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Special Report

A Definition of Initial, Fatty Streak, and Intermediate Lesions of Atherosclerosis

A Report From the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association

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Abstract

The compositions of lesion types that precede and that may initiate the development of advanced atherosclerotic lesions are described and the possible mechanisms of their development are reviewed. While advanced lesions involve disorganization of the intima and deformity of the artery, such changes are absent or minimal in their precursors. Advanced lesions are either overtly clinical or they predispose to the complications that cause ischemic episodes; precursors are silent and do not lead directly to complications. The precursors are arranged in a temporal sequence of three characteristic lesion types. Types I and II are generally the only lesion types found in children, although they may also occur in adults. Type I lesions represent the very initial changes and are recognized as an increase in the number of intimal macrophages and the appearance of macrophages filled with lipid droplets (foam cells). Type II lesions include the fatty streak lesion, the first grossly visible lesion, and are characterized by layers of macrophage foam cells and lipid droplets within intimal smooth muscle cells and minimal coarse-grained particles and heterogeneous droplets of extracellular lipid. Type III (intermediate) lesions are the morphological and chemical bridge between type II and advanced lesions. Type III lesions appear in some adaptive intimal thickenings (progression-prone locations) in young adults and are characterized by pools of extracellular lipid in addition to all the components of type II lesions. (Arterioscler Thromb. 1994;14:840-856.)

In this report we characterize lesions that precede and may initiate the development of advanced atherosclerotic lesions. Advanced lesions are defined as those in which an accumulation of lipid in the intima is associated with intimal disorganization and thickening, deformity of the arterial wall, and often with complications such as fissure, hematoma, and thrombosis. Advanced lesions may produce symptoms, but the lesions that precede them are clinically silent.

This report is the second in a series of three. The first provided a definition of the arterial intima and its atherosclerosis-prone regions. The third report will describe the different types of advanced atherosclerotic lesions and will provide a histological classification of all human atherosclerotic lesion types.

The precursors of advanced lesions are divided into three morphologically characteristic types. Both type I and II lesions represent small lipid deposits in the arterial intima, and type II includes those lesions generally referred to as fatty streaks. Type III represents the stage that links type II to advanced lesions. The term "early lesions" is sometimes used for type I and II lesions. "Early" implies that these lesions are followed by "later" (advanced) lesions. It also implies that they are found early in life. Neither implication is necessarily true, although types I and II are generally the only lesions present in children, and there is evidence that certain type II lesions are prone to proceed to type III and more advanced lesions.

The distinctions that separate individual lesion types are based on consistent morphological characteristics, which indicate that each type may stabilize temporarily or permanently and that progression to the next type may require an additional stimulus. The morphological features of each type of lesion and the time at which each tends to occur and predominate in the course of a human life are strong presumptive evidence that types I, II, and III are successive stages in the development of atherosclerosis. Each type is focal, relatively small, and contains abnormal accumulations of lipoproteins and cholesterol esters. Increased numbers of cells, mainly macrophages, and accumulations of lipid droplets, mainly within macrophages, can be demonstrated microscopically. Changes in the composition of the matrix and disruption of the intimal architecture are minimal or absent. The media adjacent to the lesions is not diseased, nor is the adventitia affected. In contrast, advanced lesions generally contain extracellular lipid deposits large enough to disrupt and deform the intima; in very advanced stages, these deposits may modify the underlying media and adventitia. In many lesions that have reached advanced stages, thrombotic mechanisms of progression become predominant, leading to accelerated progression and often clinically overt atherosclerosis. These subsequent mechanisms will be defined in the next report.

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The clinical significance of lesion types I, II, and III lies in their role as the silent precursors of possible future disease. Recognition of the period of life in which type III lesions begin should lead to concentrated preventive measures at, or preferably before, that age. Similar lesions in laboratory animals regress completely when serum cholesterol is reduced.

This report deals largely with lesions in the coronary arteries and aorta because information on initial and early lesions in other arteries is scant. Since the methods used in biological studies of arteries influence interpretation of the data obtained, technical problems are briefly discussed in the preceding report.1 The same problems apply to the studies reviewed here.

Because it is impossible to determine the composition of an initial lesion and then to follow its behavior over a lifetime, the studies that provide evidence concerning the natural history of atherosclerosis use data from lesions of many persons of different ages. The general approach has been to characterize the intima and lesions in precisely defined locations of the arteries in children and then to study the same locations in adolescents and adults. The locations chosen for study are known for their predisposition to develop clinical lesions, the so-called progression-prone or advanced lesion-prone regions of arteries.

In the following sections some mainly experimental data on the pathogenesis of atherosclerotic lesions and particularly on their initiation are summarized.

**Pathogenesis of Lesion Initiation**

**Evidence That Atherogenic Lipoproteins Initiate Lesions**

The evidence is compelling that accumulation of atherogenic, plasma-derived lipoproteins in the arterial intima launches specific cell reactions and that such accumulation constitutes the fundamental event in the initiation of lesions.2 Lesion size and complexity increase as lipoprotein accumulation continues and increases. Under normal circumstances the same lipoproteins are also present in the intima but at lower concentrations. The threshold concentration that induces their accumulation and a pathological cell reaction (initially an increase in macrophages and development of macrophage foam cells) is unknown.

Plasma lipoprotein levels are not the sole determinant of the degree of lipoprotein accumulation in the different parts of the arteries. Regions in which lipoprotein accumulation is high are exposed to mechanical forces that favor an increased residence time of circulating atherogenic particles at the lumen surface. Such forces could cause a greater influx into the intima in these locations. Mechanical forces are discussed in the section on the progression-prone type II lesion.

Increased levels of apoprotein (apo) B are reported in segments of the aorta that have a thick intima in swine3 and in human distal abdominal aortas.4 Rabbits fed a high-cholesterol diet for 8 to 16 days have increased low-density lipoprotein (LDL) levels in lesion-prone regions of the aortic intima before macrophage foam cells appear.5,6 Immunohistochemical studies demonstrate7 increases in apoA and apoB content in regions of human arteries with intimal thickening before the appearance of macrophage foam cells. As intimal thickness increased, the extracellular apoA and apoB spread from the upper to the lower parts of the intima. Within 2 hours after a bolus injection of LDL, clustering of LDL-sized particles in collocalization with apoB occurs in the matrix of atherosclerosis-prone sites of the aortic intimas of rabbits.8 Lipoproteins may be trapped in the intima by matrix components4,5,9 and then modified. (For a review of the various ways in which lipoproteins may be modified in the intima, see Reference 10.) Modified lipoproteins may be internalized by macrophages primarily via a scavenger receptor pathway. Subsequently, intimal smooth muscle cells may also participate in the uptake of lipoproteins either through native lipoprotein receptors or a scavenger receptor pathway.11 Endocytosed lipids are generally broken down and reesterified for storage. However, there is some evidence that cells retain modified (oxidized) lipids in nondegraded or minimally degraded forms.12,13

Isolated macrophages are present in the nondoised human intima14,15 and in the intima of animals that are not hypercholesterolemic. Studies in animals indicate that many more monocytes from the circulation enter the intima under conditions of hypercholesterolemia.16-19 This movement may be a response to the increased presence of oxidized lipoproteins, which have been shown to be chemotactic for monocytes in vitro.20 Radioautographic and electron microscopic studies in laboratory animals show that intimal macrophage foam cells can proliferate under conditions of hypercholesterolemia.21,22

When a high-cholesterol diet is given to laboratory animals for a few months and when serum cholesterol elevations are relatively moderate, the animals' lesions generally resemble the type I and II lesions of human subjects. At high serum cholesterol elevations, the animals' lesions resemble the atherosclerotic lesions of human subjects with homozygous familial hypercholesterolemia. Epidemiological studies of human populations support the experimental studies by indicating an association between high blood cholesterol levels and fatty streaks23,24 and the presence and severity of coronary heart disease.24,25

**Additional Hypotheses of Lesion Initiation**

According to the original "response-to-injury" hypothesis of atherogenesis,26 smooth muscle cell migration from the media into the intima and smooth muscle cell proliferation are the initial cell reactions of atherosclerosis and the cause of smooth muscle cell accumulation in the intima. Cell injury, in particular denuding endothelial cell injury, has frequently been proposed as a factor that precipitates intimal thickening.26-28 and the absence of endothelial cells over some small human lesions has been put forward as evidence.29 Over the years the response-to-injury hypothesis has been continually modified.29 According to the updated hypothesis, endothelial cells may be injured or activated and remain in place. They may be stimulated to express leukocyte adherence molecules and to secrete cytokines, which are chemotactic for leukocytes and smooth muscle cells, as well as growth factors for all of the cell types on or within the vessel wall.30

In laboratory animals a wide range of artificial exogenous stimuli have been used to produce focal intimal smooth muscle cell thickenings. These manipulations include endothelial cell denudation by scraping of the...
intimal surface,21-33 heat shock,34 viral infections,35-36 electrical stimulation,37 and injury through constriction.38 However, these experimentally produced lesions do not reproduce the structure of human atherosclerotic lesions as described by most morphologists. Nevertheless, the studies of endothelial cell injury followed by intimal smooth muscle cell proliferation may be pertinent to the progression of established lipidic lesions and to the restenosis that occurs to a variable extent after injury by angioplasty or atherectomy.

According to another hypothesis, platelet and/or fibrin deposits on the intima could be the initial event in atherogenesis. In children and young adults, arteries without advanced lesions have occasionally contained thin layers of fibrin and/or aggregated platelets on the endothelial surface of the intima.39-42 Such deposits are small and have been detected only on microscopic examination. How often, if at all, such deposits can enlarge to become advanced atherosclerotic lesions in the absence of risk factors that favor lipid deposition is unknown. Faggiotto and Ross43 report that small platelet thrombi are associated with early macrophage foam cell lesions in hypercholesterolemic pigtail monkeys. In general, thrombi may form where the endothelial surface is injured. Most authors who describe the arteries of young human populations do not report intimal regions lacking endothelial cells, either in intimas without lesions or in intimas with type I or II lesions, nor do they report the presence of thrombi. Available evidence supports the predominant view that thrombotic encrustations occur often and repeatedly on intimal lesions with advanced accumulations of lipid; that by being incorporated into the arterial wall, thrombi then also contribute to arterial narrowing; and that they underlie clinical ischemic episodes. This evidence will be reviewed in detail in the forthcoming report on advanced lesions.

According to still another hypothesis, a type of intimal thickening with a macroscopically gelatinous appearance may represent an initial atherosclerotic lesion. In unfixed collapsed aortas such structures appear as oval- or ridge-shaped elevations of the intima, semitranslucent, opalescent and shiny, pink to pale gray, and of soft consistency.44 Sometimes the peripheral parts of advanced atherosclerotic lesions have a similarly gelatinous appearance. When the aortas are immersed in a fixative, the gelatinous appearance disappears. The structures then appear as white elevations of the intima. Microscopically, gelatinous thickenings contain few cells, little or no lipid, and an abundant intercellular matrix with little collagen or elastin.45-47 The significance of the structures is unclear. Some might represent not pathological structures but a proteoglycan-rich variant of adaptive intimal thickening.

In the following sections lesion types I, II, and III, the morphological types of human lesion that represent the precursors of symptom-producing atherosclerosis, are described.

**Type I Lesions**

Type I lesions consist of the first microscopically and chemically detectable lipid deposits in the intima and the cell reactions associated with such deposits. These lesions have been characterized in studies in which the sequence of lesions was deduced from examining many persons who died at different ages. The term "initial lesion" has also been used for type I. Type I lesions have been described as being most frequent in infants and children. However, such initial lesions can also be found in adults, particularly in those with little atherosclerosis, or in locations of arteries that are lesion resistant. The type I lesions that have been described in the coronary arteries of infants44 may be microscopically identical to some of the small yellow dots at the root of the aortas of infants described by Aschoff48 and Zinserling.49 However, most type I lesions may not be visible to the unaided eye. For this reason, and because of the comparatively limited microscopy techniques available early in this century, when many young children died and detailed autopsy studies were performed, little has been written about the initial histological changes in humans. Much of what is known about the changes and mechanisms of atherosclerosis comes from studies of laboratory animals; the extent to which the experimental data hold true for humans is as yet unclear.

The initial histological changes in the human intima are minimal. Small, isolated groups of macrophages containing lipid droplets (macrophage foam cells) form45,50 (Fig 1). In coronary arteries these cells preferentially accumulate in regions of the intima that have an adaptive intimal thickening of the eccentric type. These locations are identical to those in which type II lesions are more prominent and in which type III or advanced lesions develop first in young adults if such lesions develop at all. (This topic is discussed in more detail in the section on the progression-prone type II lesion.) In the first 8 months of life, 45% of infants have macrophage foam cells in their coronary arteries and macrophages without lipid droplets are increased two-fold above normal.14,50

The accumulation of macrophages and macrophage foam cells in the arterial intima is also the initial cellular change in laboratory animals in which hypercholesterolemia is induced.16-18,22,51-57 Hypercholesterolemia causes an increased adherence of monocytes to the endothelium in swine,17 pigeons,19 rabbits,39 and monkeys,57 particularly over atherosclerosis-prone regions of the intima.

Chemical and immunochemical data indicate that the initial intimal macrophage foam cells are both a sequel to and a cellular marker of pathological accumulations of atherogenic lipoproteins, particularly in regions of the intima with adaptive thickening (ie, atherosclerosis-prone regions). Experimental data that may explain the mechanisms associated with the initial accumulations of lipoprotein in the intima, the increase in macrophages, and the development of foam cells have been summarized in the preceding section on pathogenesis.

**Type II Lesions**

**Definition of Type II Lesions**

Type II lesions include fatty streaks, which on gross inspection may be visible as yellow-colored streaks, patches, or spots on the intimal surface of arteries. Fatty streaks stain red with Sudan III49,58 or Sudan IV.59,60 Some studies use the terms "sudanophilic lesion" or "sudanophilia" to refer to fatty streaks. However, although historically the fatty streak was identified by its gross appearance, subsequent microscopic evaluations of lesion evolution indicate that while type II lesions...
include fatty streaks, not all type II lesions are fatty streaks. Whether a lesion is type II is determined by its microscopic composition, not by the fact that it is often visible as a fatty streak on the intimal surface. Some lesions that meet the microscopic criteria of type II are not visible as fatty streaks. The nature of the arterial intima with which type II lesions collocalize influences its gross as well as microscopic appearance. When type II lesions collocalize with adaptive intimal thickening, the accumulated foam cells that account for the gross sudanophilia may not be immediately below the endothelial surface; thus, the lesion may not be visible as a fatty streak.

Microscopically, type II lesions are more distinctly defined than type I lesions. They consist primarily of macrophage foam cells stratified in adjacent layers (Figs 2 and 4) rather than being present as only isolated groups of a few cells. Intimal smooth muscle cells, in addition to macrophages, now also contain lipid droplets (Fig 5). Type II lesions contain greater numbers of macrophages without lipid droplets (Fig 4) than do type I lesions or the normal intima. T lymphocytes have been identified in type II,61,62 but they are less numerous than macrophages. The number of mast cells is greater than in the normal intima, but only isolated mast cells are found; there are far fewer mast cells than macrophages.15

In laboratory animals the turnover of macrophage foam cells, endothelial cells, and smooth muscle cells is increased in experimentally produced fatty streaks.21,65-68 Details about these cells are found below under separate headings. Most of the lipid of type II lesions is in cells. The proportions of macrophages and smooth muscle cells containing lipid vary, but in most type II lesions most lipid is in macrophage foam cells. The extracellular space contains small quantities of thinly dispersed lipid droplets and vesicular particles that vary in size but that are large enough to be visible by routine electron microscopy. This extracellular lipid, which may be derived from foam cells, is in addition to the smaller extracellular lipoprotein particles that are not visible by routine microscopy.

The lipid of type II lesions consists primarily of cholesterol esters (77%), cholesterol, and phospholipids.65-68 The main cholesterol ester fatty acids are cholesteryl oleate and cholesteryl linoleate (35% and 26% of total cholesterol ester fatty acids, respectively). Cholesterol esters are also the main lipids of type II
lesions induced experimentally in rabbits, several species of macaques, and in avian species.

Because many type II lesions are visible to the unaided eye as fatty streaks, they have been sampled and studied much more than type I lesions, which are rarely grossly visible. The arteries of children generally contain type II lesions as the only grossly visible lesions. Some excellent studies of type II lesions are available from the early decades of this century, when many children died of infectious diseases and were autopsied. Type II lesions are also the most readily produced visible lesions in laboratory animals. Despite much data, the mode of progression of type II lesions to symptom-producing atherosclerosis had not been clear, and therefore the significance of type II lesions has been questioned to the present day. For the resolution of this controversy, see the following sections on the progression-prone type II lesion and the type III lesion.

Progression-Prone Type II Lesions

The locations in the arterial tree in which type II lesions can be seen with the unaided eye—the atherosclerosis-prone or lesion-prone locations—are relatively constant and predictable. Of the many type II lesions generally present in a person who has average levels of atherogenic lipoproteins, a smaller subgroup will be the first to proceed to type III lesions and then to advanced lesions, if advanced lesions are to develop at all. This smaller subgroup of type II lesions, which collocates with specific adaptive intimal thickenings in predictable locations, is called progression-prone, advanced lesion-resistant, or type Ib. Type Ib lesions either do not progress, progress slowly, or progress only in persons with very high plasma levels of atherogenic lipoproteins.

Whether a type II lesion develops at all and whether it is progression-prone or progression-resistant is largely determined by the mechanical forces that act on relevant parts of the vessel wall. The mechanical forces in locations in which type II lesions are susceptible to progression cause an increased influx and early accumulation of lipid in persons whose plasma lipoproteins exceed certain threshold levels. One of these forces, low shear stress, increases the time of interaction (residence time) between blood-borne particles (such as LDL) and the arterial wall; consequently, transendothelial diffusion also increases. Mechanical forces also appear to cause the self-limited adaptive intimal thickenings that occur in all people regardless of plasma lipoprotein levels. Because of these localized mechanical forces, the larger intimal lipid accumulations are associated with a thick intima from the start. This topic is reviewed in the first report.

Morphologically, progression-prone type Ia lesions differ from progression-resistant type Ib lesions by the presence of smooth muscle cells, the abundant intercellular matrix of the collocated adaptive thickening, the greater accumulation of lipoprotein and macrophages, and the deep intimal location of the foam cells and extracellular lipid droplets and particles. Macrophages without lipid are most numerous near the endothelial surface; macrophage foam cells accumulate at the bottom of the proteoglycan layer; and the extracellular lipid accumulates even deeper within an adaptive thickening. Although more macrophage foam cells may amass with time, when only a few layers are present they may not extend to the endothelial surface. The terms “submerged fatty streak” and “concealed fatty streak” have been applied to this histological picture. Because of the many layers of smooth muscle cells of the collocated adaptive thickening, progression-prone type Ia lesions have sometimes been misinterpreted as lesions that have advanced beyond type II.

In human subjects with very high plasma levels of atherogenic lipoproteins, such as in familial hypercholesterolemia homozygotes, type II lesions rapidly develop into advanced lesions, even in arterial locations outside the progression-prone ones. Similarly, when serum cholesterol levels much higher than those usually found in human populations are induced in laboratory animals, large lesions are widely dispersed. After early middle age, even persons without particularly high plasma cholesterol may have advanced lesions outside the progression-prone locations.

Prevalence and Location of Type II Lesions

The methods used to quantify and map grossly visible type II lesions have included planimetry, point-counting, estimating the percentage of the intimal surface area covered with lesions, and estimating the lesion extent by a 0 to 4+ grade. Only in some of the most recent studies have computer-assisted methods been used for quantification and mapping. Measurements or estimates of the prevalence and location of type II lesions are based primarily on the visibility of flat, red-colored streaks, patches, or spots on the intimal surface of arteries that were opened longitudinally at autopsy and stained with a Sudan dye. However, since progression-prone type Ia lesions are not always sudanophilic (because foam cells may be submerged within the collocated adaptive intimal thickening), the extent and location of type II lesions may not have been determined precisely. Furthermore, some type Ia lesions may be mistaken for more advanced lesions because the collocated adaptive intimal thickening may slightly protrude into the lumen of collapsed arteries.

Aorta. Lesions that are grossly visible in the aorta have been quantified and mapped in many studies. Zinsinger noted visible fatty dots in the ascending aorta near the aortic cusps in half of the infants less than 6 months old. Aschoff had designated such minimal lesions as nursing infants atherosis. Microscopically they may have had the composition of lesions we now classify as type I. Among children aged 2 to 15 years, 99% have type II lesions (fatty streaks) in the aorta. At this age the lesions may occur in the aortic arch, descending thoracic aorta, and abdominal aorta, and they are more extensive in these locations than in the ascending aorta. Type II lesions generally increase in extent throughout the length of the aorta around puberty. In aortas studied in the International Atherosclerosis Project, the extent of type II lesions increased in the descending aorta up to an age of approximately 20 years. The ascending aorta was not studied. In the abdominal aorta
the extent of such lesions increased to age 30, at which time it exceeded the extent in the thoracic aorta.

A close relation of type II lesions to the ostia of branch vessels has been noted by all authors who have studied the locations of lesions. In the children studied by Zinserling, type II lesions occurred along the dorsal wall of the aorta, between, beside, and especially distal to the orifices of intercostal and lumbar arteries, and at or near the orifices of the larger abdominal branch vessels. When measured by polar mapping, fatty streaks occurred distal and lateral to intercostal branch ostia in the aortas of the human fetuses and newborns studied by Sinzinger et al. The data of Zinserling and Sinzinger et al in young children vary slightly from data obtained by Cornhill et al in a group of 109 15- through 29-year-old males. In the latter study, probability-of-occurrence maps of the aortas were generated and analyzed by computer. In the thoracic part of these aortas the regions of highest probability of sudanophilia were midway between the origins of successive intercos-
Differences in Type II Lesions

Coronary arteries. Generally, type II lesions erupt in the coronary arteries around puberty. In Sudan-stained coronary arteries, type II lesions are not seen with the unaided eye before the age of 9 years. Wolfkoff found fatty streaks in 1 of 3 children aged 9 years, in 3 of 5 children aged 10 through 14 years, and in 6 of 8 children aged 15 through 19 years. According to Eggen and Solberg, fatty streaks in the coronary arteries begin to develop around age 15 years and slowly increase in size and number until about age 60, although the percentage of surface area involved is less than in the abdominal aorta. Montenegro and Eggen, who studied the topography of type II and advanced lesions in coronary arteries, report that type II predominated in the left coronary artery about 2 cm distal to the left coronary orifice. In children up to 15 years old, Wolfkoff found fatty streaks only at the main left bifurcation and in the proximal part of the left anterior descending branch. After age 15, they occurred in both the left and right coronary arteries, but in 115 of these 120 cases they predominated in the proximal portions of the left. In a microscopic study of the left proximal coronary arteries of young people, 65% of those in the age group around puberty (12 through 14 years) had type I or II lesions, while an additional 8% in that age group also had more advanced lesions. The intima of the left anterior descending coronary artery that is opposite the flow divider of the main bifurcation is the location in the coronary arteries in which type II (as well as type I) lesions contain more lipid-laden cells and in which advanced lesions tend to occur first.

The factors that elicit such a dramatic increase in type II lesions in humans at puberty have not yet been identified. Adolescents and young adults with many type II lesions have higher plasma cholesterol levels than do individuals with few lesions. In laboratory animals plasma cholesterol and LDL levels are also generally correlated with the presence and extent of type II lesions. However, an increase in blood lipid levels is not associated with puberty. Therefore, factors other than or in addition to relatively high serum cholesterol levels apparently come into play at puberty. One relevant factor that may increase at puberty is blood pressure.

Gender and Race as Determinants of Differences in Type II Lesions

Zinszerling and Wolfkoff did not comment on gender-related differences in the prevalence or extent of type II lesions in children. Material from the International Atherosclerosis Project indicated similar involvement in males and females for both the coronary arteries and thoracic aorta in all age groups. The presence of type II lesions in the abdominal aorta was similar for both sexes at the age of 10 years but was more extensive in women from the age of 20 years on. Microscopic studies indicate that the lesser prevalence of type II lesions in men after the age of 20 years might be due to their earlier conversion into advanced lesions. Holman et al found racial differences in females. Between the ages of 10 and 40 years, aortic type II lesions were more abundant in black than in white females.

Type III Lesions

The designation “type III lesion” applies solely to lesions that form the morphological and chemical bridge between type II lesions and atheromas. (Atheroma, classified as type IV, is the first lesion type considered as advanced by histological criteria because its lipid core, intimal disorganization, and arterial deformity predispose to sudden lesion progression and ischemic events). The type III lesion is also known as the intermediate lesion, the transitional lesion, and as preatheroma. Its characteristic histological features are microscopically visible extracellular lipid droplets and particles to the extent that pools of this material form among the layers of smooth muscle cells of the generally colocalized adaptive intimal thickening (Fig 3). Routine electron microscopy reveals that the extracellular lipid droplets are either membrane-bound or free (Figs 6 and 7). They are identical to the extracellular droplets and particles that are found thinly dispersed and in small quantities in some type II lesions. The lipid pools lie just below the layers of macrophages and macrophage foam cells, replace intercellular matrix proteoglycans and fibers, and drive smooth muscle cells apart. As in type II lesions, many intimal smooth muscle cells may contain lipid droplets. By this definition, multiple separate extracellular lipid pools that disrupt the coherence of some structural intimal smooth muscle cells constitute progression beyond a type II lesion. At this stage a massive, confluent, well-delineated accumulation of extracellular lipid (a lipid core) has now been developed. Studies of many cases indicate that the lipid core, the characteristic component of most advanced lesions, forms by the increase and confluence of the separate extracellular lipid pools that characterize a type III lesion.

When human atherosclerotic lesions are studied by lipid physical chemistry, a lesion intermediate between type II and atheroma also becomes apparent. Lesions with this composition contain more free cholesterol, fatty acid, sphingomyelin, lyssolecithin, and triglyceride than type II lesions. The melting behavior of the cholesterol ester droplets is also between that of type II lesions (higher) and atheroma (lower). Small states that histologically these intermediate lesions resemble the type III lesions described in the preceding paragraphs. In the past, the belief that clinically significant atherosclerotic lesions develop from some type II lesions was based largely on the evidence of lesion progression in hypercholesterolemic animals and in human cases of familial hypercholesterolemia. Some authors believed that type II lesions were self-limited and associ-
Fig 4. Electron photomicrograph of a detail of a type II lesion in the proximal anterior descending coronary artery from a 25-year-old man who died in an accident. Macrophages without lipid droplets (M) and macrophage foam cells (FC) occupy this upper part of the intima. The extracellular space contains the usual intimal matrix components. Extracellular lipid particles and droplets, sometimes visible in type II lesions in small quantities (and present in type III and more advanced lesions in large quantities), are not visible here (magnification ×6800).

Fig 5. Electron photomicrograph of a detail from a type II lesion in the intima of the distal thoracic aorta from a 28-year-old man. Cause of death was suicide. Part of a macrophage foam cell (FC) and a smooth muscle cell (RS) rich in rough-surfaced endoplasmic reticulum and containing lipid droplets are visible in this part of the lesion. The extracellular space contains the usual intimal matrix components (ie, collagen, elastin, basement membrane material, proteoglycans) (magnification ×12300).
ated with the fatal infectious diseases that formerly were so frequent in children. Although the latter hypothesis was subsequently rejected, the supposition that clinically manifest lesions originate in type II lesions continued to encounter considerable disbelief. Several reasons account for this skepticism. As type II lesions had been traditionally visualized, they were considered morphologically too dissimilar from atheroma to be its precursor. No precise topographic correspondence was apparent between the two lesion types, and while some persons with extensive type II lacked advanced lesions, others with advanced lesions had only a few of type II. Furthermore, the cholesterol esters of advanced lesions contain a high proportion of linoleic acid and a low proportion of oleic acid, whereas the reverse is true for type II lesions.

In spite of opposition to the idea that advanced lesions develop from type II lesions, speculation continued that a lesion type should exist that was histologically and chemically between the two. Although the existence of a type III (intermediate or transitional) morphological entity was hypothesized, only recently has this type of lesion been defined morphologically and chemically.

The morphological bridge between type II and atheroma was found in the progression-prone regions of arteries (i.e., locations with focal adaptive intimal thickening). Early in life, progression-prone locations shelter type Ia lesions. Later, in young adults, type III lesions and the first atheroma-type lesions are found in the same locations. Partly because the intima of progression-prone locations is composed of many layers of smooth muscle cells, the type Ia and type III lesions present in these locations are morphologically more similar to atheroma than are type Iib lesions, which are found in regions of the intima that are thin and consist of few smooth muscle cells. The differences in fatty acids between type II and advanced lesions may be explained by the massive overall increase in lipids and the change from intracellular to predominantly extracellular storage.

**The Cells of Type I, Type II, and Type III Lesions**

Macrophages and macrophage foam cells are the cellular components of type I lesions. In type II and III lesions, intimal smooth muscle cells and to a lesser extent lymphocytes, plasma cells, and mast cells also participate in the pathological processes. The data on these cell types are summarized below.

**Endothelial Cells**

Reliable data concerning the morphology of endothelial cells that overlie human lesions are difficult to obtain because of the relatively long interval between tissue death and tissue fixation. Thus, although the absence of endothelial cells over human fatty streaks has been suggested as a factor in the development of lesions, such changes may have occurred after death. When vessels are fixed in situ under carefully controlled conditions in anesthetized animals, endothelial cells over type II lesions are attenuated but are neither necrotic nor disrupted. In laboratory animals changes in the morphology and properties of endothelial cells, particularly those in atherosclerosis-prone regions, have been found within weeks of the induction of hypercholesterolemia. Many of the morphological changes are likely to be the result of subendothelial accumulation of macrophage foam cells and of lipid in the extracellular matrix. These changes include loss of orientation in the direction of blood flow, rounding of the cells, increases in stigmata and stomata, increases in stress fiber content, and the formation of multinucleated cells. A significant increase in the specific adherence of leukocytes to the endothelial surface, which is thought to be due to an increase in the expression of specific adherence molecules such as vascular cell adhesion molecule-1, has also been noted. Although endothelial surface erosion does not occur on human type II lesions, focal attenuation or disruption of endothelial cells over type II lesions with large accumulations of macrophage foam cells has been reported in animals. This effect is observed in large type II lesions in monkeys, rabbits, and pigeons. Platelets are sometimes visible on the exposed foam cells.

Radioautographic studies of endothelial cells situated over type II lesions induced in animals show a high rate of turnover than cells in normal endothelium. In addition, there is also a significant increase in the permeability of the endothelium over lesions to macromolecules. Recent studies of the cellular physiology of the endothelium of early lesions in humans and many different animal models demonstrate an impairment in endothelium-dependent vasodilation and a stimulation of endothelium-dependent vasoconstriction.

The basic functional properties of endothelial cells are reviewed in our first report; changes that may occur in the properties in type I through type III lesions are summarized in Table 1.

**Smooth Muscle Cells**

The smooth muscle cells that are part of human type I through type III lesions are indigenous to the locations in which the lesions are found. The number of smooth muscle cells in locations with type I or type II lesions is similar to the number that is normal for these intimal locations when the cells have been counted in children. On the basis of experimental manipulations in animals, some investigators suggest that smooth muscle cells accumulate as an initial and integral part of lesion formation (see the earlier section for additional hypotheses of lesion initiation). Intimal smooth muscle cells are normally also present in most other species. Radioautographic studies with tritiated thymidine in various normocholesterolemic laboratory animals show intimal smooth muscle cell labeling, an indication of cell division. In hypercholesterolemic animals, intimal smooth muscle cells that are colocalized with type II lesions show increased labeling. Despite speculation to the contrary, there is no evidence that medial smooth muscle cells contribute to the intimal smooth muscle cells that colocalize with type I, II, or III lesions by migration or other means.

In laboratory animals the number of intimal smooth muscle cells is often increased in regions with experimentally induced type II lesions. Smooth muscle cells rich in rough-surfaced endoplasmic reticulum (RER) (the RER-rich, or synthetic, phenotype) are the cell type that principally accounts for the smooth muscle cell increase. Some of the increase in the RER-rich cell type may be caused by a change in the phenotype of
FIG 6. Electron photomicrograph of a detail of a pool of extracellular lipid in a type III lesion in the proximal anterior descending coronary artery from a 29-year-old man who died in an accident. The pool consists of innumerable lipid droplets with (short arrows) or without (long arrows) peripheral laminated membranes and remnants of the usual extracellular matrix components. The cytoplasm of a smooth muscle cell process (S) contains inclusions that are morphologically similar to the extracellular lipid and two much larger droplets (magnification ×10 600).

FIG 7. Electron photomicrograph of a detail of a pool of extracellular lipid in a type III lesion at the main bifurcation of the left coronary artery from a 27-year-old man who died in an accident. Clear spaces represent lipid droplets. Droplets are either membrane-bound (short arrows) or they are free (long arrows). Part of an intimal smooth muscle cell (S) appears attenuated (magnification ×8800).
some existing smooth muscle cells that had not previously contained RER.

As shown by electron microscopic studies, the number of RER-rich smooth muscle cells is increased in human intimas with type II lesions (Fig 5). While this cell type is normally limited to the upper intima and upper adaptive intimal thickening, it is also found deeper in the intima when type II or III lesions are present. RER also appears in smooth muscle cells that are still recognizable as the myofilament-rich (contractile) phenotype when lipid droplets are present. Most intimal smooth muscle cells that contain lipid droplets also contain increased RER and smooth endoplasmic reticulum (SER). 41,53,106,107

Both RER-rich and myofilament-rich smooth muscle cells contain lipid droplets. Both respond to lipid inclusions with hyperplasia of the RER, Golgi apparatus, and SER. Golgi and SER hyperplasia are greater in laboratory animals on a high-cholesterol diet than in human subjects, probably reflecting the higher levels of serum cholesterol in laboratory animals.

Although the cytoplasm of many smooth muscle cells is often filled with large lipid droplets, these lipid-laden cells are generally identifiable as smooth muscle cells by electron microscopy because of their overall shape and the presence of groups of microinocytotic vesicles, basement membranes, and residual thick filaments.

Smooth muscle cells as a component of type II lesions in rabbits were identified and superbly illustrated by Antischkow as long ago as 1913. 3 Antischkow believed that smooth muscle cells in lesions were derived from the inner media adjacent to the intimal lesions. The opinion that the smooth muscle cells of human atherosclerotic lesions are also derived from the media is widespread today, although it has been shown that smooth muscle cells normally occur in the intima and that in hypercholesterolemic animals intimal smooth muscle cells proliferate at an increased rate. Antischkow noted that smooth muscle cells in lesions differed in morphology from medial smooth muscle cells in that the former were strongly basophilic; he coined for them the term "modified muscle cells" (veränderte Muskelfasern). The electron microscope reveals increased RER in the cytoplasm of lesion smooth muscle cells, which accounts for the basophilia at the light microscopic level. The term "RER-rich smooth muscle cell" is now used for this type of cell. 2,22 Other terms include "fibroblast-like smooth muscle cell," 706 "fibroblast-like cell," 108 or "ergastoplasm-rich smooth muscle cell." 109 Some authors retain Antischkow's term "modified smooth muscle cell" 44 or "modulated smooth muscle cell." 710 Some have used terms more suggestive of their function, such as "activated smooth muscle cell," 107 "metabolically active cell," 39 or "synthetic smooth muscle cell." 111,112 The cells have also been called "immature smooth muscle cells," since cultured premitotic smooth muscle cells share the same morphology. 113 Andreeva et al 114 describe a distinct subpopulation of intimal smooth muscle cells with well-developed RER that often lack other smooth muscle features completely. They use the term "stellate cells" for these cells and speculate that they originate from cells less differentiated than and different from medial smooth muscle cells.

The functional properties of arterial smooth muscle cells are reviewed in our first report; 1 changes that may occur in smooth muscle properties in lesion types I through III are summarized in Table 2.

Macrophages and Macrophage Foam Cells

Electron microscopic and immunocytochemical analyses show that type I, II, and III lesions are composed primarily of macrophages and that many of these macrophages contain large numbers of lipid droplets (macrophage foam cells). 14,22,115 Studies of macrophage foam cells isolated from rabbit lesions indicate that most of the cholesterol (75%) is esterified. 116 This may be due to increases in ACAT and acid cholesteryl-esterase activities of the cells accompanied by a decrease in the neutral cholesteryl-esterase activity. The capacity of macrophages to accumulate large amounts of lipid may be dependent on their expression of scavenger receptors. Recent studies using in situ hybridization and immunocytochemistry have demonstrated the presence of this receptor in macrophages in human fatty streaks. 117,118 Lesion macrophages also contain lipid-protein adducts that are characteristic of oxidized lipoproteins. These macrophages may also be capable of modifying lipoproteins in vivo, as the same cells that contain the oxidation-specific adducts also express 15-lipoxygenase and lipoprotein lipase.

Light microscopic radioautographic studies show that significant numbers of macrophage foam cells in induced type II lesions in laboratory animals synthesize DNA. 21,64 Dilution of the radioactive grain count of the nuclei of foam cells indicates that these cells divide at least once and that a subgroup might divide more than once. 105 Macrophage foam cells with metaphase or anaphase nuclei have been demonstrated in type II lesions by electron microscopy in monkeys 22 and by light microscopy in rabbits 8,119,120 and monkeys 24.

Macrophages within lesions also appear to be activated for immune and/or inflammatory responses. Recent studies using in situ hybridization, Northern blot analyses of the mRNA from isolated foam cells, and immunocytochemistry show that macrophages in early lesions of both humans and rabbits express major histocompatibility complex, CD antigens, and a variety of cytokines and growth regulatory molecules, including platelet-derived growth factor, tumor necrosis factor, interleukin-1, monocyte chemotactic protein-1, and macrophage colony-stimulating factor. The properties of macrophages in lesion types I through III are summarized in Table 3.

Other Cell Types

Lymphocytes have been detected in type II lesions of human subjects and animal models by light and electron microscopy and immunocytochemistry. Because lymphocytes cannot always be distinguished from macrophages, even by electron microscopy, some authors combine both cell types under the term "mononuclear cells." 723 In human type II lesions lymphocytes have been identified as T cells with monoclonal antibodies. 61,62 Data about lymphocytes in advanced lesions are plentiful and will be discussed in the next report in this series.

Mast cells occur in human intima with type II lesions. 41 However, quantification of mast cells produces inconsistent and even contradictory results. A recent study 15 indicates that there are twice as many mast cells in type II as there are in intima without lesions. It is
The precise nature of the proteoglycan type that is increased in early lesion development is unclear; however, Hoff and Wagner possible that mast cells in lesions are degranulated more often than in lesion-free intima. If that is the case, then the mast cell increase in type II could be greater than the counts indicate.

The Intercellular Matrix of Type I, Type II, and Type III Lesions

Interaction of the apoB of LDL with the sulfate groups of glycosaminoglycans may be a mechanism for trapping LDL in the arterial intima. Sulfated glycosaminoglycans, which are components of matrix proteoglycans, increase during the early stages of atherosclerosis, whereas hyaluronic acid decreases.\textsuperscript{122-124} The precise nature of the proteoglycan type that is increased in early lesion development is unclear; however, Hoff and Wagner suggest that cell-surface heparan sulfate is reduced in human lesions when atherosclerosis severity increases. Whether the heparan sulfate is involved in the process of macrophage engulfment of LDL or in the development of subendothelial foam cells is unknown. On the basis of studies that demonstrate significant enhancement of dermatan sulfate production by smooth muscle cells that have been exposed to conditioned media from cultured macrophages, recent studies have shown that dermatan sulfate binds plasma LDL under physiological conditions and at increased affinity compared with other glycosaminoglycans, including chondroitin (Type I) and chondroitin (Type II).

A significant increase in dermatan sulfate proteoglycan occurs during the progression of atherosclerosis from the initial through the intermediate stages of lesion formation.\textsuperscript{124} This change may accelerate the rate at which atherosclerosis develops; Iverius\textsuperscript{127} has shown that dermatan sulfate binds plasma LDL under physiological conditions and at increased affinity compared with other glycosaminoglycans, including chondroitin (Type I) and chondroitin (Type II). It is unclear when and how the upregulation of dermatan sulfate proteoglycans occurs. A specific role of macrophages in altering the type and amount of proteoglycan in the developing lesion can be proposed on the basis of studies that demonstrate significant enhancement of dermatan sulfate production by smooth muscle cells that have been exposed to conditioned media from cultured macrophages.\textsuperscript{128} Recent studies show that in most tissues, including arteries, there are at least two types of dermatan sulfate proteoglycans: “biglycan” and “decorin.”\textsuperscript{129} Whether biglycan or decorin genes are upregulated in atherosclerosis remains to be determined.

Heparan sulfate is reduced in human lesions when atherosclerosis severity increases. Whether the heparan sulfate is a component of the basement membrane or the cell surface proteoglycan is unknown at present. On the basis of the possible role of cell-surface heparan

### Table 1. Changes in the Characteristics of Endothelial Cells Observed in Lesion Types I, II, or III in Humans or Laboratory Animals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology, shape, orientation</td>
<td>Orientation away from direction of flow\textsuperscript{102}</td>
</tr>
<tr>
<td></td>
<td>Polyhedral/rounded shape\textsuperscript{143}</td>
</tr>
<tr>
<td></td>
<td>Increased stigmata/stomata\textsuperscript{140,143}</td>
</tr>
<tr>
<td></td>
<td>Increased cilia\textsuperscript{144}</td>
</tr>
<tr>
<td></td>
<td>Decreased microfilament bundles\textsuperscript{145}</td>
</tr>
<tr>
<td></td>
<td>Increased stress fibers\textsuperscript{102,146}</td>
</tr>
<tr>
<td></td>
<td>Increased formation of multinucleated cells\textsuperscript{140,147,147}</td>
</tr>
<tr>
<td>Turnover, injury, cell death</td>
<td>Increased proliferation\textsuperscript{104,105,106,100-102}</td>
</tr>
<tr>
<td></td>
<td>Increased cell death (uptake of IgG and other plasma proteins)\textsuperscript{150-156,155*}</td>
</tr>
<tr>
<td></td>
<td>$\ddagger$ Refraction/rupture with exposure of subendothelial foam cells</td>
</tr>
<tr>
<td>Permeability</td>
<td>Increased permeability to macromolecules\textsuperscript{150-152}</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>Increased mural thrombus formation\textsuperscript{143,140-145}</td>
</tr>
<tr>
<td></td>
<td>Increased tissue factor expression\textsuperscript{146}</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Increased leukocyte adherence</td>
</tr>
<tr>
<td>Vascular tone</td>
<td>Increased expression of VCAM-1\textsuperscript{110}</td>
</tr>
<tr>
<td></td>
<td>$\ddagger$ Increased endothelium-dependent vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Decreased endothelium-dependent vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Decreased EDRF production\textsuperscript{145,147}</td>
</tr>
<tr>
<td></td>
<td>Decreased prostacyclin release\textsuperscript{149}</td>
</tr>
</tbody>
</table>

*Studies in laboratory animals.
†Studies in humans.
§References 18, 19, 43, 54, 56, 57, and 156 are animal studies; reference 157 is a human study.
‡References 17, 18, 54, 56, 57, 63, 120, 143, 156, 164, 167, and 168 are animal studies; references 142 and 157 are human studies.
||References 170, 172, 173, and 176 are animal studies; references 171, 174, and 175 are human studies.
§§References 170, 172, 173, 177 through 178, and 182 are animal studies; references 174, 175, 178, 181, 183, and 184 are human studies.

### Table 2. Changes in the Characteristics of Intimal Smooth Muscle Cells Observed in Lesion Types I, II, or III in Humans or Laboratory Animals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell number</td>
<td>Increased cell proliferation: rabbits,\textsuperscript{64,104,105}</td>
</tr>
<tr>
<td></td>
<td>swine,\textsuperscript{191}</td>
</tr>
<tr>
<td>Morphology</td>
<td>Increase in amount of RER, increase in number of RER-rich phenotypes, changes in filaments and organelles\textsuperscript{151,152}</td>
</tr>
<tr>
<td>Cell functions</td>
<td>Production of intracellular and extracellular matrix</td>
</tr>
<tr>
<td></td>
<td>Increased expression of type I and III collagen\textsuperscript{141}</td>
</tr>
<tr>
<td></td>
<td>Increased expression of dermatan sulfate proteoglycan\textsuperscript{128}</td>
</tr>
<tr>
<td></td>
<td>Increased expression of stromelysin\textsuperscript{139}</td>
</tr>
<tr>
<td>Cytokine production</td>
<td>M-CSF expression\textsuperscript{144,145,156}</td>
</tr>
<tr>
<td></td>
<td>TNF expression\textsuperscript{146}</td>
</tr>
<tr>
<td></td>
<td>MCP-1 expression\textsuperscript{147}</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>Accumulation of lipoproteins, uptake of native and modified lipoproteins primarily via native lipoprotein receptor pathways and nonspecific phagocytosis\textsuperscript{148}</td>
</tr>
<tr>
<td></td>
<td>Expression of scavenger receptor\textsuperscript{11}</td>
</tr>
<tr>
<td></td>
<td>Lipoprotein lipase expression\textsuperscript{190,200}</td>
</tr>
</tbody>
</table>

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†Studies in humans.
‡References 18, 19, 43, 54, 56, 57, and 156 are animal studies; reference 157 is a human study.
§§References 17, 18, 54, 56, 57, 63, 120, 143, 156, 164, 167, and 168 are animal studies; references 142 and 157 are human studies.
||References 170, 172, 173, and 176 are animal studies; references 171, 174, and 175 are human studies.
§§References 170, 172, 173, 177 through 178, and 182 are animal studies; references 174, 175, 178, 181, 183, and 184 are human studies.

RER indicates rough endoplasmic reticulum; M-CSF, macrophage colony-stimulating factor; TNF, tumor necrosis factor; MCP-1, monocyte chemotactic protein-1.
TABLE 3. Changes in the Characteristics of Intimal Macrophages Observed in Lesion Types I, II, or III in Humans or Laboratory Animals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid metabolism</td>
<td>Increased free and esterified cholesterol content$^{115,202-204,201}$†</td>
</tr>
<tr>
<td></td>
<td>Increased ACAT, increased acid cholesterol-ester hydrolyase, decreased neutral cholesterol-ester hydrolyase activities$^{204,205}$*</td>
</tr>
<tr>
<td>Expression of scavenger</td>
<td>receptor$^{17,117}$†</td>
</tr>
<tr>
<td>Expression of 15-lipoxygenase$^{118}$†</td>
<td></td>
</tr>
<tr>
<td>Expression of lipoprotein</td>
<td>oxidation products$^{116,206,207,206}$†</td>
</tr>
<tr>
<td>Expression of lipoprotein</td>
<td>lipase$^{200,204}$†</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Proliferation$^{16,22,64,103-105}$,119$^{*,208}$ !</td>
</tr>
<tr>
<td>Expression of MCP-1$^{119}$†</td>
<td></td>
</tr>
<tr>
<td>Expression of M-CSF$^{104}$†</td>
<td></td>
</tr>
<tr>
<td>Expression of IL-1$^{109x}$</td>
<td></td>
</tr>
<tr>
<td>Expression of TNF$^{196}$†</td>
<td></td>
</tr>
<tr>
<td>Expression of PDGF$^{211}$</td>
<td>1$^{*,212}$†</td>
</tr>
<tr>
<td>Expression of CD antigens</td>
<td>$^{213,25}$†</td>
</tr>
<tr>
<td>Expression of tissue factor</td>
<td>$^{206}$†</td>
</tr>
</tbody>
</table>

ACAT indicates acyl CoA: cholesterol acyltransferase; MCP-1, monocyte chemotactic protein-1; M-CSF, macrophage colony-stimulating factor; IL-1, interleukin-1; TNF, tumor necrosis factor; PDGF, platelet-derived growth factor.

*Studies in laboratory animals.
†Studies in humans.

sulfate in the regulation of cell proliferation,$^{130,133}$ changes in heparan sulfate might cause a lack of control over cell proliferation during lesion progression.

As macrophages accumulate in a type II lesion, a battery of enzymes that will eventually degrade proteoglycans may be produced. Proteolytic degradation of the large-molecular-weight chondroitin sulfate proteoglycan versican could have significant consequences, since this major proteoglycan of the intracellular space normally retains the passage of plasma materials and maintains the viscoelastic property of the vessel wall. In advanced human atherosclerotic lesions this proteoglycan is structurally altered and has a reduced capacity to bind to hyaluronic acid.$^{132,133}$

Changes in and the accumulation of collagen types I and III occur primarily after extensive necrosis. A consistent change in the minor collagen types with an increase in types V and IV has been reported.$^{134,135}$ Increases in collagen types may be a result of smooth muscle cell hyperplasia in developing atherosclerotic lesions.$^{136,137}$

Although there are significant decreases in elastin content in advanced atherosclerotic lesions, few changes are reported in initial and fatty streak lesions. A variety of elastases attack elastic fibers, and the possibility exists for macrophages$^{138}$ and smooth muscle cells$^{139}$ to produce such proteases. Significant consequences may result from damage to the elastic fibers in early lesions, since elastin-derived peptides are extremely chemotactic for macrophages.
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A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association.

H C Stary, A B Chandler, S Glagov, J R Guyton, W Insull, Jr, M E Rosenfeld, S A Schaffer, C J Schwartz, W D Wagner and R W Wissler

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