

Whether formula feeding, compared to breast-feeding, affects lipoprotein metabolism in humans is less certain and the results have been conflicting. In a follow-up study of nearly 6000 elderly men whose preweaning feeding methods had been recorded, total and LDL cholesterol concentrations and coronary heart disease mortality were higher among those exclusively breast-fed than among those who were breast-fed and weaned at 1 year or who were breast- and bottle-fed. Men who had been exclusively bottle-fed also had high cholesterol concentrations and high mortality rates resulting from coronary heart disease. Bottle feeding 70 years ago was quite different from modern formula feeding, and these results cannot be equated with those obtained from baboons, but they confirm the concept that infant feeding can affect adult lipoprotein metabolism in later life.

The many advantages of breast-feeding over formula feeding are well documented and these observations from experimental animals do not warrant recommending any changes in current practices that encourage breast-feeding. However, understanding the mechanism of this effect would be a valuable addition to our knowledge of factors regulating lipoprotein metabolism and thereby affecting the risk of adult atherosclerotic cardiovascular disease.

**Obesity in Childhood**

The long-term health effects of obesity (hypertension, coronary heart disease, stroke, non-insulin-dependent diabetes, and cholelithiasis) are well known. The prevalence of childhood obesity in the United States is high. As with hyperlipidemia, obesity has both genetic and environmental causes, with caloric intake and energy expenditure being the major environmental and controllable factors.

Obesity also is associated with more extensive and more severe atherosclerosis in children and young adults independently of its association with hyperlipidemia, hypertension, and diabetes. As with diet-induced hyper-
lipidemia, a controlled clinical trial to determine whether control of obesity in childhood will reduce the incidence of coronary heart disease in adults is not feasible. However, obesity in childhood and young adulthood accelerates the progression of atherosclerosis, particularly the conversion of fatty streaks to fibrous plaques.

**Infant (Preweaning) Nutrition Effects on Obesity**

The effects of litter size on adipose tissue in rats suggested that overfeeding in infancy may predispose individuals to adult obesity. Lewis and associates tested this hypothesis in baboons by over- and underfeeding infants with dilute or concentrated infant formula. Overfeeding accelerated overall body growth during the preweaning period but did not lead to increased fat-cell size or fat-cell hyperplasia. When the infants were reared to adulthood on a calorie-dense high-fat diet, females that had been overfed as infants had about three times as much fat mass as those normally fed or underfed as infants. The greater fat mass was entirely due to enlargement of fat cells and not to increased numbers of fat cells. The infant feeding regimen had no effect on adult adiposity in males. As yet, there is no obvious mechanism to explain the deferred effect of overfeeding during the preweaning period on adult adiposity, and there are no comparable results from observational human studies.

**Conclusions**

During childhood, adolescence, and young adulthood, deposits of cholesterol and its esters, known as fatty streaks, accumulate in the intima of the large muscular and elastic arteries. Some of these fatty streaks increase in extent and thickness and are converted into more advanced lesions, fibrous plaques, which years later undergo other changes and lead directly to thrombotic arterial occlusion and clinical disease.

The physiologic variables identified as risk factors for adult coronary heart disease vary among children, adolescents, and young adults as they do among middle-aged and older persons, but at lower overall levels. The extent and severity of atherosclerotic lesions in young persons are associated with the same risk factors that predict the occurrence of coronary heart disease in adults.

Extensive evidence from animal experimentation and limited observations in humans suggest that preweaning nutrition affects lipid and lipoprotein metabolism to predispose individuals to obesity and to unfavorable lipoprotein profiles in adults. The mechanisms of these effects are not yet known and the implications for optimal infant feeding are not yet clear.

Nutrition in childhood and adolescence is a major determinant of elevated LDL cholesterol concentrations and of obesity. There is no evidence that modest reduction of total fat intake, limitation of saturated fatty acid intake, and restriction of cholesterol intake impair growth, affect markers of health, or reduce the quality of life of children. A reasonable conclusion is that children over the age of 2 years may safely consume the same fat-modified diets that are recommended for adults and that adoption of such diets will contribute substantially to the long-range primary prevention of atherosclerotic disease in adults.


60. Lewis DS, McMahan CA, Mott GE. Breast feeding and formula feeding affect differently plasma thyroid hormone concentrations in infant baboons. Biol Neonate 1993;63:327–35.


Invited Comment

Israel Lerman

Mexico is in an epidemiologic transition period. It still has high mortality rates in the neonatal period and early childhood years, but there is now an increased life expectancy at birth. As a direct consequence of this, there is an increased prevalence of chronic degenerative diseases including coronary heart disease. Recent studies have shown that coronary mortality has increased in the past three decades. Actually, for some states in the country, it has become the leading cause of death. 1

In his paper, Professor Henry C. McGill addresses the relevance of childhood nutrition in coronary risk factors and adult atherosclerotic heart disease. He clearly developed the following concepts:

1) Atherosclerosis is a multifactorial disease that evolves step by step from a fatty streak to a complicated plaque. Identifying the conditions that accelerate progression from fatty streaks to fibrous plaques and conditions that destabilize the intimal covering of the plaque are major objectives of current research in atherosclerosis.

2) Some risk factors can be controlled; others cannot. The concept that modification of risk factors by changes in diet and lifestyle or by drugs could reduce the incidence of atherosclerotic disease was proposed many years ago and has been clearly demonstrated with a large number of experimental trials in humans.

3) The traditional coronary risk factors and the likely mechanism through which they become atherogenic were mentioned and we were introduced to the knowledge of the problem in childhood. The atherosclerotic process begins in childhood but becomes clinically manifest later in life.

4) The Pathobiologic Determinants of Atherosclerosis in Youth (PDAY) is an important study in which it is clearly established that atherosclerotic plaques are directly related to the prevalence of different traditional coronary risk factors, even in young individuals.

5) The change of dietary habits, particularly in children, can favorably improve the lipid profile and reduce the prevalence of obesity. Currently accepted recommendations for children over the age of 2 years are limitation of fat, saturated fatty acid, and cholesterol intake as recommended for adults. Several studies have demonstrated its efficacy and its safety, issues that years ago were a topic of controversy. The impact in adult life of these changes in dietary habits in childhood must be significant; it is not feasible to maintain an experimental study in humans for the 30–40 years that would be required to test its effect on clinically manifest atherosclerotic disease.

6) It is important not to forget that there are individuals at a greater risk for premature atherosclerotic disease, like those with familial dyslipidemias, which in many cases can be identified during childhood with only an adequate familial history. A general public health strategy must be reinforced to promote reductions of coronary risk factors with adequate dietary habits from childhood.

I would like to use this opportunity to add several comments related to this topic. As stated by Professor McGill, it is important to know the mean values of blood lipids, body mass index, and blood pressure; the prevalence of dyslipidemias, hypertension, diabetes, obesity, and smoking during childhood and adolescence; and the trend toward smoking in the different age groups and its correlation with geographic location, socioeconomic status, and prevalence in the adult population. This information should be useful not only to the pediatrician but to all of us who are concerned with the impact of atherosclerosis and its various clinical manifestations in the adult population.

To determine the mean total cholesterol (TC) concentrations and the prevalence of hypercholesterolemia (HC), an epidemiologic survey was carried out in a representative nationwide Mexican population sample that included...