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Review

Composition and classification of human atherosclerotic lesions

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Summary. Human atherosclerotic disease can be resolved into eight types of lesion, each characterized by its composition and structure and the absence or degree of intimal injury. The eight types have been arranged in the sequence in which they may progress in complexity from the initial change in childhood or youth to the clinical endpoints in older persons. While lesions at first increase primarily by intra- and extracellular accumulation of lipid, this in itself rarely accounts for symptomatic obstruction. Lipidic lesions become symptomatic primarily by means of successively superimposed deposits of thrombotic material. Non-homogeneity of hemodynamic forces within the length of an artery account for local differences in intima thickness (*adaptive intimal thickening*) and, in persons with risk factors, differences in susceptibility to lesion formation. According to the degree to which they can accumulate or retain lipid and bring about secondary mechanisms, specific locations of the arterial tree have been designated as *atherosclerosis-resistant*, *atherosclerosis-prone* and *progression-prone*.

Key words: Atheroma – Fibroatheroma – Hemorrhage – Thrombosis – Calcification

Introduction

Various classifications have been used in pathological studies of atherosclerosis. Because of local tradition or habit, different terms are often used for lesions with identical morphologies. However, the same term is sometimes used for lesions that look alike when viewed with the unaided eye or by conventional microscopy but which, with advanced techniques, have various identities. For example, the term *fibrous plaque*, as it has been generally used, covers a range of specific atherosclerotic lesions and has also been employed for non-atherosclerotic intimal thickenings. An insufficient knowledge of arterial structure and of the composition and evolutionary sequence of atherosclerotic lesions is the main cause of ambiguous terminology. Today, a term like *fibrous plaque* can perhaps be justified in macroscopic studies, but the term is inadequate when refined methods are available. Clearly, the term, as it has been used, fails to say much about composition, genesis, or prognosis. The lack of a uniform and biologically valid terminology and classification impedes communication between investigators of atherosclerosis and leads to serious misunderstandings when the data of different studies are compared.

Recent autopsy studies employing new methods in tissue processing, new developments in microscopy, immunology and microchemistry, and the availability of atherectomy specimens (Barbano et al. 1989; Dartsch et al. 1989; Höfling et al. 1989; Backa et al. 1991) have increased our understanding of the composition and structure of arteries and atherosclerotic lesions. With the new knowledge, atherosclerotic lesions can be defined, distinguished from adaptive (non-atherosclerotic) intimal thickening, and arranged into a developmental sequence.

In clinical arteriography, terms unlike those of pathologists are used. Refinements in the angiographic resolution of lesions allow recognition not only of the degree of arterial obstruction but also of specific morphologies. Characteristics being distinguished include concentricity or eccentricity, eccentric smooth or eccentric irregular lesions, multiple irregularities (Ambrose et al. 1986), sawtooth appearance (Ambrose 1989b), rough lesions, abrupt lesions (Ellis et al. 1989), and plaque fissure (Myler et al. 1990). Some authors have described the angiographic morphology of non-occlusive thrombi (Williams et al. 1988), although Ambrose (1989a) cautioned against attempts to distinguish intracoronary thrombus from complex plaques in a patent vessel. Attempts at resolving the characteristics of lesions have also been made by sonography (Eckmann et al. 1990; Barnes 1991) and magnetic resonance imaging (Editorial 1990). Some correlations between histological findings and the ultrasound images have been described (Goes et al. 1990).

These new clinical methods contribute to an understanding of the progression of atherosclerotic lesions in symptomatic patients (Fuster et al. 1990; Ip et al. 1990) and to an understanding of the feasibility and rate of regression after dietary and drug interventions (Brown et al. 1990; Cashin-Hemphill et al. 1990; Kane et al. 1990; Ornish et al. 1990). As better resolution of lesions is being achieved in living persons, it is imperative that a classification reflecting the biological composition and structure of lesions precisely, at all stages of development be provided.

In this article I describe the composition of physiological (adaptive) increases in intimal thickness and of eight characteristic atherosclerotic lesion types from their initial appearance to clinical endstages. The lesion types are arranged in a biological classification, taking into consideration the order of their development and the degree of their complexity. The data on which the classification is largely based were obtained from studies of the coronary arteries and aortas of 1286 autopsied human subjects. Since we could not examine an initial lesion histologically and then follow its behavior over a lifetime, we studied instead the lesions of a large number of children and adults who died at different ages. Our approach was to characterize the initial changes in youth in precisely defined anatomical locations of coronary arteries and the aorta and then to study their progression in these same anatomical sites in adults. The sites chosen for study were those known for their predisposition to develop clinical lesions. Details of the methods whereby this material was studied are described elsewhere (Stary 1989, 1990).

To put the present work into perspective, classifications established by other investigators are briefly reviewed. For discussions of the various hypotheses of atherogenesis the reader is referred to other authors (Ross 1986; Clarkson et al. 1987; Roessner et al. 1987; Ip et al. 1990; Kovanen 1990; Steinberg and Witztum 1990; Fuster et al. 1991). The origins of the terms *atherosclerosis* and *arteriosclerosis* and the history of atherosclerotic disease in general have also been considered by other authors (Jores 1921; Aschoff 1933; Long 1933, 1967; Gotto 1985).

Adaptive increases in intimal thickness: eccentric and diffuse intimal thickening

The arteries of all human beings normally have regions in which the intima is thicker than elsewhere. The thick regions are present from infancy, develop apparently in the fetus, are self-limited in growth, and do not obstruct blood flow at any age (Stary et al. 1992). They are defined here to allow separation from atherosclerotic and other vascular disease. The thick regions represent physiological adaptations of the artery to local changes in blood flow or wall tension. In these locations either wall shear stress is reduced or wall tensile stress is elevated or both may be the case (Zarins et al. 1983; Caro et al. 1985). Thus, intima thickens in response to reduced wall shear, reducing lumen diameter to elevate flow velocity and thereby restore wall shear to baseline values. In response to increased tensile stress, intimal thickening strengthens the arterial wall to maintain normal values of tensile stress. The terms *eccentric* and *diffuse* are used to differentiate between two patterns of adaptive intimal thickening, although the two patterns may be contiguous and then can not be clearly delineated from each other.

Eccentric thickening is a focal increase in the thickness of the intima associated with branches and orifices. At an arterial bifurcation, the thickening involves about half the circumference (the outer wall, that opposite the flow divider) of the parent and daughter vessels and extends for a short distance along the length of a bifurcation. In a cross-section of an artery fixed under physiological pressure, eccentric thickening is a crescent-shaped increase in intimal thickness (Fig. 1). At the thickest point of the crescent, intima may be up to nearly twice the thickness of the media in coronary arteries of children, although considerable individual variation in degree has been found (Stary 1987a). Eccentric thickening has also been described in the aorta and in carotid, cerebral, and renal arteries. Its three-dimensional extent and thickness were graphically outlined only in the coronary arteries (Stary 1989).

Diffuse intimal thickening is a spread-out and often circumferential pattern of adaptive intimal thickening not clearly related to specific geometric configurations of arteries. In coronary arteries the degree of thickness is less than that of eccentric thickening, although more extensive.

Adaptive intimal thickening is composed of two histologically distinct layers. The layers may not always be distinguishable when the thickening is minimal. The inner layer, subjacent to the lumen, has been called the *proteoglycan layer* because it contains an abundance of finely reticulated non-fibrous connective tissue identified as proteoglycan ground substance by electron microscopy (Wight and Ross 1975; Richardson et al. 1988). Elastic fibers are scarce. Smooth muscle cells are both rough endoplasmic reticulum (RER)-rich and myofilament-rich phenotypes and occur as widely spaced single cells rather than in layers. The part of the proteoglycan layer near the endothelium contains isolated macrophages. The thicker layer underlying the proteoglycan layer (and adjacent to the media) has been called the *musculoelastic layer* because of the abundance of smooth muscle cells and elastic fibers. This layer also contains more collagen. Smooth muscle cells are of the myofilament-rich phenotype and arranged in close layers.

Adaptive intimal thickening was described in the fetal human aorta by Thoma (1883, 1920), who took it for a universal feature in human arterial development.

Subsequently, many other authors described similar intimal thickening in human coronary arteries (Edholm 1912; Wolkoff 1923, 1929; Bremer 1924; Ehrich et al. 1931; Gross et al. 1934; Dock 1946; Fangman and Hellwig 1947; Minkowski 1947; Schornagel 1956; Moon 1957; Robertson 1960; Neufeld et al. 1962; Geer et al. 1968; Velican and Velican 1977; Stary 1987a) and in the human aorta (Wilens 1951; Movat et al. 1958).

Various terms have been used for intimal thickening

of the eccentric pattern: intimal cushion (Dock 1946; Robertson 1960; Pflieger and Goerttler 1970), spindle-cell cushion (Stehbens 1960), intimal pad (Stehbens 1960), musculoelastic plaque (in baboons) (McGill et al. 1960), localized fibrous plaque (Moon 1957), mucoid fibromuscular plaque (McMillan 1965), normal intimal cell mass (in swine) (Kim et al. 1984; Imai et al. 1985), and focal intimal hyperplasia (Glagov and Zarins 1989). Another term for the diffuse pattern is diffuse intimal fibrosis (Moon 1957). Many authors have not distinguished between the eccentric and diffuse patterns. Such general terms include musculoelastic intimal thickening (Geer et al. 1968), musculoelastic layering (Jaffe et al. 1971), fibromuscular intimal thickening (McGill 1974), and intimal fibromuscular hypertrophy (Glagov and Zarins 1989).

Although the terms attached to adaptive intimal thickening and the significance attributed to them have varied, the microscopic descriptions and illustrations published by these authors resemble each other closely and doubtless represent either one or the other, or both, of the patterns of adaptive intimal thickening.

In laboratory animals, adaptive thickening differs functionally from adjacent regions without thickening. The turnover of endothelial cells (Wright 1968; Stary 1974), smooth muscle cells (Stary 1974), and the concentrations of lipoproteins (Schwenke and Carew 1989) and other plasma components are greater in adaptive thickening than in adjacent regions of intima without thickening. The difference in lipoproteins has also been documented in man (Spring and Hoff 1989). These increases should not be considered abnormal unless they enter a range associated with tissue damage.

The relationship between adaptive intimal thickening and atherosclerosis

The necessity to distinguish adaptive intimal thickening from atherosclerotic disease can not be emphasized strongly enough. Focal accumulations of intimal smooth muscle cells identical to those constituting adaptive intimal thickening have been designated as atherosclerotic by many authors. The fact that some of the smooth muscle cells are of the RER-rich phenotype has been taken as evidence in support of disease. Because they can impress by their thickness when viewed under the microscope and because they protrude into the arterial lumen when arteries are studied in their collapsed and contracted postmortem state, adaptive thickenings have been taken not only for initial lesions but misinterpreted as arterial stenoses or occlusions (Yater et al. 1948; Enos et al. 1953; Strasser 1980; Velican and Velican 1980).

A wide range of artificial exogenous impulses, including endothelial denudation through mechanical injury of the arterial wall (Björkerud 1969; Björkerud and Bondjers 1973; Stemerman and Ross 1973) have been applied in laboratory animals and found to produce smooth muscle cell accumulations in arterial intima. However, the experimental lesions do not match the histological structure of adaptive intimal thickening described in this article. Nor is there evidence that any of the injurious agents applied to laboratory animals are present in all human beings at birth.

Nevertheless, there is a relationship between adaptive intimal thickening and atherosclerosis. When lipoprotein is excessive in the plasma it tends to accumulate above all in intima with adaptive thickening. Eventually, intimal cell reactions evoked by excess lipid may modify adaptive thickening. In fact, specific adaptive thickenings tend to accumulate more lipid than others. Because these are first to turn into advanced lesions, the term *progression-prone* is applied to this subgroup (see section on the *progression-prone type II* lesion).

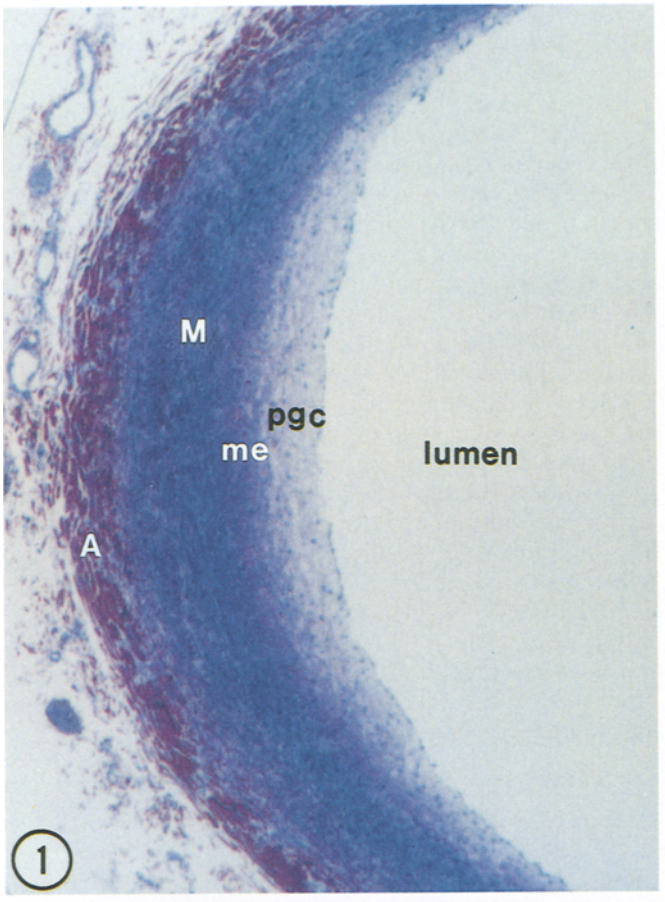
The colocalization of adaptive thickening with more or less prominent lipid accumulation has supported the view that adaptive thickening is part of the atherosclerotic process. However, if adaptive thickening is accepted as a self-limited physiological response to hemodynamic forces in specific artery locations, then the development of a lesion refers only to changes that are superimposed. The hemodynamic forces cause the thickening whether high concentrations of atherogenic lipoproteins are present or not. When atherogenic plasma lipoproteins exceed critical levels, the same forces enhance lipoprotein accumulation in the same locations.

Atherosclerotic lesions: history of their classification

At the beginning of the century, two types of intimal lesions were recognized and associated with atherosclerosis. They were called *fatty streaks* (thin lipidic lesions in children) and *fibrous plaques* (thick fibrolipidic lesions in adults). However, the two types of lesions were not universally accepted as the early and advanced expressions of a single disease.

The Freiburg pathologist Ludwig Aschoff was a main proponent among those who regarded the morphologically different intimal lipid deposits of children and adults as early and late stages of one disease (Aschoff 1924, 1930, 1933). Aschoff recognized two components of the disease. One was lipid, deposited in the intima from infancy and thereafter. Aschoff designated this stage as *atherosis*; in his American publication (1924) he used the term *atheromatosis*. The other was fibrosis (sclerosis, collagenization, scar formation), added to the lipid in adults. Only the fibrolipidic stage was designated as *atherosclerosis*. Aschoff subdivided pre-adult atherosis into an infant and a pubertal phase so that in fact he spoke of three developmental stages: atherosis of infants, atherosis at puberty, and atherosclerosis in adults.

Atherosis in infants was described as yellow dots, visible with the naked eye at the root of the aorta. Atherosis at puberty consisted of more extensive yellow streaks in many parts of the aorta and in coronary arteries. Microscopically, infant and pubertal dots and streaks were similar, consisting of intracellular and extracellular lipid in the intima. Both differed from adult lesions in the absence of fibrosis. In adults, atherosis and fibrosis (now called atherosclerosis) formed fibrous plaques (the German term was *fibröse Platten*). Why and how the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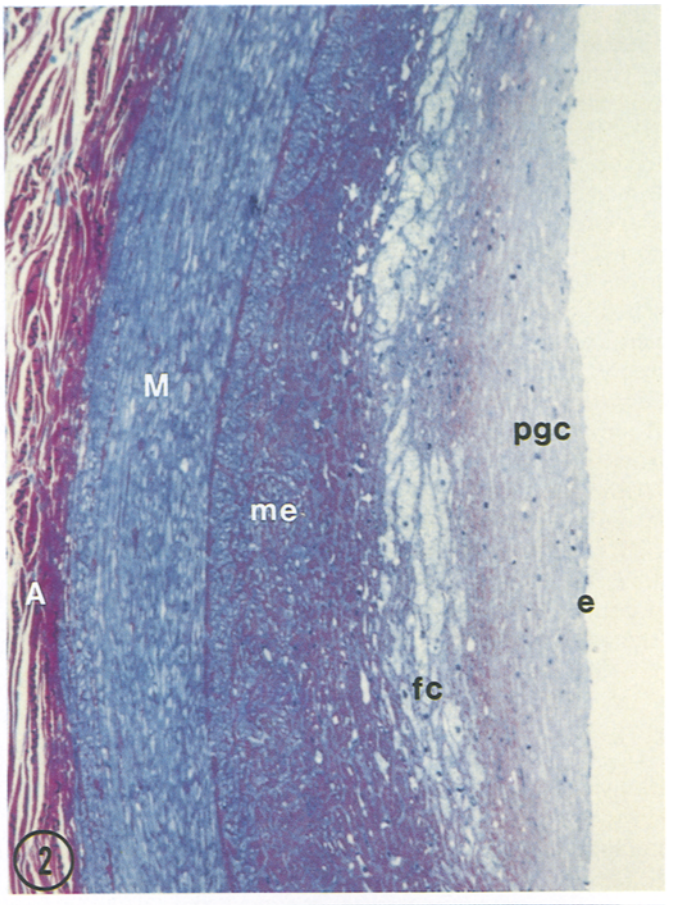
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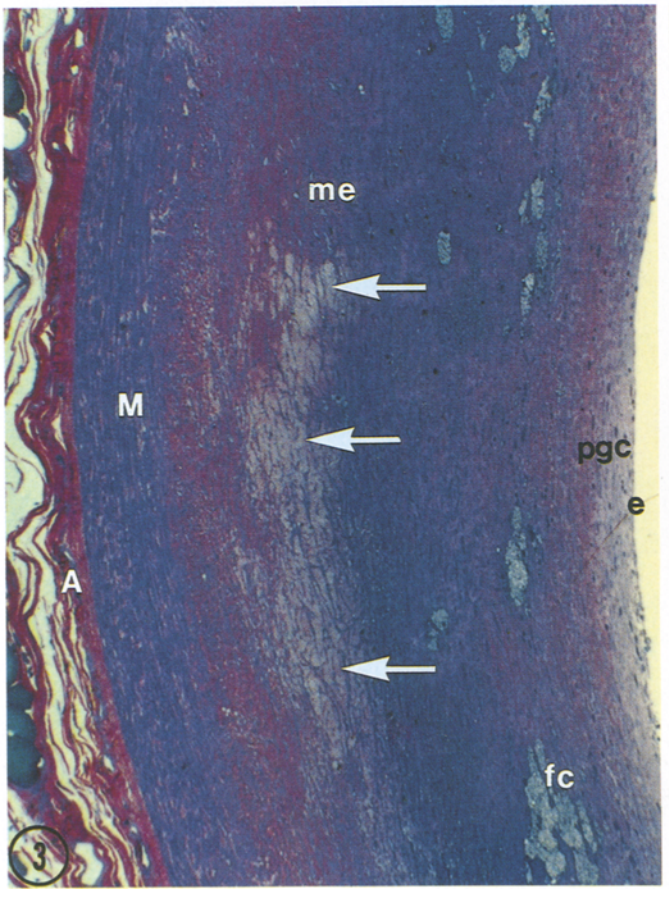
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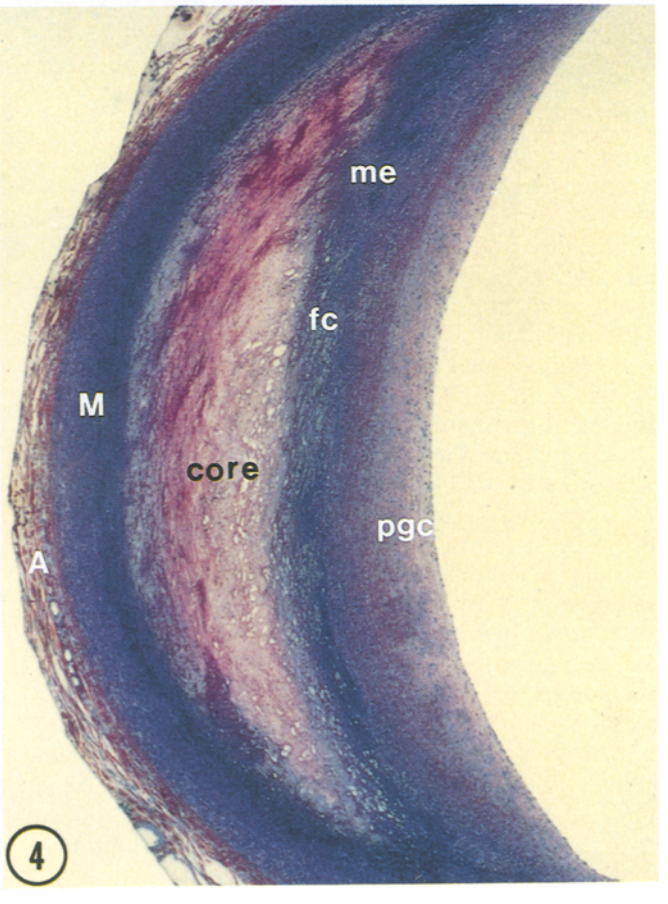
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lipid deposits of children transformed into the lesions of adults was not explained. Aschoff's sequence appears correct except that now, with more sensitive methods, intermediate stages that answer some questions about development and progression, and a range of advanced stages that answer clinical questions, can be resolved.

After Aschoff, structured classifications were developed by pathologists for the purpose of estimating the prevalence of individual lesion types in epidemiological studies. In these studies, lesions seen on the intimal surface of arteries that had been opened longitudinally, flattened, and fixed in formalin were examined with the unaided eye. This method permitted the rapid estimation of the percentage of atherosclerotic lesions covering the intimal surface of an artery. The terms for lesions used in these studies were close to the terms used by Aschoff. A classification first described by Gore and Tejada (1957) and used on a large scale in the International Atherosclerosis Project (Guzman et al. 1968) consists of the sequence *fatty streak*, *fibrous plaque*, and *complicated lesion*. The latter term was used for fibrous plaques that had eroded or fissured and developed hemorrhage and thrombotic deposits. Duff and McMillan (1951) had used the term *complication* in connection with thrombosis superimposed on advanced lesions.

A classification by the World Health Organization (1958) includes, in addition to the three terms above, the term *atheroma* to distinguish advanced lesions with a predominantly lipid component (atheroma) from those with a predominantly collagenous one (fibrous plaque).

Where the terms fibrous plaque or atheroma are used in the above classifications, other authors substitute *fibroatheroma*, *atheromatous plaque*, *fibrolipid plaque*, or *fibrofatty plaque* (Cotran et al. 1989). The term atheroma used in the WHO classification for a lesion type has been used by some (Davies 1986) to designate the entire disease process, analogous to the term atherosclerosis.

Haimovici (1977) arranged atherosclerotic disease into one preclinical, and two clinical stages. The first stage includes fatty streaks and unobstructive fibrous plaques; the second represents symptomatic atherosclerotic lesions; and the third includes evidence of myocardial infarction, stroke, or gangrene.

A classification based on the pathophysiology of the presumed vascular injury has been proposed by Fuster and colleagues (1992). In this classification, type I injury consists of functional change in endothelial cells, which is postulated as the cause of the initial accumulation of lipids and monocytes in the intima. Type II injury includes loss of endothelial cells, injury of intimal structure, adherence of platelets, and moderate proliferation of smooth muscle cells. In type III injury, lesions are disrupted, thrombi form, and smooth muscle cells proliferate markedly to incorporate the thrombus into the arterial wall and cause permanent and marked thickening.

Fig. 1. A crescent-shaped (eccentric) adaptive intimal thickening in the left anterior descending coronary artery at the level of the main bifurction. pgc = proteoglycan intima layer, me = musculoelastic intima layer, M = media, A = adventitia, lumen = lumen of the artery. From a 6-month-old boy. Homicide was the cause of death. Case no. 949 (P-1949). The artery was fixed by perfusion with glutaraldehyde under pressure, tissue was embedded in Maraglas, and the one-micron section was stained with toluidine blue and basic fuchsin. Magnification about ×90.

Fig. 2. A type IIa (progression-prone fatty streak) lesion colocalized with an adaptive thickening in the proximal part of the left anterior descending coronary artery. Macrophage foam cells (fc) occupy the intima at the junction of the proteoglycan (pgc) and musculoelastic (me) intima layers. e = endothelial cells at the artery lumen, M = media, A = adventitia. From a 25-year-old woman. A traffic accident was the cause of death. Case no. 775 (P-1775). Fixation by pressure-perfusion with glutaraldehyde. Maraglas embedding. One-micron section stained with toluidine blue and basic fuchsin. About ×140.

Fig. 3. A type III (preatheroma) lesion colocalized with an adaptive thickening in the left main coronary artery just proximal to the main bifurcation. Extracellular lipid (arrows) is pooled in the musculoelastic layer (me). Smooth muscle cells, normally closely packed, are separated, compressed, and attenuated by the extracellular lipid. Macrophage foam cells (fc) are some distance above the pooled extracellular lipid. e = endothelial cells at the artery lumen, pgc = proteoglycan intima, M = media, A = adventitia. From a 25-year-old man who died in a traffic accident. Case no. 372 (P-1372). The artery was fixed by perfusion with glutaraldehyde under pressure, tissue was embedded in Maraglas, and the one-micron thick section was stained with toluidine blue and basic fuchsin. About ×95.

Fig. 4. A type IV (atheroma) lesion in the most proximal part of the left anterior descending coronary artery. In addition to all the changes seen in type IIa and III lesions a massive aggregate of extracellular lipid (lipid core) occupies the musculoelastic layer (me). Macrophage foam cells (fc) are above the lipid core. pgc = proteoglycan intima layer, M = media, A = adventitia. From a 23-year-old man. Homicide was the cause of death. Case no. 917 (P-1917). Fixation by pressure-perfusion with glutaraldehyde. Maraglas embedding. One-micron thick section was stained with toluidine blue and basic fuchsin. Magnification about ×40.

Atherosclerotic lesions: definitions and an updated biological classification

General comments

In the following sections, the compositions of eight morphologically characteristic types of atherosclerotic lesions are described in the sequence in which they may evolve in the course of a life. In the first three decades, the composition of the lesions is predominantly lipidic and relatively predictable. In the fourth decade, and subsequently, the composition of advanced lesions becomes unpredictable because some continue to increase by mechanisms additional to lipid deposition.

Type I and II lesions, sometimes combined under the term *early lesions*, generally are the only ones that occur in infants and children, although they occur in adults also. Such lesions do not obstruct or modify blood flow. Type III lesions may evolve soon after puberty and, in their composition, are intermediate between fatty streaks

Table 1. Classification of human atherosclerotic lesions

Classification of atherosclerotic lesion types based on microscopic and chemical composition			Conventional terms based on appearance with the unaided eye	Comments
Recommended terms		Description		
Type I	(initial lesion)	Lipoprotein accumulation in intima; lipid in macrophages; these changes discernible only microscopically or chemically; no tissue damage	None	Types I and II are sometimes combined as "early lesions"
Type II	(fatty streak)	Lipoprotein accumulation in intima; lipid in macrophages and smooth muscle cells; quantities large enough to be visible to the unaided eye but still no tissue damage	Fatty streak	
IIa	(progression-prone: colocalized with specific adaptive thickening)			
IIb	(progression-resistant)			
Type III	(preatheroma)	All type IIa changes plus multiple deposits of pooled extracellular lipid; microscopic evidence of tissue damage and disorder	None	An "intermediate" or "transitional" lesion had been suspected
Type IV	(atheroma)	All type IIa changes plus confluent mass of extracellular lipid (lipid core) with massive structural damage to intima	Fibrous plaque; fibrolipid plaque; plaque	Types IV to VIII are sometimes combined as "advanced lesions"
Type V	(fibroatheroma)	All type IV changes plus development of marked collagen and smooth muscle cell increase (cap) above lipid core		
Type VI	(complicated fibroatheroma)	All type V changes plus a thrombotic deposit, and/or hemorrhage, and/or erosion or fissure	Complicated plaque	
VIa	(thrombo-hemorrhagic)			
VIb	(thrombotic)			
VIc	(hemorrhagic)			
Type VII	(calcific lesion)	Any advanced lesion type composed predominantly of calcium; substantial structural deformity	Calcified plaque	
Type VIII	(fibrotic lesion)	Any advanced lesion type composed predominantly of collagen; lipid may be absent	Fibrous plaque	

(type II) and atheroma (type IV). In this classification, the term *advanced lesion* is used as an umbrella term for lesions beyond type III. Advanced lesions of type IV are frequent from the third decade and lesions more advanced (V–VIII) from the fourth decade of life. Destruction and deformity of a part of the intima is the biological measure we use to designate a lesion as *advanced. Advanced* in this sense does not necessarily indicate that a lesion is visible angiographically or that it is clinically overt.

In type IV, destruction of intimal structure is caused almost solely by means of a mass of extracellular lipid localized in the deep intima (the lipid core). In type V, intima is replaced and thickened by a lipid core *and* a subsequently formed fibrous component. Thrombotic deposits and/or hemorrhage add damage and deformity and accelerate conversion from clinically silent to overt disease (type VI lesions). In this paper, the term *fibrotic lesion* (type VIII) is applied when predominantly collagenous scar tissue but little or no lipid is present. It must be remembered, however, that lesions that appear completely collagenous represent the scarred end result of earlier atherosclerotic lesion components. The same is true for *calcific* (type VII) lesions which consist largely of calcium.

In medium-sized arteries, type IV lesions are almost always only mildly obstructive and therefore clinically silent. Type VI are unstable and generally symptomatic in medium-sized arteries. Types V, VII and VIII may be silent or overt depending on the degree of stenosis they cause. All advanced lesion types are larger in the aorta than in arteries of medium size but become symptomatic in the aorta later and generally not because of stenosis.

In Table 1, atherosclerotic lesions are listed in their developmental sequence and their typical features are summarized. Table 1 represents a biological classification of the lesions from their inception to clinical endstages. In Table 2, cellular and intercellular components and distinguishing characteristics are listed and compared in a semiquantitative manner.

Type I lesion (initial lesion)

Initial lesions represent the first, only microscopically and chemically perceivable, lipid deposits and accompa-

Table 2. Quantitation[a] of the components of adaptive thickening (AT) and of human atherosclerotic lesions type I to VIII

	AT	I	IIa	IIb	III	IV	V	VIa	VIb	VIc	VII	VIII
Lipid deposition												
intracellular	0	1	2	2	3	3	3	3	3	3	2	1
extracellular	0	0	1	1	3	5	5	5	5	5	3	1–2
Lipid core	0	0	0	0	0	1–5	2–5	2–5	2–5	2–5	0–2	0–1
SMC												
myofilament-rich	4	4	3	2	3	2	2	2	2	2	2	2
RER-rich	1	1	2	1	2	2	3	4	4	2	2	3
BM-rich	0	0	0	0	0	1	2	3	3	1	2	2
SMC												
without lipid	5	1–5	2	1	2	2	3	4	4	3	3	5
with lipid	0	0	3	2	3	3	4	4	4	3	3	2
Macrophages												
without lipid	1	2	2	2	2	3	3	3	3	3	2	3
with lipid	0	1	3	2	4	5	5	5	5	5	3	3
Lymphocytes	0	0	2	1	2	3	3	3	3	3	?	?
Mast cells	1	1	2	1	2	2	2	2	2	2	?	?
Plasma cells	0	0	1	0	1	1	1	1	1	1	?	?
Tissue damage-deformity	0	0	0	0	1	3	3	5	4	4	5	4
Neovascularization	0	0	0	0	0	1	1–3	2–4	2–4	2–4	1–3	1–3
Collagenization	0	0	0	0	0	1	3	3	3	3	3	5
Thrombotic deposit	0	0	0	0	0	0	0–1	2–5	2–5	0–1	0–1	0–1
Hemorrhage	0	0	0	0	0	1	1	2–5	1	2–5	1	1
Fissure-erosion	0	0	0	0	0	0	0	0–5	0–2	0–5	0–3	0–1
Calcium deposition	0	0	0	0	0	0–3	0–3	0–3	0–3	0–3	5	0–3

[a] The cellular and intercellular components and complications have been estimated semiquantitatively on a scale of 0–5 (0–5+)
SMC, smooth muscle cells; RER, rough endoplasmic reticulum; BM, basement membrane

nying cell reactions in the intima. Microscopically, the histological change is minimal, consisting of isolated groups of macrophages filled with lipid droplets (macrophage foam cells). Macrophages without lipid droplet inclusions are twice the number present in intima normally. Such minimal accumulations of macrophages with and without lipid droplets were found in the coronary arteries of 45% of infants in the first 8 months of life (Stary 1987a), but some older children and adults also have only this minimal degree of lipid and cell reaction. Initial lesions coinciding with adaptive intimal thickening of the eccentric pattern contained six times as many macrophages and five times as many macrophage foam cells as intima outside eccentric thickening. Adaptive thickenings with the most distinct type I lesions are those in which the type II lesions of older children are also most prominent, and identical to the locations in which type III, IV and V lesions develop first in an adult if advanced lesions develop at all.

Accumulations of macrophages and macrophage foam cells occur in arterial intima of laboratory animals generally within days (Duff et al. 1957) or a few weeks (Still and O'Neal 1962; Stary 1976; Joris et al. 1983; Simionescu et al. 1986) after having been made hypercholesterolemic. Hypercholesterolemia causes increased adherence of monocytes to the endothelium particularly over atherosclerotic lesions (Gerrity 1981; Joris et al. 1983; Faggiotto et al. 1984; Lewis et al. 1985). The initial intimal macrophage foam cells are a sequel and a cellular marker of unphysiological increases in intimal lipoproteins. Rabbits receiving a high-cholesterol diet for 4–16 days had increased low-density lipoproteins in thick intima locations of the aorta before macrophage foam cells appeared in the intima (Schwenke and Carew 1989). Extracellular lipid droplets were visible by electron microscopy in the aortic intima of rabbits within 2 weeks after receiving a high-cholesterol diet while macrophages and macrophage foam cells were noticed after only 4 weeks (Simionescu et al. 1986). The experimentally induced increases in lipoproteins, macrophages, and macrophage foam cells are most marked in regions with focal intimal thickening. Extracellular lipid particles and debris of the type visible by electron microscopy in and characteristic of more advanced lesions are not present in the initial lesions.

Type II lesion (fatty streak)

Type II lesions are composed of more lipid-laden cells than initial lesions. One or more layers of macrophage foam cells, frequently interdigitating by means of their

microvilli, are present. The number of macrophages without droplet inclusions in coronary artery type II lesions is 1.7 times the number in normal intima at 10–19 years and 1.5 times the number at 20–29 years. The number of macrophage foam cells in type II lesions exceeds the number in type I lesions two- or threefold (Stary 1990). Isolated T-lymphocytes (Munro et al. 1987; Katsuda et al. 1992), mast cells, and plasma cells may be present, but these are less numerous than macrophages.

Of the smooth muscle cells present in locations of intima in which type II lesions develop, a variable proportion also contains lipid droplet inclusions, although generally the number of lipid droplets per smooth muscle cell is smaller than the number per macrophage foam cell. In human subjects, the number of intimal smooth muscle cells in a fatty streak is similar to the number in the same intima region when a lesion is not present. An increase in the proportion of RER and smooth endoplasmic reticulum, observed within some of both intimal smooth muscle cell phenotypes, may be a sign of degradation of intracellular lipid droplets. While most of the electron microscopically visible lipid is within cells, some smaller lipid particles are extracellular. Fatty streaks differ from more advanced lesions by the smaller amount of extracellular lipid particles and debris, and the absence of visible damage of intimal structure, reparative tissue reaction, or deformity.

Intimal macrophage foam cells accumulate in the deep part of the proteoglycan layer. In most arterial locations the proteoglycan layer is thin and a few layers of foam cells fill the layer to the level of the endothelial cells. The term *fatty streak* is derived from the layers of foam cells visible with the unaided eye through the endothelial surface. However, macrophage foam cells accumulating in eccentric intimal thickening (in which the proteoglycan layer is thick) may not be visible from the intima surface.

Chemically, the lipid of fatty streaks is predominantly cholesterol and its esters. The predominant cholesterol ester is oleate (Geer and Malcom 1965; Smith and Smith 1976).

Progression-prone type II lesion

The locations in the arterial tree in which type II lesions develop are relatively constant (Cornhill et al. 1990), and have been called *atherosclerosis-prone* (or lesion-prone) locations. However, of the many type II lesions generally present in a person with average levels of atherogenic lipoproteins only a subgroup will readily proceed to advanced lesions if advanced lesions develop in a person at all. This subgroup is colocalized with specific adaptive intimal thickenings and may be called *progression-prone* or type IIa. The larger subgroup of type II lesions that do not progress, or only slowly, or only in persons with very high plasma levels of atherogenic lipoproteins, may be called *progression-resistant* or type IIb.

Whether a type II lesion develops at all, and whether it is progression-prone or resistant, is determined in great part by the hemodynamic forces acting on a particular part of the vessel wall. The hemodynamic forces found in these locations cause adaptive thickening in all persons and increased focal lipid accumulation in those with high plasma levels of atherogenic lipoproteins.

Morphologically, type IIa lesions differ from type IIb by the smooth muscle cells and abundant intercellular matrix of colocalized adaptive thickening, the larger accumulation of lipoprotein, macrophages, macrophage foam cells and extracellular lipid debris, and by the deep intimal location of the foam cells and lipid debris (Fig. 2). While macrophages without fat are most numerous near the endothelial surface, macrophage foam cells which accumulate at the bottom of the proteoglycan layer can be relatively deep when colocalized with adaptive thickening. Although with time more macrophage foam cells pile up they may not extend to the endothelial surface. The terms *submerged fatty streak* and *concealed fatty streak* have been applied to this morphological picture. Because of the colocalized adaptive thickening, type IIa lesions have been misinterpreted as lesions advanced beyond type II.

In human subjects with very high plasma levels of atherogenic lipoproteins, such as in familial hypercholesterolemia homozygotes, type II lesions proceed to advanced types rapidly also in arterial locations outside the progression-prone ones. Similarly, when serum cholesterol levels much higher than those usual in human populations are induced in laboratory animals there is wide dispersal of lesions. After early middle age, even persons with average plasma levels of atherogenic lipoproteins may have advanced lesions outside the progression-prone locations. Advanced lesions (type VI) may extend beyond progression-prone locations by incorporation of adjoining thrombi. Such advanced lesions may also be concentric rather than eccentric.

Type III lesion (preatheroma)

The type III lesion is the connecting link between a progression-prone type II lesion and the first type that can be considered as advanced: type IV (atheroma). The characteristic histological features are microscopically visible extracellular lipid and debris particles to the extent that pools of this material form among the layers of smooth muscle cells of a colocalized adaptive intimal thickening (Fig. 3). The lipid pools are just below the layers of macrophage foam cells and replace intercellular matrix proteoglycans and fibers, and drive smooth muscle cells apart. Neither death nor proliferation of smooth muscle cells are evident at this stage of progression. Cholesterol crystals are rarely present. By this definition, multiple scattered pools of extracellular lipid, disrupting the coherence of some structural intimal smooth muscle cells, constitute progression beyond a type II lesion. A massive, confluent, accumulation of extracellular lipid (a lipid core) has not yet developed. The study of many cases indicates that a lipid core, and thus the advanced lesion we call atheroma, forms through the fusion of the separate small pools of extracellular lipid.

When human atherosclerotic lesions were studied by lipid physical biochemistry, a lesion connecting fatty streaks and atheroma also became apparent (Katz et al. 1976; Small 1988). Lesions with this composition contained more free cholesterol, more fatty acid, sphingomyelin, lysolecithin and triglyceride than fatty streaks. The melting behavior of the cholesterol ester droplets was also between that of fatty streaks (higher) and atheroma (lower). Small (1988) stated that histologically the lesions resemble the preatheroma described in the preceding paragraphs.

The term *preatheroma* has been applied to type III lesions because it heralds the formation of atheroma. This term may be more descriptive and chronologically correct than terms such as *intermediate* or *transitional lesion*. The latter terms could apply to any one of the lesions in the sequence between the beginning and the clinical endpoints of the disease.

In the past, the belief that clinically significant atherosclerotic lesions develop from some type II lesions of juveniles had been based, to a large degree, on evidence of progression of fatty streaks in hypercholesterolemic animals and in human cases of familial hypercholesterolemia. Some authors who had opposed this belief thought of fatty streaks as self-limited lesions associated with the fatal infectious diseases that were so frequent in children. While this hypothesis was subsequently rejected (Jores 1924; Schmidtmann 1925), the supposition that clinical lesions originate in fatty streaks had nevertheless remained controversial (Mitchell and Schwartz 1965; Smith and Smith 1976; Mauer 1986, 1987).

Several reasons account for this skepticism. As fatty streak and advanced lesions had been traditionally viewed, they differed too sharply from each other. There was thought to be a lack of a precise topographical correspondence between the two lesion types (Mitchell and Schwartz 1965). Some persons with abundant fatty streaks were without advanced lesions while others with advanced lesions had few fatty streaks. By chemical analysis, the cholesteryl esters of advanced human lesions contain a high proportion of linoleic acid and a low proportion of oleic acid (Smith and Smith 1976). In fatty streaks the reverse is true (Geer and Malcom 1965; Smith and Smith 1976).

If advanced lesions develop from fatty streaks then a lesion type histologically and chemically intermediate between the two should exist. Although the existence of an intermediate (transitional) morphology has been suspected and discussed (McGill 1974; McMillan 1985; Steinberg and Witztum 1990) this type of lesion had not been defined and included in classifications of atherosclerosis until recently (Stary 1987b, 1989, 1990).

The supposed morphological incompatibility between fatty streaks – as they have been conventionally viewed in thin intima segments – and atheroma is resolved by understanding that fatty streaks developing in youth in specific adaptive thickenings are rich in macrophage foam cells and extracellular lipid and that, not much later in life, lesions of preatheroma or atheroma morphology are found in the same locations. The differences in fatty acids may be explained by the massive overall increase in lipids and the change from intra- to predominantly extracellular storage.

Type IV lesion (atheroma)

Type IV lesions are characterized by a massive aggregate of extracellular lipid (a *lipid core*) (Fig. 4). Additional components such as a thick fibrotic (collagenous) *cap*, thrombosis, or hemorrhage are still absent. The classic picture of a lipid core is produced when sufficient extracellular lipid has accumulated at the depth of an adaptive intimal thickening to displace pre-existing intimal smooth muscle cells. Lipid cores thicken the arterial wall and generally are large enough to be visible to the unaided eye. Intimal smooth muscle cells within the region of the lipid core are dispersed and relatively or absolutely decreased. Remaining cells have attenuated and elongated cell bodies and may have unusually thick basement membranes (BM-rich smooth muscle cells). The organelles of some smooth muscle cells may be calcified and calcium particles may be among the extracellular lipid of the core. The part of the adaptive thickening between the lipid core and the endothelial surface contains macrophages and smooth muscle cells with and without lipid droplet inclusions, T-lymphocytes (Jonasson et al. 1986), and mast cells. Granulation tissue with capillaries may border the lipid core at the lateral margin (shoulder) of the eccentric thickening. This is also the region in which most macrophages and macrophage foam cells are located. The part above a lipid core should not, at this point in atherogenesis, be considered as having been entirely formed by the atherosclerotic process. The lipid core of an atheroma precedes the smooth muscle cell proliferation and collagen deposition that eventually may thicken the region above the lipid core greatly, which then could be called the fibrotic cap of the lesion (see type VI fibroatheroma). In the atheroma stage, most of the tissue above the lipid core represents the upper (proteoglycan) part of the pre-existing adaptive thickening.

Although, by definition, complications such as thrombosis or hemorrhage are not part of atheroma, the risk for these, because of the destructive and deforming nature of the lipid core, is now present. For this reason atheroma is considered as the first *advanced*, or potentially clinical lesion type.

Since it generally coincides with adaptive thickenings of the eccentric type, atheroma is an eccentric rather than concentric lesion. Measurements indicate that while the wall can be quite thick, arterial lumen is not much reduced. Some autopsy studies of coronary arteries (Yater et al. 1948; Enos et al. 1953; Strasser 1980; Velican and Velican 1980) overestimated the degree of stenosis caused by atheroma because collapsed arteries were studied. Nevertheless, lesions of the atheroma type can become symptomatic in severe forms of familial hypercholesterolemia through their great lipid bulk.

Type V lesion (fibroatheroma)

A type V lesion has formed when, in addition to the components of an atheroma, a thick layer composed of newly formed layers of RER-rich smooth muscle cells and collagen (a fibrotic cap) thickens the region between the lipid core and the endothelial cell layer at the arterial lumen (Fig. 5). The new components replace the proteoglycan intima layer, sometimes add several fold more thickness to the arterial wall than the underlying lipid core, and they decrease lumen size. Granulation tissue and capillaries at the lateral and luminal margins of the lipid core may be larger than in the atheroma stage and microhemorrhages may be present around the capillaries. Initially, granulation tissue and collagen formation are absent from the aspect of the lipid core facing the media.

It is certain that the thickness of some fibrotic caps is the result of, or has been enhanced by, periodic thrombotic deposits on the lesion surface, although by the time of study these have been incorporated and replaced with smooth muscle and collagen. Such lesions are classified as type V although they would be classified as type VI if ingredients of a thrombus could be detected. When thrombotic deposits are not suspected (more often in young adults and in early middle age) a fibrotic cap of only modest thickness is present. In this case, smooth muscle cells and collagen formed gradually in response to injury and deformity caused by the increasing lipid core alone. Such uncomplicated fibroatheroma does not appear to obstruct blood flow much.

Type VI lesions (complicated fibroatheroma)

Lesions having visible thrombotic deposits and/or marked hemorrhage, in addition to lipid and collagen, are type VI (complicated fibroatheroma, or complicated lesions) (Fig. 6). Thrombosis and hemorrhage accelerate growth and complexity of the lesions. Type VI lesions may be subdivided to reflect the dominant complicating factors: type VIa to indicate both thrombus and hemorrhage as important components, type VIb – thrombus without hemorrhage, and type VIc – hemorrhage without thrombus.

Thrombotic deposits may be visible only with the microscope, or they may be large enough to be visible with the unaided eye. Clinically (angiographically), complicated lesions with an obstructive but labile thrombus are known as *unstable lesions* and are thought of as the morphological counterpart of unstable angina (Fuster et al. 1992). Thrombotic deposits set in motion mechanisms which accelerate lesion growth by stimulating intimal smooth muscle proliferation and collagen production. In our studies, when platelets and fibrin were visible on the surface or within lesions then the number of smooth muscle cells as well as the amount of collagen and the thickness of the lesions was more often greater than when such evidence was not present.

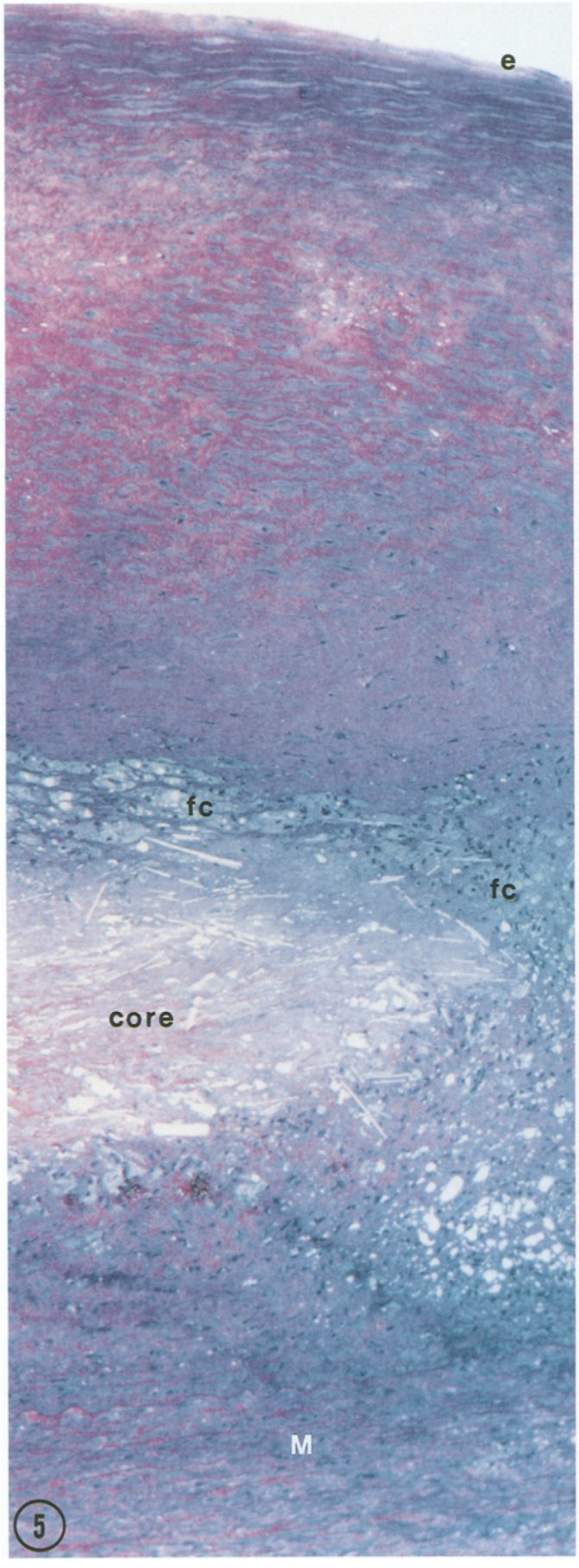
The causes of hemorrhages and/or thrombotic deposits are multiple. Erosion or ulceration of the lesion surface have long been known to constitute one cause. Some authors published evidence that shearing tears (fissures) of the lesion surface are a principal cause of massive hemorrhage into the lesion, thrombotic deposits, rapid lesion expansion, and symptomatic disease (Constantinides 1966, 1990; Davies and Thomas 1985; Richardson et al. 1989; Falk 1991). Although large hemorrhages appear to be the consequence of shearing tears or erosions of the surface, there is evidence that smaller hemorrhages within lesions are caused by breaks in newly formed capillaries (Barger et al. 1984; Beeuwkes et al. 1990). It has been proposed that these hemorrhages can rupture into the arterial lumen, thus precipitating thrombosis (Beeuwkes et al. 1990). Isolated, only microscopically visible hemorrhages occur in some type IV and V lesions in young people (Stary 1990). Such microhemorrhages are not associated with breaks in the lesion surface or with thrombosis and we do not classify such lesions as type VI.

Thrombotic deposits on lesions can form without a surface defect or hemorrhage. The causes may include changes in blood flow secondary to deformity of the surface by the underlying lesion, facilitating platelet deposition in susceptible individuals. High plasma fibrinogen levels have been found in persons with clinical ischemic episodes (Møller and Kristensen 1991; Yarnell et al. 1991). Functional impairment of endothelial cells or loss of small groups of endothelial cells, impossible to detect even microscopically, might also facilitate thrombus formation.

Most type VI lesions by far reach that stage after the third or fourth decade, after having passed through the atheroma stage first. However, fissures, massive hemorrhage, and thrombotic deposits have occasionally been observed in association with lesions of only the fatty streak type. Thus, the possibility of unusual modes of lesion progression must be kept in mind.

Fig. 5. A type V (fibroatheroma) lesion in the distal part of the abdominal aorta. The part of the lesion above the lipid core and above the layer of macrophage foam cells (fc) consists of dense bands of collagen and RER-rich smooth muscle cells. e = endothelial cells at the artery lumen, M = media, From a 40-year-old man who died suddenly and unexpectedly from myocardial infarction because of Type VI lesions in the coronary arteries. Case no. 1349 (P-2349). The aorta had been opened and fixed flat by immersion in formalin, tissue was embedded in Maraglas, and the one-micron thick section was stained with toluidine blue and basic fuchsin. Magnification about ×140.

Fig. 6. A type VI (complicated) lesion in the distal part of the abdominal aorta. A recent thrombotic deposit (th) is at the luminal surface of the lesion and a small hemorrhage (red blood cells = rb) is in the uppermost part of the lesion. core = lipid core of the lesion, M = media. From a 37-year-old woman who died of intracerebral hemorrhage. Case no. 1280 (P-2280). The aorta had been opened and fixed flat by immersion in fomalin, tissue was embedded in Maraglas, and the one-micron thick section was stained with toluidine blue and basic fuchsin. Magnification about ×140.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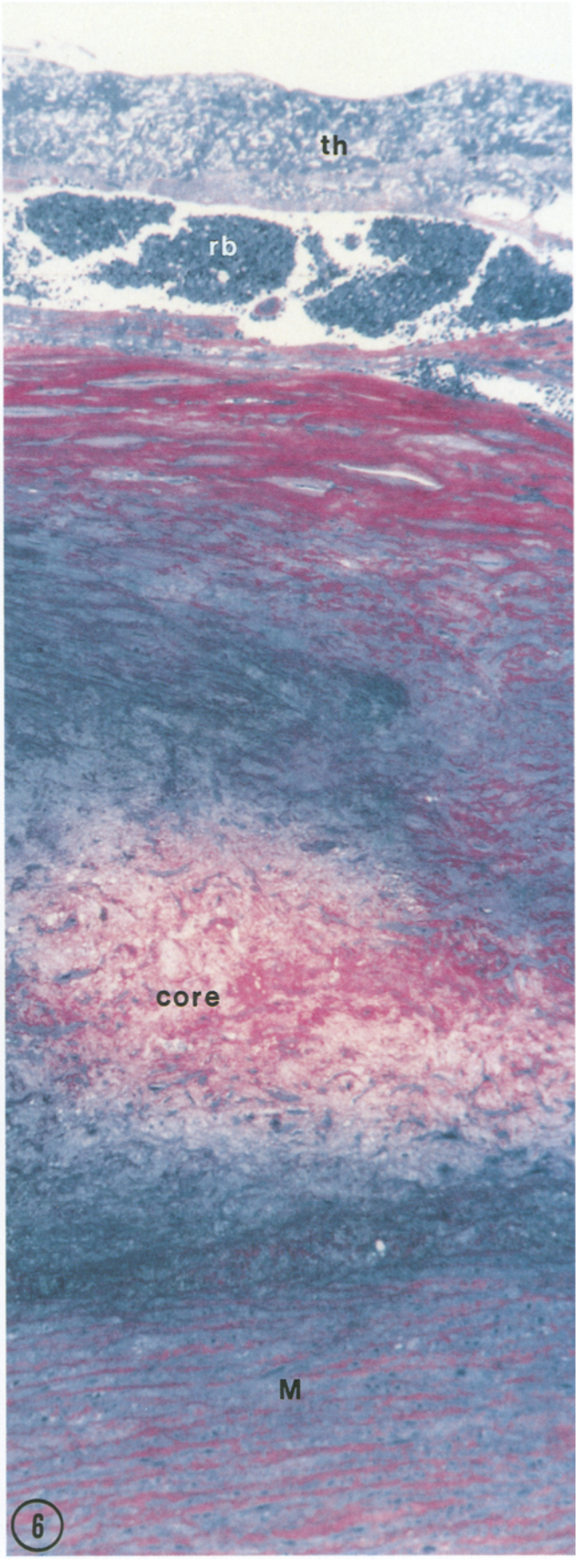
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Type VII (calcific) lesion

Some advanced atherosclerotic lesions, particularly after the fourth decade, are largely mineralized. The term *calcific lesion* (type VII) may be applied here. Calcium deposits replace the accumulated remnants of dead cells and extracellular lipid. Rather than enlarging lesions further, calcium may add permanence to the deformity.

Variable amounts of calcium are present in most advanced lesions. With refined microscopic methods, even the type IV lesions of younger adults may reveal small aggregates of crystalline calcium among the lipid particles of lipid cores and within the cytoplasm of smooth muscle cells trapped and injured within lipid cores (Stary 1990). Since many, perhaps most, advanced lesions contain some calcium deposits from their onset, the type VII classification is appropriate only when mineralization dominates the picture. However, it is understood that lesion components such as lipid deposits and increased fibrous tissue may also be present.

Type VIII (fibrotic) lesion

Some atherosclerotic lesions, possibly more often in arteries of lower extremities, may consist entirely or almost entirely of scar collagen. The lipidic component here is minimal or absent. Lipid may have regressed or it may never have been present in a thrombotic (now collagenous) propagation of a lipid lesion. Such lesions may obstruct the lumen of medium-sized arteries severely and may even be occlusive. The term fibrotic lesion is best reserved for lesions with this morphology.

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References

Ambrose JA (1989a) Coronary arteriographic analysis and angiographic morphology. J Am Coll Cardiol 13:1492–1494

Ambrose JA (1989b) Coronary morphology in unstable angina (letter). Am J Cardiol 64:256

Ambrose JA, Winters SL, Arora RR, Eng A, Riccio A, Gorlin R, Fuster V (1986) Angiographic evolution of coronary artery morphology in unstable angina. J Am Coll Cardiol 7:472–478

Aschoff L (1924) Lectures on pathology. Hoeber, New York

Aschoff L (1930) Die Arteriosklerose. Med Klinik [Suppl 1]:1–20

Aschoff L (1933) Introduction. In: Cowdry EV (ed) Arteriosclerosis. A survey of the problem. Macmillan, New York, pp 1–18

Backa D, Nerlich A, Höfling B (1991) Histologic predictors for restenoses in primary arteriosclerotic lesions. Arterioscler Thromb 11:1508a

Barbano EF, Newman GE, McCann RL, Hackel DB, Stack RS, Palmos LE, Mikat EM (1989) Correlation of clinical history with quantitative histology of lower extremity atheroma biopsies obtained with the Simpson atherectomy catheter. Atherosclerosis 78:183–196

Barger AC, Beeuwkes R III, Lainey LL, Silverman KJ (1984) Hypothesis: vasa vasorum and neovascularization of human coronary arteries. A possible role in the pathophysiology of atherosclerosis. N Engl J Med 310:175–177

Barnes RW (1991) Noninvasive diagnostic assessment of peripheral vascular disease. Circulation 83 [Suppl I]:I-20-I-27

Beeuwkes R III, Barger AC, Silverman KJ, Lainey LL (1990) Cinemicrographic studies of the vasa vasorum of human coronary arteries. In: Glagov S, Newman WP, Schaffer SA (eds) Pathobiology of the human atherosclerotic plaque. Springer, Berlin Heidelberg New York, pp 425–432

Björkerud S (1969) Reaction of the aortic wall of the rabbit after superficial, longitudinal, mechanical trauma. Virchows Arch [A] 347:197–210

Björkerud S, Bondjers G (1973) Arterial repair and atherosclerosis after mechanical injury: tissue response after induction of a larger superficial transverse injury. Atherosclerosis 18:235–255

Bremer JL (1924) On the variations of wall thickness in embryonic arteries. Anat Rec 27:1–14

Brown G, Albers JJ, Fisher LD, et al (1990) Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 323:1289–1298

Caro CG, Parker KH, Fish PJ, Lever MJ (1985) Blood flow near the arterial wall and arterial disease. Clin Hemor 5:849–871

Cashin-Hemphill L, Mack MJ, Pogoda J, Sanmarco ME, Azen SP, Blankenhorn DH (1990) Beneficial effects of colestipol-niacin on coronary atherosclerosis: a four year follow-up. JAMA 264:3013–3017

Clarkson TB, Weingand KW, Kaplan JR, Adams MR (1987) Mechanisms of atherogenesis. Circulation 76 [Suppl I]:20–28

Constantinides P (1966) Plaque fissuring in human coronary thrombosis. J Atheroscler Res 6:1–17

Constantinides P (1990) Plaque hemorrhages, their genesis and their role in supra-plaque thrombosis and atherogenesis. In: Glagov S, Newman WP, Schaffer SA (eds) Pathobiology of the human atherosclerotic plaque. Springer, Berlin Heidelberg New York, pp 394–411

Cornhill JF, Herderick EE, Stary HC (1990) Topography of human aortic sudanophilic lesions. Monographs on atherosclerosis, vol 15. Karger, Basel, pp 13–19

Cotran RS, Kumar V, Robbins SL (1989) Pathologic basis of disease, 4th edn. Saunders, Philadelphia, p 562

Dartsch PC, Bauriedel G, Schinko I, Weiss HD, Höfling B, Betz E (1989) Cell constitution and characteristics of human atherosclerotic plaques selectively removed by percutaneous atherectomy. Atherosclerosis 80:149–157

Davies MJ (1986) Color atlas of cardiovascular pathology, chapter 6. Ischemic heart disease. Harvey Miller, London

Davies MJ, Thomas AC (1985) Plaque fissuring: the cause of acute myocardial infarction, sudden ischaemic death and crescendo angina. Br Heart J 53:363–373

Dock W (1946) The predilection of atherosclerosis for the coronary arteries. JAMA 131:875–878

Duff L, McMillan GC (1951) Pathology of atherosclerosis. Am J Med 11:92–108

Duff GL, McMillan GC, Ritchie AC (1957) The morphology of early atherosclerotic lesions of the aorta demonstrated by the surface technique in rabbits fed cholesterol. Am J Pathol 33:845–873

Eckmann A, Schmiedt W, Storket S, Kuhn FP (1990) Zur Diagnostik atherosklerotischer Läsionen der extrakraniellen arteria carotis mit Duplexsonographie und IA-DSA. Eine prospektive und pathologisch-anatomisch kontrollierte Studie. ROFO 153:48–55

Edholm G (1912) Über die arteria coronaria cordis des Menschen. Anat Anz 42:124–128

Editorial (1990) Lancet 335:139–140

Ehrich W, Chapelle C de la, Cohn AE (1931) Anatomical ontogeny. B. Man. I. A study of the coronary arteries. Am J Anat 49:241–282

Ellis S, Alderman EL, Cain K, Wright A, Bourassa M, Fisher

L (1989) Morphology of left anterior descending coronary territory lesions as a predictor of anterior myocardial infarction: a CASS registry study. J Am Coll Cardiol 13:1481–1491
Enos WF, Holmes RH, Beyer J (1953) Coronary disease among United States soldiers killed in action in Korea. Preliminary report. JAMA 152:1090–1093
Faggiotto A, Ross R, Harker L (1984) Studies of hypercholesterolemia in the nonhuman primate. I. Changes that lead to fatty streak formation. Arteriosclerosis 4:323–340
Falk E (1991) Coronary thrombosis: pathogenesis and clinical manifestations. Am J Cardiol 68:28B–35B
Fangman RJ, Hellwig CA (1947) Histology of coronary arteries in newborn infants (abstract). Am J Pathol 23:901–902
Fuster V, Stein B, Ambrose JA, Badimon L, Badimon JJ, Chesebro JH (1990) Atherosclerotic plaque rupture and thrombosis. Evolving concepts. Circulation 82 [Suppl II]:II-47-II-59
Fuster V, Badimon L, Badimon JJ, Ip JH, Chesebro JH (1991) The porcine model for the understanding of thrombogenesis and atherogenesis. Mayo Clin Proc 66:818–831
Fuster V, Badimon L, Badimon JJ, Chesebro JH (1992) The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 326:242–250, 310–318
Geer JC, Malcom GT (1965) Cholesterol ester fatty acid composition of human aorta fatty streaks and normal intima. Exp Mol Pathol 4:500–507
Geer JC, McGill HC, Robertson WB, Strong JP (1968) Histologic characteristics of coronary artery fatty streaks. Lav Invest 18:565–570
Gerrity RG (1981) The role of the monocyte in atherogenesis. I. Transition of blood-borne monocytes into foam cells in fatty lesions. Am J Pathol 103:181–190
Glagov S, Zarins CB (1989) Is intimal hyperplasia an adaptive response or a pathologic process? Observations on the nature of nonatherosclerotic intimal thickening. J Vasc Surg 10:571–573
Goes E, Janssens W, Maillet B, Freson M, Steyaert L, Osteaux M (1990) Tissue characterization of atheromatous plaques: correlation between ultrasound image and histological findings. J Clin Ultrasound 18:611–617
Gore I, Tejada C (1957) The quantitative appraisal of atherosclerosis. Am J Pathol 33:875–885
Gotto AM Jr (1985) Some reflections on arteriosclerosis: past, present, and future. Circulation 72:8–17
Gross L, Epstein EZ, Kugel MA (1934) Histology of the coronary arteries and their branches in the human heart. Am J Pathol 10:253–273
Guzman MA, McMahan CA, McGill HC Jr, Strong JP, Tejada C, Restrepo C, Eggen DA, Robertson WB, Solberg LA (1968) Selected methodologic aspects of the International Atherosclerosis Project. Lab Invest 18:479–497
Haimovici H (1977) Atherogenesis. Recent biological concepts and clinical implications. Am J Surg 134:174–178
Höfling B, Polnitz A von, Backa D, Meissner R, von Arnim T, Jauch G, Remberger K (1989) Angiographische und funktionelle Ergebnisse sowie histologische Befunde nach perkutaner Atherektomie bei Patienten mit arterieller Verschlusskrankheit. Z Kardiol 78:561–566
Imai H, Connell CE, Lee KT, Kim DN, Thomas WA (1985) Differential counts by electron microscopy of cell types in normal intimal cell masses in swine abdominal aortas. Exp Mol Pathol 42:377–388
Ip JJ, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH (1990) Syndromes of accelerated atherosclerosis: role of vascular injury and smooth muscle cell proliferation. J Am Coll Cardiol 15:1667–1687
Jaffe D, Hartroft WS, Manning M, Eleta G (1971) Coronary arteries in newborn children. Acta Paediatr Scand [Suppl] 219:1–28
Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK (1986) Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. Arteriosclerosis 6:131–138
Jores L (1921) Die Entwicklung der Lehre von der Arteriosklerose seit Virchow. Virchows Arch 235:262–272
Jores L (1924) Arterien. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie und Histologie, vol 2. Herz und Gefässe. Springer, Berlin Heidelberg New York, pp 608–786
Joris I, Zand T, Nunnari JJ, Krolikowski FJ, Majno G (1983) Studies on the pathogenesis of atherosclerosis. I. Adhesion and emigration of mononuclear cells in the aorta of hypercholesterolemic rats. Am J Pathol 113:341–358
Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ (1990) Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA 264:3007–3012
Katsuda S, Boyd HC, Fligner C, Ross R, Gown AM (1992) Human atherosclerosis. III. Immunocytochemical analysis of the cell composition of lesions of young adults. Am J Pathol 140:907–914
Katz SS, Shipley GG, Small DM (1976) Physical chemistry of the lipids of human atherosclerotic lesions. Demonstration of a lesion intermediate between fatty streaks and advanced plaques. J Clin Invest 58:200–211
Kim DN, Lee KT, Schmee J, Thomas WA (1984) Quantification of intimal cell masses and atherosclerotic lesions in coronary arteries of control and hyperlipidemic swine. Atherosclerosis 52:115–122
Kovanen PT (1990) Atheroma formation: defective control in the intimal round-trip of cholesterol. Eur Heart J 11 [Suppl E]:238–246
Lewis JC, Taylor RG, Jerome WG (1985) Foam cell characteristics in coronary arteries and aortas of White Carneau pigeons with moderate hypercholesterolemia. Ann NY Acad Sci 454:91–100
Long ER (1933) The development of our knowledge of arteriosclerosis. In: Cowdry EV (ed) Arteriosclerosis. A survey of the problem. McMillan, New York, pp 19–52
Long ER (1967) Development of our knowledge of arteriosclerosis. In: Blumenthal HT (ed) Cowdry's arteriosclerosis. A survey of the problem. Thomas, Springfield, pp 5–20
Mauer AM (1986) Risk factors in children and early atherosclerosis (letter). N Engl J Med 314:1579
Mauer AM (1987) Atherosclerosis (letter). Pediatrics 79:651–653
McGill HC (1974) The lesion. In: Schettler G, Weizel A (eds) Atherosclerosis III. Springer, Berlin Heidelberg New York, pp 27–38
McGill HC, Strong JP, Holman RL, Werthessen NT (1960) Arterial lesions in the Kenya baboon. Circ Res 8:670–679
McMillan GC (1965) The onset of plaque formation in arteriosclerosis. Acta Cardiol [Suppl XI]:43–62
McMillan GC (1985) Nature and definitions of atherosclerosis. In: Lee KT (ed) Atherosclerosis. Ann NY Acad Sci 454:1–4
Minkowski WL (1947) The coronary arteries of infants. Am J Med Sci 214:623–629
Mitchell JRA, Schwartz CJ (1965) Arterial disease. Davis, Philadelphia
Møller L, Kristensen TS (1991) Plasma fibrinogen and ischemic heart disease risk factors. Arterioscler Thromb 11:344–350
Moon HD (1957) Coronary arteries in fetuses, infants, and juveniles. Circulation 16:263–267
Movat HZ, More RH, Haust MD (1958) The diffuse intimal thickening of the human aorta with aging. Am J Pathol 34:1023–1031
Munro JM, Van der Walt JD, Munro CS, Chalmers JAC, Cox EL (1987) An immunohistochemical analysis of human aortic fatty streaks. Hum Pathol 18:375–380
Myler RK, Shaw RE, Stertzer SH, Bashour TT, Ryan C, Hecht HS, Cumberland DC (1990) Unstable angina and coronary angioplasty. Circulation 82 [Suppl II]:II-88-II-95
Neufeld HN, Wagenvoort CA, Edwards JE (1962) Coronary arteries in fetuses, infants, juveniles, and young adults. Lab Invest 11:837–844
Ornish DM, Brown SE, Scherwitz LW, Billings JH, Armstrong

WT, Ports TA, McLanahan SM, Kirkeeide RL, Brand RJ, Gould KL (1990) Can lifestyle changes reverse coronary heart disease? Lancet 336:129–133
Pflieger H, Goerttler K (1970) Konstruktionsprinzipien der Aortenwand im Ursprungsbereich der interkostalen, intestinalen und renalen Aortenäste. Arch Kreislaufforsch 62:223–248
Richardson M, Hatton MWC, Moore S (1988) Proteoglycan distribution in the intima and media of the aortas of young and aging rabbits: an ultrastructural study. Atherosclerosis 71:243–256
Richardson PD, Davies MJ, Born GVR (1989) Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet II:941–944
Robertson JH (1960) The significance of intimal thickening in the arteries of the newborn. Arch Dis Child 35:588–590
Roessner A, Schmitz G, Sorg C (1987) What's new in the pathology of atherosclerosis? Pathol Res Pract 182:694–698
Ross R (1986) The pathogenesis of atherosclerosis: an update. N Engl J Med 314:488–500
Schmidtmann M (1925) Das Vorkommen der Arteriosklerose bei Jugendlichen und seine Bedeutung für die Ätiologie des Leidens. Virchows Arch 255:206–223
Schornagel HE (1956) Intimal thickening in the coronary arteries in infants. Arch Pathol 62:427–432
Schwenke DC, Carew TE (1988) Quantification in vivo of increased LDL content and rate of LDL degradation in normal rabbit aorta occurring at sites susceptible to early atherosclerotic lesions. Circ Res 62:699–710
Schwenke DC, Carew TE (1989) Initiation of atherosclerotic lesions in cholesterol-fed rabbits. I. Focal increases in arterial LDL concentration precede development of fatty streak lesions. Arteriosclerosis 9:895–907
Simionescu N, Vasile E, Lupu F, Popescu G, Simionescu M (1986) Prelesional events in atherogenesis. Accumulation of extracellular cholesterol-rich liposomes in the arterial intima and cardiac valves of the hyperlipidemic rabbit. Am J Pathol 123:109–125
Small DM (1988) Progression and regression of atherosclerotic lesions. Arteriosclerosis 8:103–129
Smith EB, Smith RH (1976) Early changes in aortic intima. In: Paoletti R, Gotto AM Jr (eds) Atherosclerosis reviews, vol 1. Raven Press, New York, pp 119–136
Spring PM, Hoff HF (1989) LDL accumulation in the grossly normal human iliac bifurcation and common iliac arteries. Exp Mol Pathol 51:179–185
Stary HC (1974) Proliferation of arterial cells in atherosclerosis. In: Wagner WD, Clarkson TB (eds) Arterial mesenchyme and arteriosclerosis. Adv Exp Med Biol 43:59–81
Stary HC (1976) Coronary artery fine structure in rhesus monkeys: the early atherosclerotic lesion and its progression. Primates Med 9:359–395
Stary HC (1987a) Macrophages, macrophage foam cells, and eccentric intimal thickening in the coronary arteries of young children. Atherosclerosis 64:91–108
Stary HC (1987b) Atheroma arises in eccentric intimal thickening from concurrent fatty streak lesions. Fed Proc 46:418
Stary HC (1989) Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis 9 [Suppl I]:19–32
Stary HC (1990) The sequence of cell and matrix changes in atherosclerotic lesions of coronary arteries in the first forty years of life. Eur Heart J 11 [Suppl E]:3–19
Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull W, Rosenfeld ME, Richardson M, Schaffer SA, Schwartz CJ, Wagner WD, Wissler R (1992) A definition of the intima of human arteries and of its atherosclerosis-prone regions. Circulation 85:391–405
Stehbens WE (1960) Focal intimal proliferations in the cerebral arteries. Am J Pathol 36:289–301
Steinberg D, Witztum JL (1990) Lipoproteins and atherogenesis. Current concepts. JAMA 264:3047–3052
Stemerman MB, Ross R (1973) Experimental arteriosclerosis: 1. Fibrous plaque formation in primates: an electron microscopic study. J Exp Med 136:769–789
Still WJS, O'Neal RM (1962) Electron microscopic study of experimental atherosclerosis in the rat. Am J Pathol 40:21–35
Strasser T (1980) Primary prevention: the role of the World Health Organization. In: Lauer RM, Shekelle RB (eds) Childhood prevention of atherosclerosis and hypertension. Raven Press, New York, pp 473–476
Thoma R (1883) Über die Abhängigkeit der Bindegewebsneubildung in der Arterienintima von den mechanischen Bedingungen des Blutumlaufes. Erste Mitteilung. Virchows Arch 93:443–505
Thoma R (1920) Über die Strömung des Blutes in der Gefässbahn und die Spannung der Gefässwand. I. Teil. Beitr Pathol Anat Allg Pathol 66:92–158
Velican C, Velican D (1977) Studies on human coronary arteries I. Branch pads or cushions. Acta Anat 99:377–385
Velican C, Velican D (1980) The precursors of coronary atherosclerotic plaques in subjects up to 40 years old. Atherosclerosis 37:33–46
Wight TN, Ross R (1975) Proteoglycans in primate arteries. I. Ultrastructural localization and distribution in the intima. J Cell Biol 67:660–674
Wilens SL (1951) The nature of diffuse intimal thickening of arteries. Am J Pathol 27:825–839
Williams AE, Freeman MR, Chisholm RJ, Patt NL, Armstrong PW (1988) Angiographic morphology in unstable angina pectoris. Am J Cardiol 62:1024–1027
Wolkoff K (1923) Über die histologische Struktur der Coronararterien des menschlichen Herzens. Virchows Arch 241:42–58
Wolkoff K (1929) Über die Atherosklerose der Coronararterien des Herzens. Beitr Pathol Anat Allg Pathol 82:555–596
World Health Organization (1958) Classification of atherosclerotic lesions; report of a study group. WHO Tech Rep Ser 143:1–20
Wright HP (1968) Endothelial mitosis around aortic branches in normal guinea pigs. Nature 220:78–79
Yarnell JWG, Baker IA, Sweetnam PM, Bainton D, O'Brien JR, Whitehead PJ, Elwood PC (1991) Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. Circulation 83:836–844
Yater WM, Traum AH, Brown WG, Fitzgerald RP, Geisler MA, Wilcox BB (1948) Coronary artery disease in men eighteen to thirty-nine years of age. Am Heart J 36:334–372, 481–526, 683–722
Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S (1983) Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ Res 53:502–514