CHAPTER 43

Nature of the Atherosclerotic Lesions Underlying IHD

Hypothesis-2 is fully stated at the outset of Chapter 39. In order to discuss it (in Chapters 44, 45, and 46), we need to become more specific about "the coronary arteries" and about the lesions of "coronary atherosclerosis" --- which we described in Chapter 39 only as a build-up in the arterial wall of material (atherosclerotic "plaque") which finally intrudes into the lumen and obstructs the blood-flow, partially or completely.

• Part 1. The Walls of the Coronary Arteries

The right and left coronary arteries each depart, from the ascending aorta, very close to the aorta's exit from the the heart's left side. The right and left coronary arteries "return" to the exterior surface of the heart, where they each divide into several branches which have their own names and which are known collectively as "the coronary arteries" or just "the coronaries." The coronary arteries supply the heart with the freshly oxygenated blood which it (like other organs) requires in order to survive and to operate.

The artery is an elastic tube which consists of three major structural regions, or layers, named the intima, the media, and the adventitia. These three regions show major dissimilarities in composition. The dangerous events occur mainly, but not totally, in the intimal layer of the arterial wall.

The Intimal Layer and Internal Elastic Membrane

The inner aspect of the intimal wall (the aspect next to the flowing blood) is lined by a single layer of cells known as endothelial cells. Much has been said and written, about the role of injury to these endothelial cells in development of atherosclerosis, but little is known with certainty.

The intima, when it is healthy, is the thinnest layer of the arterial wall. The intima consists of a little cellular material and a sparse matrix of collagen fibers. There are relatively few elastic fibers in the intima.

Separating the intima and the media is a continuous structure made of elastic tissue, and referred to as the internal elastic membrane, or "the internal elastica." Approximately 1% of the area of the internal elastica consists of channels or "fenestra" (Young 1960), linking the intima with the next layer, the media.

The Media Layer

The media layer is that layer which contributes to the elastic functions of the arterial wall. Normally, the media is much thicker than the intima. There are two major elements in the media layer: (1) a thick network of elastic tissue, which is interspersed with (2) smooth muscle cells (akin to those in the intestinal walls, the uterine muscle walls, and still other organs).

The Adventitia

The adventitia is the outer coat of the arterial wall. It consists primarily of fibrous tissue of the collagen variety, rather than elastin. There are very small vessels in the adventitia, whose function appears to be the provision of nourishment and waste disposal for the arterial wall itself.

Relative Thicknesses of the Layers

In arteries with an outer diameter of about 2,000 micrometers, measurements have shown the following ranges, in micrometers (Gofman 1963, p.203): Intima, 2.5-5.8. Internal Elastica, 3.7-6.1. Media, 182-212. Adventitia, 71-91. Arteries require a blood-supply of their own, of course, and it is delivered by the "vasa vasorum" within the artery wall.

The Presence of "Collaterals"

When the lumen of an artery becomes obstructed, the body commonly attempts to generate a network of capillaries and arterioles which by-pass the obstruction. When this process (angiogenesis) is successful, the resulting new vessels are called "collaterals." The stimulation of coronary angiogenesis is an active field of research.

• Part 2. Coronary Atherosclerosis: Still a Controversial Topic

• "Thrombus formation is the proximate cause of myocardial infarction, but atherosclerosis, the chief underlying cause, is a chronic disease that progresses over decades of life" (Ridker 1997, p.973, citing Fuster 1992).

2a. Raging Debates on Initiation, Progression, Reversal of the Process

Atherosclerotic lesions or atheromata, commonly called "plaques," develop in the intima and then ultimately protrude into the lumen to various degrees. The plaques are localized, with regions free from the pathology adjacent to regions which are deeply involved. Why discontinuity occurs, needs explanation.

There is anything BUT agreement on exactly what starts the atherosclerotic process, what determines its rate of progression, and what reversibility there is for different types of the pathological material laid down in the artery wall. The differences among investigators are large, and many diverse proposals are made, and re-made, concerning the events which describe the evolution of various lesions. Moreover, confirmation of one hypothesis would not automatically rule out validity for several other hypotheses. There may be more than one route to a single result, and within any route, co-action by multiple causes may be required.

While some books and articles describe the atherosclerotic process as though it were thoroughly understood, it is not. In 1997, Attilio Maseri editorialized about atherosclerosis and ischemic events in the New England Journal of Medicine. He commented (Maseri 1997, p.1015): "Ischemic heart disease is appearing to be an ever more complex syndrome ..."

2b. An "Infinite Variety" of Lesions Observed

What does seem quite certain is that some pathologic changes occur acutely, while other changes occur in a sequence of events over months, years, and decades. Legions of investigators frequently have to study a lengthy process from evidence which represents just one particular stage --- but different stages for different investigators. They necessarily see different things and report different findings. They are often studying different "snapshots" (frames) extracted from a three-hour "film epic." Elspeth B. Smith, who has made some excellent contributions on the problem of what happens in arterial walls, has commented perceptively (Smith 1977, p.673):

"Clearly, there is a very complicated system within the intima ... This system must be infinitely variable, which would be compatible with the infinite variety of lesions found in human arteries."

2c. Efforts to Define and Classify Atherosclerotic Lesions

In any attempt to communicate, shared definitions help a lot. Chemists would not make much progress if they were at liberty to define the element "carbon" in any way they wish. So, to facilitate fruitful communication among the legions of investigators in Ischemic Heart Disease, the American Heart Association formed a committee. In 1994, the committee took over 8 pages of fine-print and a list of 213 references to present and discuss "A Definition of Initial, Fatty Streak, and Intermediate

Lesions of Atherosclerosis" (Stary 1994 in our Reference List). We quote from the first page (Stary 1994, p.840):

"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." And (Stary 1994, p.840):

"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 advanced, trouble-making lesions, also classified by the American Heart Association, are types IV, Va, Vb, Vc, and VI. (Stary 1995 in our Reference List).

• Part 3. Characteristics of the "Typical" Lesions

Despite the variety of atherosclerotic lesions, the literature is filled with some very good attempts to describe "typical" or "usual" lesions. Below, we present a few, in approximately chronological order. With some workers stressing one aspect more than another, the combined descriptions cover the topic well. It may be worth noting that the word "athero" itself is Greek for gruel or porridge. According to legend, pathologists who saw a resemblance between such food and many arterial lesions, produced the name "atherosclerosis."

3a. 1976, Earl P. Benditt's Description of a Commonly Seen Plaque

Earl P. Benditt is a professor of pathology (now emeritus) at the University of Washington School of Medicine in Seattle. He has provided a very good description of the chief morphological changes which occur with atherosclerosis development. We quote (Benditt 1976, p.96):

"The form of the atherosclerotic lesions most commonly seen in vessels of humans at autopsy is a smooth-surfaced mass raised above the level of surrounding nonatherosclerotic vascular intima. Such raised lesions which vary in color from pearl gray to faint yellow-gray, are, on histological examination, composed of cells embedded in dense extracellular connective tissue. Selective stains identify collagen as the main connective tissue fibrillar constituent and elastin usually as a minor or variable constituent. Glycosaminoglycans [GAG] are present in varying amounts in the extracellular matrix. These histological findings are confirmed by electron microscopy. The electron microscope reveals, furthermore, that the cells embedded in and responsible for the production of the extracellular matric substances have properties that identify them as smooth muscle (Haust 1960, + Geer 1961, + Doud 1964)." And (Benditt 1976, p.96):

"Lipid stains and electron microscope examination show that the smooth muscle cells usually contain very little fat, except in the deeper layers of the plaques. In some plaques, lipid is present, and substantial amounts of cholesterol can be found both in the deeper layers of the plaque and underlying the plaques. Smooth muscle cells in the deeper layers of plaques, adjacent to the atheromatous debris, frequently exhibit pathologic fatty changes, indicative of cell injury, and cells in the deepest layers frequently appear to be dying and disintegrating." And (Benditt 1976, p.96):

"All of the plaque mass lies in the intima beneath the endothelium and entirely on the luminal side of the internal elastica of the artery. These masses are usually sharply raised (but not sharply demarcated) from the adjacent intima. However, some features of the cellular mass and associated extracellular matrix set it off from the underlying media: Cells of plaques appear to be smaller than cells of normal media. The main extracellular material produced by plaque cells is collagen, whereas elastin is a major item in the aortic media. The arrangement of cells of the plaque lacks the order found in the arterial media, and the number of intercellular junctions appears to be reduced ..." And lastly (Benditt 1976, p.96):

"The impressive feature of the human lesion is the presence of an excessive and apparently useless mass of cells that resemble in many respects, but differ in the subtle ways indicated, the cells

and structures that comprise the media of arteries."

We should emphasize that the "apparently useless mass of cells" and the "atheromatous debris" are by no means INNOCUOUS. This useless debris constitutes important parts of the atherosclerotic process which almost always underlies the clinical occurrence of Ischemic Heart Disease.

3b. 1977, Elspeth B. Smith on the Range of Characteristics

Dr. Elspeth B. Smith was (in 1977) in the Department of Chemical Pathology, University of Aberdeen in Scotland. Smith comments (Smith 1977, p.669):

"The plaque with its central pool of atheroma lipid is obviously heterogeneous, and its chemistry changes from region to region ..." And (1977, p.672-673): "The most typical gelatinous lesion has loosely packed, thick, linear collagen bundles lying between rather sparse smooth muscle cells. However, one encounters a complete spectrum of lesion morphology and biochemistry, extending from extremely loose lesions that seem to contain pools of plasma insudate (Haust 1971) and have an LDL [low-density lipoprotein] content five to six times greater than adjacent normal intima, to mounds of densely packed smooth muscle cells with a lower than normal LDL content which frequently have not accumulated lipid (Smith 1976). Are these originally the same lesions that have developed differently, or do the gelatinous lesions have a different origin from the pure smooth-muscle-cell proliferation ... ?"

Here is probably an example of the "snapshot" phenomenon (Part 2b). Whenever pathologists study "snapshots" of a disorder which is progressing through days, weeks, months, and many years, the "snapshots" may be very difficult to convert into the real sequence of what preceded what (or what occurred independently), and into an explanation of how nature accomplished it.

3c. 1977 & 1993, Russell Ross on Features of Atherosclerotic Lesions

The late Dr. Russell Ross was in the Department of Pathology, University of Washington School of Medicine, in Seattle. Ross and co-workers state (Ross 1977, p.676):

"Three principal events are associated with the formation of the lesions of atherosclerosis. These are: a) intimal proliferation of smooth muscle cells, b) formation by these cells of large amounts of connective tissue matrix including collagen, elastic fibre proteins, and proteoglycans, and c) deposition of intracellular and extracellular lipid that eventually results in the formation of a pool of lipid and cell debris in the deeper portion of the more extensive or complicated lesions." For comparison, we also provide a description by Ross in 1993 (Ross 1993, p.801):

"The earliest recognizable lesion of atherosclerosis is the so-called 'fatty streak,' an aggregation of lipid-rich macrophages and T lymphocytes within the innermost layer of the artery wall, the intima ... Animal observations have shown that fatty streaks precede the development of intermediate lesions, which are composed of layers of macrophages and smooth muscle cells and, in turn, develop into the more advanced, complex, occlusive lesions called fibrous plaques. The fibrous plaques increase in size and, by projecting into the arterial lumen, may impede the flow of blood. They are covered by a dense cap of connective tissue with embedded smooth muscle cells that usually overlays a core of lipid and necrotic debris. The fibrous plaques contain monocyte-derived macrophages, smooth muscle cells and T lymphocytes, many of which are activated ..." Later in the same paper, Ross takes note of another fact (Ross 1993, p.804):

"During the most advanced stages of atherogenesis as the lesions become thicker, fibrous plaques become vascularized and contain large numbers of capillary and venule-like channels."

3d. 1988, Munro and Cotran on a "Typical Cellular Plaque"

J. Michael Munro and Ramzi S. Cotran were (in 1988) in the Departments of Pathology at Brigham and Women's Hospital and Harvard Medical School, when they presented an "overreview" on the pathogenesis of atherosclerosis (Munro 1988). In their paper, they state (Munro 1988, p.250):

"Plaques exhibit histologic variability, but a typical cellular plaque consists of: a fibrous cap, composed mostly of smooth muscle cells with a few leukocytes, and relatively dense connective tissue

containing elastin, collagen fibrils, proteoglycans, and basement membrane (Kramsch 1971, + Murata 1986, + Yla-Herttuala 1986); a cellular area beneath and to the side of the cap consisting of a mixture of macrophages, smooth muscle cells, and T lymphocytes (Jonasson 1986); and a deeper 'necrotic core' which contains cellular debris, extracellular lipid droplets, cholesterol crystals, and calcium deposits. This necrotic core often contains numerous large foam cells of both the macrophage and smooth muscle type. [Foam cells are cells whose cytoplasm looks "foamy" due to the presence therein of lipids.] Finally, one can sometimes see, particularly around the periphery of the lesions, proliferating small blood vessels, which are evidence of neo-vascularization from the direction of the adventitia. The relative content of fibrous tissue and lipid within a plaque is variable; coronary artery lesions are often largely fibrous."

3e. 1995, Peter Libby on the "Typical" Atherosclerotic Plaque

Peter Libby was (in 1995) in the Department of Medicine's Vascular Medicine and Atherosclerosis Unit, at Brigham and Women's Hospital in Boston, when he wrote (Libby 1995, p.2845):

"... pathological studies have shown repeatedly in humans and in experimental animals that over much of its history, growth of an atherosclerotic plaque occurs by outward, abluminal [away from the lumen] expansion (Clarkson 1994, + Glagov 1987, + Armstrong 1989). Hence, most obstructive plaques may pass through a phase that may last many years or even decades of so-called 'remodeling' without encroaching on the arterial lumen. Only after the plaque burden approaches half of the luminal area does the plaque usually protrude into the lumen, becoming visible by angiography and capable of impairing flow." Blankenhorn and Hodis also emphasize this point (Blankenhorn 1994, p.178):

"The arterial wall undergoes compensatory remodeling as lesions form (Glagov 1987) in response to changing shear stress on the endothelium (Stary 1992). As a result, extensive atherosclerosis can be present before lesions intrude into the vessel lumen (Glagov 1987)." We return now to Libby (Libby 1995, p.2845):

"Atherosclerotic plaques typically consist of a lipid-rich core in the central portion of the eccentrically thickened intima. The lipid core is bounded on its luminal aspect by a fibrous cap, at its edges by the 'shoulder' region, and on its abluminal aspect by the base of the plaque. The central, lipid-rich core of the typical lesion contains many lipid-laden macrophage foam cells derived from blood monocytes. Once resident within the arterial wall, these cells imbibe lipid, which accounts for their foamy cytoplasm."

Of course, it is the natural function of macrophages to attempt to engulf any "foreign" material --- any material which is "out of place" in the body.

• Part 4. A Recent Warning about Defects in Clinical Evaluations

David H. Blankenhorn was, at the time he gave the George Lyman Duff Memorial Lecture for the American Heart Association in November 1992, at the Atherosclerosis Research Institute of the University of Southern California School of Medicine. Soon thereafter, he became very ill with recurring prostate cancer. Before his death in May 1993, Dr. Blankenhorn requested Howard N. Hodis to complete the work entitled "Arterial Imaging and Atherosclerosis Reversal," from which we quote (Blankenhorn 1994).

Among the many important points in their paper, Blankenhorn and Hodis emphasize that the ability to DETECT whether atherosclerotic disease is progressing or regressing, as the result of various therapies, is critical to improvement of treatments (p.178). "Lesion staging is necessary for studies of progression and regression ... scales used to grade atherosclerosis from images are rudimentary. Angiography [an xray procedure] measures the internal vessel lumen, and we infer lesion severity from the extent of lumen lost."

They explain that the most widely used measure is "%S" --- meaning percent stenosis (narrowing) at the narrowest point in a vessel, compared with the diameter of a "normal" segment. And (p.178): "Clinicians typically stage coronary artery lesions on a scale of 3: complete occlusion, >= 50%S, and <50%S." A "high-grade" stenosis is regarded as >= 70%S.

The warning given by Blankenhorn and Hodis is that, not only is angiography unable to detect progression or regression for all the plaques which do not intrude into the lumen, but that too much emphasis is placed on the most stenotic lesions: "Accumulating evidence indicates that acute clinical events [myocardial infarction, unstable angina, sudden ischemic death] result from instability of small, lipid-rich plaques rather than large, fibrotic, calcified, stenosing plaques (Fuster 1992). Although large plaques tend to progress to total occlusion more frequently than small plaques, occlusion by large plaques infrequently results in acute clinical events because of the formation of collateral vessels."

They argue that more progress will be made in reducing IHD mortality when angiography is supplemented by some additional techniques which can also measure the pre-intrusive atherosclerotic lesions in study-populations and in the population at large.

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