I am honored to be among the distinguished physicians and scientists invited to deliver the George Lyman Duff Memorial Lecture. I knew Dr. Duff from a distance, somewhat like an uncle, since he was a contemporary and friend of my chief, Russell Holman. Dr. Holman, just a few years younger than Dr. Duff, died, tragically and prematurely, a few years later than Dr. Duff, at almost exactly the same age, and of the same disease — cancer of the lung. I can recall firsthand how crisp and lucid were Duff’s contributions to the early meetings of this society at the Knickerbocker Hotel in Chicago. Senior Fellows of the Council will recall that we threaten to return there when we are unhappy with the American Heart Association.

The discussions in those early meetings centered around issues such as whether John Gofman’s new technique of separating lipoproteins with the ultracentrifuge was more useful than simply measuring serum cholesterol. Coronary heart disease mortality rates set a new record every year, just like NIH budgets, and it seemed that annual increases in both might go on forever. Rabbits and chickens were popular experimental animals, but monkeys were never mentioned because they did not respond to a fat-and cholesterol-enriched diet. Occasional papers concerned with how hyperlipidemia seemed to run in families and might be inherited were greeted with a few polite questions. Atherosclerotic lesions contained only foam cells and fibroblasts. The debate went on, year after year, whether dietary saturated fat, or dietary cholesterol, or both, had anything to do with coronary heart disease, and what we ought to tell the public about it.

Whether you were there or not, you will recognize that some things have changed, and some have not. Gofman’s heresy that some lipoproteins are atherogenic and others are not is now dogma. We now know that neither coronary heart disease rates nor NIH budgets will increase every year. Rabbits are still with us, and Duff, who used them extensively but critically, would be pleased with the Watanabe rabbit. Monkeys have made a comeback — if you don’t believe it, ask Dr. Clarkson, your past chairman. Our meetings are full of reports on the genetics of hyperlipidemia, and each year we expect to clone a new gene or find a new apolipoprotein polymorphism. Smooth muscle cells now make connective tissue, as fibroblasts were supposed to do; and fibroblasts make LDL receptors. One thing has not changed: the diet-heart debate still goes on in committees, journals, editorials, Duff Lectures, presidential addresses, and many undocumented corridor and cocktail consultations.

In those days, atherosclerosis seemed quite mysterious, but what we knew about it seemed rather simple. Now, atherosclerosis seems equally mysterious, but our knowledge about it is more complex. Among our accumulated knowledge, we may have the pieces from several different jigsaw puzzles mixed together, and we need to find which puzzle each piece belongs to before fitting them together.

Natural History

The main puzzle we are concerned with is outlined in Figure 1, which was drawn in rough form by Russell Holman in the mid-1950s. The diagram corresponds closely to the pathogenesis of atherosclerosis described in Duff’s 1951 review. The major features of the age-related sequence of lesions have been confirmed repeatedly in studies of autopsied persons from many different populations. Arrows describe the presumed pathogenetic relationship among different types of lesions.

Fatty streaks appear in the aorta in the first decade, and later in the coronary and cerebral arteries. Fibrous plaques with necrotic, lipid-rich cores surrounded by smooth muscle and connective tissue appear in the third decade. These lesions undergo
vascularization, hemorrhage, and ulceration, and some eventually are covered by thrombi which occlude the artery and cause ischemic necrosis in one or another tissue. The clinical syndrome varies with the organ affected, but the underlying arterial lesions are similar.

Although many questions remain about what triggers the terminal occlusive episode, there is little controversy about the close relationship of fibrous plaques to clinical disease. However, we are less certain about, first, whether some other change precedes the fatty streak and therefore is the true beginning of atherosclerosis; and, second, whether fibrous plaques arise from fatty streaks, or from some other precursor. If these questions could be answered, we could then answer the question of when atherosclerosis really begins, and could better focus our efforts on discovering the causes and preventing early progression.

Childhood Origin of Coronary Atherosclerosis

What evidence do we have that atherosclerosis begins in childhood? It is now common knowledge that healthy young adults in our population often have coronary atherosclerosis, and that, when lesions are present, they often are more severe in the proximal portion of the left anterior descending coronary artery than in other sites. This segment is highly vulnerable to fatty streaks as well as to other more advanced lesions.15

Herbert Stary, taking advantage of this site’s predilection to atherosclerosis, has studied this area systematically by light and electron microscopy in several hundred children and young adults.16-18 He finds that the coronary intima at this site becomes as thick as the media very early in life, often within the first few months. The thickened intima is made up of smooth muscle, elastic and collagen fibers, and glycosaminoglycan matrix lying beneath an intact and structurally normal endothelium. The intimas of children as young as one month frequently contain isolated monocytes and macrophage foam cells.

In children older than about 10 years, Stary finds clusters of monocytes and macrophage foam cells, and, adjacent to the clusters, lipid-containing smooth muscle cells. As a matter of historical interest, the electron micrographs that showed lipid inclusions in smooth muscle cells of human20 and experimental21 atherosclerotic lesions in the early 1960s contributed to the strong interest in smooth muscle during the following two decades. For some time we thought that the initial lesion of atherosclerosis might be a disturbance in the metabolism or proliferation of intimal smooth muscle cells. Now it appears that smooth muscle cell lipid accumulation may follow monocyte and macrophage infiltration.

By age 15, in addition to clusters of monocytes, macrophage foam cells, and lipid-filled smooth muscle cells, foci of necrosis appear in the coronary intima. After age 20, necrotic foci associated with lipid-filled smooth muscle cells and macrophage foam cells become larger and more frequent. Some of these lesions grossly resemble uncomplicated fatty streaks, even though they contain necrotic foci; others have the gross characteristics of fibrous plaques.

These observations, focused by Stary on a highly vulnerable site in the left anterior descending coronary artery, amplify and extend previous observations22,23 which indicated that the fibromuscular intima of the coronary arteries is a normal structure, and that leucocytic infiltration, extra- and intracellular lipid accumulation, and necrosis were hallmarks of progressive atherosclerosis early in the third decade. More specifically, Stary’s findings suggest that the process may begin with monocyte and macrophage foam cell infiltration into the coronary intima as early as age 10, and possibly earlier; and that smooth muscle cell lipid accumulation and intimal necrosis are later developments which represent relatively advanced changes. The significance of isolated monocytes and macrophages in the intimas of younger children is more difficult to ascertain.

Figure 2 shows the overall average extent of fatty streaks and fibrous plaques or raised lesions in the coronary arteries of about 1000 New Orleans white males.24 In boys under 10 years, no fatty streaks are visible grossly, even with Sudan staining; but recall that, microscopically, the coronary intima contains isolated monocytes and macrophage foam cells. At 10 to 14 years, no fibrous plaques are visible to the naked eye, but recall that, in this age group, microscopically, there are clusters of monocytes and macrophage foam cells in the intima, and smooth muscle cells have begun to accumulate lipid. By age 20, fatty streaks have increased threefold, and fibrous plaques begin to appear; but recall that, microscopically, areas of necrosis are frequent at this age.
In summary, the topographical association of fatty streaks with fibrous plaques in a highly vulnerable segment of the coronary arteries, combined with the sequence that begins at about age 10 with clusters of monocytes and macrophage foam cells and culminates one or more decades later in gross fibrous plaques, support the idea that coronary atherosclerosis does begin in childhood.

**Childhood Origin of Aortic Atherosclerosis**

The aorta presents a different story. Gross fatty streaks appear in the aorta much earlier than in the coronary arteries. They increase rapidly in extent during the second decade. In young persons, the thoracic aorta has more fatty streaks than the abdominal aorta, blacks have more aortic fatty streaks than whites, and females of both races have more aortic fatty streaks than males. These anatomic, sex, and race differences are different than those for fibrous plaques in adults, in whom the extent of fibrous plaques is reversed in each anatomic, sex, and race comparison.

Furthermore, aortic fatty streaks occur in all children over 3 years of age from all populations around the world, regardless of sex or race, and regardless of adult coronary heart disease rates. Aortic fatty streaks probably always have been there. W.D. Zinsenning, working in Professor Anitschkow's department in Leningrad, reported in 1925 a high incidence of fatty streaks in the aortas of about 300 children and a rapid increase in extent with age to 12 years. There were more in the ascending than in the descending aorta, and there was no relationship to cause of death. These characteristics of juvenile aortic fatty streaks were identical to those we found in children from many populations in the 1960s.

Microscopically, juvenile aortic fatty streaks appear identical to coronary artery fatty streaks — monocytes, macrophage foam cells, and lipid-filled smooth muscle cells. One also can find lesions that appear to be transitional between fatty streaks and fibrous plaques. However, since there is no limited anatomic site in the aorta where advanced lesions are likely to develop, as in the coronary arteries, it is more difficult to trace the evolution of fatty streaks to fibrous plaques. Consequently, we have no marker that differentiates the aortic fatty streak destined to become a fibrous plaque, and no clue as to why some aortic fatty streaks behave so differently than those in the coronary arteries. The examination of aortic fibrous streaks often has led to the conclusion that fatty streaks do not progress to fatty plaques, a conclusion opposite to that usually reached when coronary arteries are examined. It is ironic that most experimental atherosclerosis and most arterial wall cellular and molecular biology are based on observations on the aorta rather than the coronary arteries.

In conclusion, in a highly vulnerable site in the coronary arteries, we can trace the evolution of clusters of monocyte and macrophage foam cells at
about age 10 into fatty streaks and well developed fibrous plaques at about age 20. These observations indicate that coronary atherosclerosis does begin in childhood. Aortic lesions also begin in childhood, but their progression appears to be controlled by different (and unknown) factors.

**Endothelial Injury**

Endothelial injury as the primary or initial lesion in atherogenesis has been reviewed many times, including Russell Ross's 1981 Duff Lecture.28 This idea has been attractive because a variety of experimental manipulations damage endothelium, cause proliferation of underlying smooth muscle cells, and enhance lipid deposition in the presence of hyperlipidemia. One can readily visualize plasma lipoproteins pouring through permeable endothelium, platelets adhering to damaged endothelium, and monocytes migrating into the intima. However, it has not been possible to demonstrate functional or structural alterations in endothelium overlying sites predisposed to atherosclerosis in humans. As the sensitivity of observational methods improves, we eventually may find a precursor lesion in endothelium overlying the clusters of monocytes and macrophage foam cells in the coronary intima.

In 1957, we reported that Evans blue selectively stained the arterial intima of normal dogs at sites susceptible to necrotizing lesions in the presence of renal insufficiency.29 Other investigators later showed that plasma proteins penetrated the stained areas more rapidly,30 that stained areas were more susceptible to diet-induced atherosclerosis,31 and that stained intima in normal animals was structurally different from unstained intima.32

It has been widely assumed that Evans blue staining marks areas of increased endothelial permeability, but it could also be due to some other difference in the handling of macromolecules. Whatever the mechanism, physiologic variations in endothelial function could account for the localization of atherosclerotic lesions. Several research groups are working on the pathophysiology of this phenomenon.

Endothelial changes occur readily after intimal lipid has accumulated, and, in the terminal occlusive episode, endothelial damage is likely to be involved in precipitating thrombosis over advanced fibrous plaques. However, these changes in end-stage disease should not be equated with the elusive initial endothelial lesion.

In summary, endothelial injury accelerates atherogenesis in experimental animals, but no current method can identify an endothelial lesion that precedes or predisposes to atherosclerosis in humans. The absence of a lesion does not prove that none exists; it just means we cannot find it. Naturally occurring variations in permeability may account for lesion localization. Perhaps some of the marvelous knowledge about endothelial biology is part of a puzzle other than that of atherosclerosis.

**Proliferation**

The role of intimal cellular proliferation in the early stages of atherosclerosis has a long and distinguished history. Gardner McMillan and the same Duff whose memory we honor reported in 1948 that mitoses occurred frequently in the lesions of hypercholesterolemic rabbits, and suggested that the increase in cells might be due to proliferation rather than to infiltration or migration.33

Wilbur Thomas and his colleagues have studied smooth muscle cell proliferation in aortic intimal cell masses of the aortas of young pigs.34 These intimal cell masses are normal structures, similar to the human coronary artery intima, but they are sites of predilection for lesions in the presence of hypercholesterolemia. Figure 4 shows, in the lower panels, the number of cells in each cross-section before, and the number in corresponding cross sections after, 90 days on a basal diet. There is little change in the numbers of cells per cross-section of intimal cell mass with normal growth. However, as shown in the top panel, an atherogenic diet for the same 90 days causes a three- to fourfold increase in number of

![Figure 4](http://atvb.ahajournals.org/)

**Figure 4.** Numbers of intimal cells in cross sections of the abdominal aortas of swine fed a mash diet at baseline (lower panel); other swine, also fed a mash diet, 90 days later (middle panel); and other swine fed a hyperlipidemia-inducing diet for an equivalent 90 days (top panel) (re-drawn from reference 34).
smooth muscle cells in the same sites, a number consistent with about two doublings.

Thymidine indices of these cells confirm the proliferative activity, and indicate that it begins within a few days after starting the diet, after serum cholesterol begins to rise but before arterial lipid accumulation can be detected by conventional methods. This rapid response of intimal cells to increased plasma lipoprotein concentrations (or some other intervening variable related to diet) is a remarkable phenomenon.

Another special aspect of proliferation was raised by Earl Benditt's observation just 10 years ago that most human fibrous plaques are monotypic — that is, they are made up of cells of either the A or the B isoenzyme of G6PD in mosaic females. Benditt suggested that fibrous plaques are monoclonal, that is, that each plaque arises from mutation or transformation of a single cell. Others contend that monotypism may result from preferential proliferation of cells with one or the other isoenzyme markers, so that only the cells of one type remain in the plaque.

Thomas Pearson found that most fatty streaks were ditypic, that is, they contained cells with both isoenzyme markers, and therefore could not have arisen from a single cell. However, a number of fatty streaks were intermediate in their isoenzyme distribution, with one or another isoenzyme predominant but not enough to fulfill the rigid criteria for monotypism. The intermediate fatty streaks were rare in young women and old women, and occurred most frequently in women between 36 and 50 years. This observation suggests that cellular proliferation in fatty streaks, over a number of years, gradually leads to selective survival of one or the other isoenzyme cell types, and eventually results in a monotypic fibrous plaque.

The presence of smooth muscle in the coronary intima, described previously in the discussion of childhood lesions, has caused much confusion about smooth muscle proliferation as a feature of early atherogenesis. We compared the coronary arteries of young North Americans and Europeans, who were likely to develop severe coronary atherosclerosis, with coronary arteries of young persons from other countries who were less likely to develop advanced atherosclerosis. There was no tendency for young persons from high risk populations to have thicker coronary intimas than young persons from low risk populations. We concluded, as most others have, that this structure represents normal arterial development, and is not a pathologic response to injury.

In summary, intimal smooth muscle cell proliferation is a prominent and rapid response to consumption of an atherogenic diet by animal models, and this phenomenon merits investigation as an unusual effect of a nutritional perturbation. However, proliferation does not seem to be a major factor in the initiation or progression of atherosclerosis in children and young adults.

**Monocyte-Macrophage**

Many years ago, macrophages were thought by some investigators to be the principal cell in the pathogenesis of atherosclerosis. Macrophages went out of style and were replaced by the smooth muscle cell. The macrophage is now in style again, with a new reputation for many functions potentially relevant to atherogenesis. For example, the macrophage interacts extensively with lipoproteins, a topic reviewed by Daniel Steinberg in the 1982 Duff Lecture.

Colin Schwartz and his associates recently have identified two other properties of the monocyte-macrophage that may be related to atherogenesis. Monocytes, but not polymorphonuclear leucocytes, are attracted by a substance produced by cultured smooth muscle cells. This material appears to be a protein of about 10,000 daltons. It is attractive to hypothesize that secretion of this material by intimal smooth muscle might account for localized monocyte migration into the intima.

The second observation concerns the formation of macrophage foam cells from monocytes in the presence of hyperlipidemia. Carrageenan, a polysaccharide extracted from seaweed, produces a massive accumulation of monocytes when injected into the subcutaneous tissue of rabbits. In normocholesterolemic rabbits, the monocytes remain free of lipid. In hypercholesterolemic rabbits, the monocytes attracted by carrageenan were initially free of lipid, but within 28 days, they take up huge amounts of cholesterol esters. Thus, monocytes attracted to one site by a foreign substance become lipid-filled foam cells only in the presence of hyperlipidemia. Would hyperlipidemia lead to lipid accumulation, intimal foam cells, and their sequelae in the arterial intima if there were no monocytes?

The monocyte-macrophage is capable of so many diverse functions that it may be difficult to decide whether it is hero or villain. Monocytes, when stimulated, produce superoxide and peroxide anions. These highly active anions of oxygen are responsible for the monocyte's ability to destroy bacteria and tumor cells. Recall that, in children, monocytes and macrophages were seen in the intima before smooth muscle cells had accumulated lipid. Monocytes and macrophages could injure nearby smooth muscle cells and thereby cause them to undergo lipid accumulation, a common cellular reaction to injury.

Whatever their role, the current interest in the monocyte-macrophage seems well justified by its many functions and its prominence in the earliest lesions we can relate to human atherosclerosis. We must be alert to its potential dual role as both fireman and fire.
particularly coronary heart disease. Abundant evidence relates hyperlipidemia to atherosclerosis in experimental animals. However, we have had difficulty in linking serum cholesterol levels to human atherosclerosis, especially in its early stages. Only recently has direct evidence bearing on this question been available.42

The Oslo Study43 obtained antemortem measures of serum cholesterol and postmortem measures of atherosclerosis in over 200 men 40 to 56 years of age. There was a linear relationship of serum cholesterol to advanced coronary atherosclerosis, with a correlation coefficient of about 0.4. There also was an inverse association of the ratio of high density lipoprotein (HDL) cholesterol to total cholesterol minus HDL cholesterol with coronary lesions, with a correlation coefficient of about -0.4. However, these subjects were 40 to 56 years, not children or young adults. Similar data on persons under 40 are almost nonexistent.

Figure 5 compares the rank order of serum cholesterol concentrations of 12 geographic and ethnic groups from the International Atherosclerosis Project13 by males26 and estimated serum cholesterol concentration in the corresponding populations.44

A preliminary report from the Bogalusa Heart Study by Gerald Berenson46 shows a remarkably high correlation of aortic fatty streaks with β-lipoprotein cholesterol. This correlation was derived from direct measurement of lesions in accident victims from a group of children whose serum lipids had been measured in a prospective epidemiological study. However, we must view this correlation with caution because of the limited number of cases. The Bogalusa Heart Study now has accumulated a number of additional young subjects for whom both pre-mortem serum lipids and postmortem measures of atherosclerosis are available, and should soon be able to amplify this sample. These are the only data I know of that test directly the association of serum or lipoprotein cholesterol levels with atherosclerosis in children, except for a few cases of familial hypercholesterolemia.

You may ask, when there is overwhelming evidence linking hypercholesterolemia to advanced atherosclerosis, why do we need more data on this simple issue? Some of the Council members may recall the agony of producing the first American Heart Association diet statement for children in 1978.47 This statement cautiously recommended that dietary modification for all children might be advisable. It was widely criticized by some for being too conservative, and by others for going too far.

Others were involved in preparing the 1983 diet statement,48 which took a great leap of faith and recommended limiting dietary fat and cholesterol for all children after the age of 2 years. This recommendation is still based on extrapolation backward from risk factor data on adults, because no one has followed a cohort of children for 40 years or more into the coronary heart disease age group, nor is anyone likely to at any time soon.

The extrapolation is easy in a congregation of true believers, but it is much harder among the unconvinced. Furthermore, there could be hazards beyond our limited view. John Zabriskie in the 1983 Connor Memorial Lecture49 described an inverse association of rheumatic heart disease with meat consumption. A few examples like this help us to understand why pediatricians have been so conservative. Any demonstration of a direct association of serum lipid levels with atherosclerotic lesions in children would add compelling support to the argument for dietary modification in children as well as in adults.

The search for these associations in young persons would be much simpler if we could focus on a single atherogenic lipoprotein species. With the help of a review article by Robert Mahley50 and consultation with several experts, I compared findings from cell biology and animal experimentation with what we know about lipoproteins in human atherogenesis (Table 1). Low density lipoproteins (LDL) are positively, and HDL are negatively associated with atherosclerosis in adults. The greater severity of atherosclerosis in Type III hyperlipidemic subjects implicates beta very low density lipoprotein (VLDL).
The only lipoproteins consistently identified in human lesions are LDL, possibly modified LDL.

In experimental animals, a wider variety of lipoprotein species have been indicted. Some believe that LDL are positively associated, and HDL are negatively associated with lesions in most species.

Many interactions between lipoproteins and cells induce lipid accumulation in macrophages, or stimulate monocyte or smooth muscle cell responses that are potentially atherogenic. One can amplify this matrix vertically by subdividing lipoproteins, and horizontally by considering different animal species and different cell types, but the outcome will be similar: we cannot yet select the lipoprotein-cell interactions that are important in the pathogenesis of human lesions, nor can we be certain that the relationships of lipoproteins to experimental lesions observed in animals also apply in humans.

Thus much as we would like to apply the findings from molecular and cellular biology to human atherosclerosis, right now we would settle for some solid evidence that any indicator of plasma lipids or lipoproteins is associated with atherogenesis in the 10- to 20-year-old human. Meanwhile, our recommendations for diet modification in all children must remain based on extrapolation from observations on adults.

### Hypertension

Hypertension has been known as a risk factor for coronary heart disease as long as serum cholesterol concentration. It is associated with accelerated atherosclerosis in adult humans and in experimental animals. The Oslo Study showed a strong relationship of blood pressure to arterial lesions in 40- to 56-year-old men.43

It is widely believed that hypertension augments atherosclerosis directly by way of increased pressure, but some investigators have suggested that renin (or a related vasoactive hormone) may be an independent atherogenic factor. The failure of antihypertensive drug therapy to reduce the incidence of coronary heart disease as much as it reduces other hypertensive sequelae has encouraged the idea that some component of hypertensive pathophysiology other than blood pressure may be atherogenic.

We recently completed an experiment with baboons in which we examined the interaction of a moderate elevation of blood pressure (about 30 mm Hg) and modest diet-induced hypercholesterolemia (200 mg/dl) in their effect on experimental atherosclerosis. This degree of hypertension increased the extent of atherosclerosis in the carotid arteries threefold and in other arteries twofold, but did not affect atherosclerosis in the thoracic aorta. Multiple regression analysis showed that, in the carotid arteries, lipoprotein cholesterol level combined with blood pressure predicted about 60% of the variance in lesions, and that inclusion of either serum potassium level or plasma renin activity significantly increased the predicted variance. These results revive the idea that one or more of the vasoactive hormones in hypertension may influence atherogenesis directly. However, the most remarkable aspect of our experiment was that, within 14 months, a modest elevation in blood pressure (not enough to cause cardiac hypertrophy) dramatically augmented atherogenesis at selected sites in the presence of serum cholesterol levels equal to those of the average American.

Surveys of blood pressures in children and teenagers have found a surprisingly wide range of blood pressures.52 Furthermore, blood pressures track over time and it appears likely that many of the children with blood pressures in the high normal range may become frankly hypertensive when they become adults.

I know of no observations bearing on the relationship of blood pressure to atherosclerosis in humans under age 40. Until proven otherwise, it seems possible that the higher levels of blood pressure in children and young adults, even though not hypertensive by conventional adult standards, may accelerate the rapid progression of atherosclerosis in the second and third decades of life, and may be a major factor in transforming fatty streaks into fibrous plaques in young people.

### Infection

In my medical school pathology text, Howard Karsner speculated that "no single cause will be found for atherosclerosis... . It is our opinion that of the various factors, infectious diseases play a prominent part."53 This opinion from 40 years ago has been cited as evidence of our rapid progress in knowledge about atherosclerosis. However, the same techniques of molecular biology that have contributed so much to our knowledge of lipoprotein metabolism, lipoprotein-cell interactions, and monocyte functions recently have yielded evidence of both herpesvirus and cytomegalovirus infection of cells in human atherosclerotic lesions.

Both viruses are notorious for ubiquity, latency, chronicity, and ability to transform cells. It is easy to

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### Table 1. Atherogenicity of Lipoproteins

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<th>Lipoprotein</th>
<th>Humans Epide-</th>
<th>Pathology</th>
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<td>Chylomicron remnants</td>
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The atherogenicity of lipoproteins is shown in this table. The table indicates the atherogenicity of various lipoproteins in humans, animals, and cells.

**PATHOGENESIS OF ATHEROSCLEROSIS**

McGill

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hypothesize that viral infection in the vicinity of a juvenile fatty streak could stimulate lipid accumulation, necrosis, proliferation, or other responses that could accelerate the progression of a fatty streak to a fibrous plaque. These observations may be pieces of the puzzle of atherosclerosis, or they may belong to some other puzzle concerned with viral biology. We must be alert to either outcome.

Summary

In concluding this eclectic review, I believe that we can say with certainty that coronary atherosclerosis has its origins in childhood, at least by age 10 and possibly earlier.

Endothelial changes follow lipid accumulation, but, with present methods, there is no evidence that endothelial injury precedes lipid accumulation.

Proliferation is a prominent feature of accelerated experimental atherosclerosis, but we do not see evidence that proliferation is a major feature of early naturally occurring human atherosclerosis.

The prominence of the monocyte-macrophage in the earliest detectable lesions of atherosclerosis in childhood justifies the current interest in monocyte biology.

Hyperlipidemia, in the sense of the average high levels common in our population, seems almost certain to contribute to accelerated atherogenes in children, but conclusive proof is still lacking.

Mild hypertension in children, or even the high range of normal blood pressure, may accelerate the transition of innocuous childhood fatty streaks to more ominous fibrous plaques.

The putative relationship of adult coronary heart disease risk factors to the childhood lesions of atherosclerosis is largely based on extrapolation from adult data. Direct evidence bearing on these relationships, however difficult to obtain, would be helpful in designing and promoting effective preventive regimens for children.

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