Lessons From Sudden Coronary Death
A Comprehensive Morphological Classification Scheme for Atherosclerotic Lesions
Renu Virmani, Frank D. Kolodgie, Allen P. Burke, Andrew Farb, Stephen M. Schwartz

This review will reconsider the current paradigm for understanding the critical, final steps in the progression of atherosclerotic lesions. That scheme, largely an outgrowth of observations of autopsy tissues by Davies and colleagues,1,2 asserts that the cause of death in atherosclerotic coronary artery disease is rupture of an advanced atherosclerotic lesion. Although this assumption may be partially true, recent autopsy studies suggest that it is incomplete.

To reconsider this paradigm, we reexamined the morphological classification scheme for lesions proposed by the American Heart Association (AHA).3,4 This scheme is difficult to use for 2 reasons. First, it uses a very long list of roman numerals modified by letter codes that are difficult to remember. Second, it implies an orderly, linear pattern of lesion progression. This tends to be ambiguous, because it is not clear whether there is a single sequence of events during the progression of all lesions. We have therefore tried to devise a simpler classification scheme that is consistent with the AHA categories but is easier to use, able to deal with a wide array of morphological variations, and not overly burdened by mechanistic implications.

The Current Paradigm

The current paradigm is based on the belief that type IV lesions, or “atheromas,” described by the AHA are stable because the fatty, necrotic core is contained by a smooth muscle cell–rich fibrous cap. Virchow’s analysis5 in 1858 pointed out that historically, the term “atheroma” refers to a dermal cyst (“Grützbalg”), a fatty mass encapsulated within a cap. Extending Virchow’s argument, the fibrous cap over the lipid mass of an atherosclerotic plaque is analogous to the capsule containing an abscess, and like an abscess, the plaque can be ruptured. Rupture of the fibrous cap exposes thrombogenic material, initiating platelet aggregation and coagulation in the infiltrating and overlying blood. These thrombotic changes result from activation of the clotting cascade by tissue factor, and further propagation of the thrombosis results from the interaction of platelets with the active thrombogenic matrix.6 Platelet activation and thrombin formation combined with the evulsion of thrombogenic plaque contents into the lumen then result in sudden occlusion.7

This widely held concept of atherosclerotic death is based on morphological data from autopsies as well as clinical angiographic studies, in which the presence of surface irregularities has been interpreted as plaque rupture.8–10 Previous pathological studies of sudden coronary death have demonstrated evidence of plaque rupture associated with thrombosis in 73% of cases.2 Of the remaining cases, 8% consist of plaque fissure with intraplaque fibrin deposition and hemorrhage, while 19% show no evidence of thrombi.2 Consequently, recent reviews of atherosclerosis have uniformly accepted plaque rupture as the critical event leading to coronary artery death.6

Limitations

The major limitation of the present paradigm is the lack of a direct, experimental test in a prospective model in humans or animals. For example, lesions in current animal models rarely progress beyond the stage of atheroma (ie, a well-developed fibrous cap overlying a necrotic core). More often, lesions consist of masses of lipid-laden intimal macrophages without a well-developed fibrous cap. Lesions with this histology are rarely clinically significant except in examples of severe hyperlipemia, in which the lumen can become occluded by the sheer plaque burden.11 As we will review, this situation is quite atypical of human disease. The general failure to observe clinically significant lesions in animals may be a simple function of the relatively short duration of most experimental studies, as suggested by 1 long-term study in a unique strain of hyperlipemic swine.12

Analysis of human arteries also has its inadequacies. Given the limited ability of current clinical imaging methods to visualize the vessel wall, as opposed to the lumen,13 we are highly dependent on autopsy material. Those autopsy studies are not entirely consistent with the current paradigm. These inconsistencies, as discussed below, could mean that the
Autopsy population is biased (ie, representing mostly young, sudden coronary death victims and excluding nonfatal clinical events), that the paradigm is incorrect, or, as we will suggest, that the paradigm is incomplete. If the latter is the case, we need to consider other ways, besides rupture, in which an atherosclerotic plaque can produce sudden coronary death.

It is very important to realize that the presence of a plaque rupture does not imply a causal association with the thrombus that occluded the lumen. There is ample evidence that nonfatal lesions can contain areas of rupture. For example, Arbustini and collaborators found a 10% incidence of plaque ruptures in lesions of people who died of noncardiovascular causes. These findings suggest that advanced plaques may undergo many nonfatal ruptures without causing death. Moreover, the existence of nonruptured but fatal lesions suggests that the equation of rupture with death is overly simplistic.

**Exceptions to the Current Paradigm**

Exceptions to the current paradigm have arisen because of 2 recent articles. First, in a series of 20 patients with sudden cardiac death, van der Wal et al found plaque rupture in only 60% of lesions with thrombi; the remaining 40% showed only “superficial erosion.” The term “superficial erosion” was defined as a thrombus confined to the most luminal portion of a fibrous cap in the absence of fissure or rupture after serial sectioning. Approximately half of the eroded lesions showed a fibrous cap heavily infiltrated by macrophages and T lymphocytes overlying an atheromatous core. The remaining cases were associated with fibrocellular caps without a necrotic core containing mostly smooth muscle cells and a paucity of macrophages and T lymphocytes.

The second set of data evolved from examinations in the laboratory performed by 1 of us (R.V.). We studied the coronary vasculature of >200 cases of sudden coronary death (Table 1). The definition of “sudden coronary death” was based on an unexpected death witnessed within 6 hours of the onset of symptoms or death of a person known to be in stable condition for <24 hours antemortem. The histological criteria for sudden coronary death included luminal thrombi in 1 or more arteries or in at least 1 major coronary artery with 75% cross-sectional area luminal narrowing. As shown in Table 1, only one third of the lesions in our studies could be described as plaque rupture, and remarkably, 35% of lesions with thrombi failed to show rupture. Many of these lesions, unlike those described by van der Wal et al, did not show significant inflammation. In our series, macrophages and other inflammatory cells were the exception; instead, abundant, often arborized smooth muscle cells embedded in a proteoglycan-rich matrix characterized the eroded tissue.

Altogether, these data suggest that coronary thrombi can arise without rupture. Furthermore, because the plaque subjacent to the thrombus in erosion typically does not show inflammatory cells, the data also contradict the prevailing notion that inflammation is a necessary event leading to thrombotic occlusion of coronary arteries. Thrombotic occlusion in the absence of rupture also raises a critical question about the central role of rupture in the current AHA paradigm. If thrombi occur without rupture, how can one know whether the presence of rupture in a thrombosed vessel is not an incidental phenomenon?

**Issues Excluded From the AHA Classification Scheme**

Table 2 shows the current classification scheme as proposed by the AHA. Not addressed in this scheme in direct relation to sudden coronary death are 2 matters that, though potentially important, complicate efforts of classifying lesions. These issues are death without occlusion and the relationship of luminal narrowing to other features of plaque progression.

Despite the diagnosis of sudden coronary death, direct implication of death resulting from sheer plaque burden in the absence of thrombi is vexing. In our series, 26% of cases classified as sudden coronary death failed to show direct evidence of thrombi but were diagnosed as undergoing sudden cardiac arrest with severe coronary atherosclerosis (Table 1). In these cases, lesions of AHA category types Va, Vb, and Vc—all plaques showing significant stenosis without thrombi—were the presumed cause of death because a complete autopsy, including a toxicology screen, failed to indicate other causes. It is conceivable that death associated with severe coronary narrowing resulted from noncardiac causes or a lethal arrhythmia triggered by myocardial ischemia. Alternatively, healed myocardial infarcts were found in 50% of these stable lesions without thrombi at the time of death.

### Table 1. Distribution of Culprit Plaques by Sex and Age in 241 Cases of Sudden Coronary Death

<table>
<thead>
<tr>
<th>Acute Thrombi</th>
<th>Men</th>
<th>Women</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;50 years</td>
<td>&gt;50 years</td>
<td>&lt;50 years</td>
</tr>
<tr>
<td>Rupture</td>
<td>45 (46)</td>
<td>19 (23)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Erosion</td>
<td>17 (17)</td>
<td>8 (10)</td>
<td>14 (42)</td>
</tr>
<tr>
<td>Calcified Nodule</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Organized Thrombi</td>
<td>15 (15)</td>
<td>27 (33)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>No Thrombi: Fibrocalcific Plaque</td>
<td>45 (46)</td>
<td>52 (22)*</td>
<td>13 (40)</td>
</tr>
</tbody>
</table>

*Organized thrombi with healed myocardial infarct (HMI) = 46/52, 89%.
†No thrombi (stable plaque) with HMI = 32/64 (50%); thus, 32/241, or 13%, of sudden death cases have stable plaque with HMI.
autopsy, indicating that at some point during the life of the patient, a thrombus was most likely present. Thus, the “culprit lesion” in these patients initially had a thrombus that underwent spontaneous lysis, recanalized, or was nonocclusive.

The second topic is the relationship of lesion morphology to lumen area reduction. Some pathologists are of the opinion that severe stenosis is a prerequisite for plaque rupture and luminal thrombosis. However, angiographic studies before and after myocardial infarction frequently show that preexisting lesions at the sites of complete occlusion are not usually accompanied by hemodynamically significant stenosis (ie, >50% diameter reduction). From experience in 1 of our laboratories (R.V.), cross-sectional luminal narrowing of >75% is not a prerequisite for luminal thrombosis, either acute or healed, or for the development of intraplaque hemorrhage. We have shown that in sudden coronary death patients who died of luminal thrombosis, at least 50% of the thrombi occurred at lesion sites with <75% cross-sectional area stenosis by plaque (corresponding to <50% diameter reduction).

Repeated ruptures, however, may be responsible for plaque progression. In a recent report (R.V.), healed plaque ruptures had an overall final stenosis of 80% cross-sectional area luminal narrowing, although the percent stenosis before the final rupture (old lumen) showed only 66% cross-sectional area narrowing (<50% diameter reduction). We will return to this issue later as part of the discussion of the use of our classification scheme to identify critical mechanisms of sudden coronary death.

**Modifications of the AHA Classification**

Our proposed changes to the AHA classification are shown in Table 3 and Figure 1. This modification focuses primarily on the AHA classification of type IV, V, and VI lesions. These

<table>
<thead>
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<th>TABLE 2. Current AHA Classification</th>
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<tr>
<td>Terms for Atherosclerotic Lesions in Histological Classification</td>
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<tr>
<td>Type I lesion: Initial lesion</td>
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<tr>
<td>Type II lesion:</td>
</tr>
<tr>
<td>IIa Progression-prone type II lesion</td>
</tr>
<tr>
<td>IIb Progression-resistant type II lesion</td>
</tr>
<tr>
<td>Type III lesion: Intermediate lesion (preatheroma)</td>
</tr>
<tr>
<td>Type IV lesion: Atheroma</td>
</tr>
<tr>
<td>Va Fibroatheroma (type V lesion)</td>
</tr>
<tr>
<td>Vb Calcific lesion (type VII lesion)</td>
</tr>
<tr>
<td>Vc Fibrotic lesion (type VIII)</td>
</tr>
<tr>
<td>Type VI lesion: Lesion with surface defect and/or hematoma/hemorrhage and/or thrombotic deposit</td>
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<th>TABLE 3. Modified AHA Classification Based on Morphological Description</th>
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<tr>
<td>Description</td>
</tr>
<tr>
<td>Nonatherosclerotic intimal lesions</td>
</tr>
<tr>
<td>Intimal thickening</td>
</tr>
<tr>
<td>Intimal xanthoma, or “fatty streak”</td>
</tr>
<tr>
<td>Progressive atherosclerotic lesions</td>
</tr>
<tr>
<td>Pathological intimal thickening</td>
</tr>
<tr>
<td>Erosion</td>
</tr>
<tr>
<td>Fibrous cap atheroma</td>
</tr>
<tr>
<td>Erosion</td>
</tr>
<tr>
<td>Thin fibrous cap atheroma</td>
</tr>
<tr>
<td>Plaque rupture</td>
</tr>
<tr>
<td>Calcified nodule</td>
</tr>
<tr>
<td>Fibrocalcific plaque</td>
</tr>
</tbody>
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TABLE 4. Morphological Characteristics of Culprit and Rupture-Prone Plaques in Cases of Sudden Coronary Death

<table>
<thead>
<tr>
<th>Plaque Type</th>
<th>Necrotic Core, %</th>
<th>Cholesterol Clefts, %</th>
<th>Macrophages, %</th>
<th>Mean No. of Sections With Intraplaque Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture</td>
<td>34±17*</td>
<td>12±12†</td>
<td>26±20‡</td>
<td>2.5±1.3§</td>
</tr>
<tr>
<td>Thin fibrous cap atheroma</td>
<td>23±17</td>
<td>8±9</td>
<td>14±10</td>
<td>...</td>
</tr>
<tr>
<td>Erosion</td>
<td>14±14</td>
<td>2±5</td>
<td>10±12</td>
<td>0</td>
</tr>
<tr>
<td>Fibrocalcific</td>
<td>15±20</td>
<td>4±6</td>
<td>6±8</td>
<td>0.05±0.6</td>
</tr>
</tbody>
</table>

*P<0.003 vs erosion, 0.01 vs fibrocalcific
†P<0.002 vs erosion, 0.04 vs stable plaque, 0.03 vs thin fibrous cap atheroma
‡P<0.001 vs erosion and stable plaque, 0.03 vs thin fibrous cap atheroma
§P<0.01 vs erosion and fibrocalcific plaque

Intimal Thickening (Figures 1 and 2)

While some human lesions may begin as intimal xanthomata, we, along with the authors of the AHA classification scheme, agree that most adult human lesions originate as preexisting intimal masses. Evidence for this tenet comes in part from studies by Kim et al., who showed that atherosclerotic lesions produced in the coronary arteries of hypercholesterolemic swine arise almost exclusively from intimal cell masses. Moreover, the distribution of these normal, developmental intimal masses in children can be correlated with the distribution of characteristic lesions seen in adult humans.25,30

The origin of fat accumulation subjacent to initially small, very focal, preexisting intimal masses may explain the following paradox. There is very little evidence of cell replication except in early lesions, yet the smooth muscle cells of adult lesion are usually clonal.30,31 Very few replications over a long time could easily account for quite sizeable atherosclerotic lesions. Thus, the clonality of the lesions may provide a teleological clue, suggesting that the properties of these normal intimal structures may be relevant to the earliest events in the formation of human lesions. Tabas et al., for example, have proposed that the extracellular matrix at these sites may contain enzymes capable of retaining lipids, an initial event in the formation of the necrotic core. Unfortunately, there are very few articles on the evolution of early intimal cell masses in humans, and none of these clarify their precise pathological mechanisms of development.

Another reason for considering the role of the intima in giving rise to clinically significant lesions comes from our observation that the majority of erosions occur over areas of intimal thickening, with minimal or no evidence of a lipid core. Figure 1 suggests that erosion may occur in response to the existence of “pathological intimal thickening.” At present, the criteria for classifying this putative lesion, other than the existence of an overlying region of thrombosis and absence of an endothelium, remain unclear.

Intimal Xanthomata (Figures 1 and 2)

We propose the term “intimal xanthoma” instead of the type I, “fatty streak,” or “initial lesion” in the AHA’s scheme. “Xanthoma” is a general pathological term that describes focal accumulations of fat-laden macrophages. In humans, most of these intimal xanthomata regress, since the distribution of lesions in the third decade of life and beyond is very different from the fatty streaks seen in children.25

We must emphasize that the presence of an intimal xanthoma is not a basis for categorizing lesions in current animal models as “atherosclerotic.” This is problematic, based on the fact that the distribution of lesions in animal models is very different from that in the adult human population27,28 and the potential for these lesions to regress.27,28

Fibrocalcific Plaques (Figures 1 and 3)

The AHA classification distinguishes between lesion types IV and V on the basis of the degree of fibrous cap formation, which distinguishes the type of plaque from the type of lesion. However, it is clear that the plaque morphology is not a basis for categorizing lesions in current animal models as “atherosclerotic.” This is problematic, based on the fact that the distribution of lesions in animal models is very different from that in the adult human population27,28 and the potential for these lesions to regress.27,28

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the extent to which the lipid core becomes rich in cellular debris, and the development of complicating features. Because there is no clear evidence of a specific sequence of events that relate the extent of changes in the lipid core to the development of a fibrous cap, we suggest the use of descriptive terms for plaque classification.

We define a “fibrous cap” as a distinct layer of connective tissue completely covering the lipid core. The fibrous cap consists purely of smooth muscle cells in a collagenous-proteoglycan matrix, with varying degrees of infiltration by macrophages and lymphocytes. Thus, a fibrous cap atheroma may have a thick or thin cap (see below) overlying a lipid-rich core. The lipid core is also part of our classification. As lesions progress, the core of necrotic debris surrounded by macrophages becomes increasingly consolidated into 1 or more masses comprising large amounts of extracellular lipid, cholesterol crystals, and necrotic debris.

**Thin Fibrous Cap Atheromata (Figures 1, 4, and 5)**

We have added the “thin fibrous cap atheroma” as a specific lesion type not recognized by the current AHA classification. We have done this because in our experience, lesions with thin, fibrous caps are those that are most likely to rupture. The AHA’s discussion suggests this as well; however, their classification scheme also describes type IV lesions as showing fissuring and hemorrhage, including rupture, of the fibrous cap.

We define a “thin,” fibrous cap as 1 that is <65 μm thick. This definition was derived from a morphometric series of 41 ruptured plaques, in which 95% of the caps measured <64 μm thick; the mean±SD plaque thickness was 23±19 μm. The thin, fibrous cap is distinguished from the earlier fibrous cap lesions by the loss of smooth muscle cells, extracellular matrix, and inflammatory infiltrate. The necrotic core underlying the thin, fibrous cap is usually large; hemorrhage and/or calcification is often present; and intraplaque vasa vasorum are abundant.

In our series of >200 sudden death cases, ~60% of acute thrombi resulted from rupture of thin fibrous cap atheromata. In these patients, thin fibrous cap atheromas without rupture were found in 70% of cases. On the contrary, these plaques were less frequent (30%) in patients who died of fibrocalcific lesions, with or without a healed myocardial infarct, or plaque erosion. Although the classification scheme in Figure 1 shows the thin fibrous cap atheroma as a separate category, this lesion does not necessarily develop rupture. Other relevant descriptive features of the fibrous cap lesions include the extent of inflammation in the cap, fissuring, calcification, intraplaque vasa vasorum, or intraplaque hemorrhage.

**Lesions With Thrombi (Figures 1 and 4)**

Rather than creating separate lesion types for rupture and thrombosis, the simplified scheme proposes to classify le-
sions with thrombi as being affected principally by 3 distinct processes: rupture, erosion, and, less frequently, the calcified nodule. These processes can occur in the setting of a fibrous cap atheroma or, in the case of erosion, pathological intimal thickening. As we will discuss below, a single lesion may contain morphological evidence of both rupture and erosion. Often, we see a fatal lesion having 1 area of the thrombus in communication with a necrotic core through a ruptured fibrous cap and another area overlying a smooth muscle cell–rich plaque representing plaque erosion (Figure 6).

**Rupture**

“Plaque rupture” is defined by an area of fibrous cap disruption whereby the overlying thrombus is in continuity with the underlying necrotic core. Ruptured lesions typically have a large necrotic core and a disrupted fibrous cap infiltrated by macrophages and lymphocytes. The smooth muscle cell content within the fibrous cap at the rupture site may be quite sparse.

Plaque ruptures are found in 60% of individuals dying suddenly with luminal thrombi and are the most frequent cause of death in young men (<50 years) and older women (>50 years; Table 1). Risk factors most predictive for this type of lesion are hypercholesterolemia, low serum HDL, and a high total cholesterol to HDL cholesterol ratio. In women >50 years old, ruptured plaques compose the vast majority of atherosclerotic lesions associated with acute thrombi, and similar to men, there is an association with increased total cholesterol levels.

**Erosion**

“Plaque erosion” is identified when serial sectioning of a thrombosed arterial segment fails to reveal fibrous cap rupture. Typically, the endothelium is absent at the erosion site. The exposed intima consists predominantly of smooth muscle and proteoglycans, and surprisingly, the eroded site contains minimal inflammation. We have chosen to use the term “erosion,” despite its mechanistic implication, because we are unaware of evidence that such large areas of endothelium are ever absent in nonthrombosed vessels, even over advanced lesions. Erosions constitute ~40% of cases of thrombotic sudden coronary death. Plaque erosions are more common in young women and men <50 years of age (Table 1) and are associated with smoking, especially in premenopausal women.

Figure 1 refers to the intima underlying an area of erosion as “pathological intimal thickening,” because we assume that some as-yet-identified property leads to this event. It is important to note that this form of thrombotic occlusion does not require a necrotic core, but if present, is usually small. In contrast to plaque rupture, smooth muscle cells are abundant while the presence of macrophage and/or T lymphocytes is variable.

**Confusion Between Rupture and Erosion as a Primary Event**

The existence of a spontaneous thrombotic occlusion without rupture complicates the assumption that an occlusive thrombus in rupture is dependent on the rupture. Ruptures in some cases could be incidental events. For example, Figure 6 (A and B) represents a low- and high-power view of a distal coronary section at the level of a rupture site. A more proximal section, however (C and D), is histologically indistinguishable from an eroded plaque. This case exemplifies the morphological diversity of some lesions, in which the origin of thrombus development resulting in the patient’s demise is confusing.
Calcified Nodule

A second lesion, albeit an infrequent cause of thrombotic occlusion without rupture, is referred to as a “calcified nodule.” This term refers to a lesion with fibrous cap disruption and thrombi associated with eruptive, dense, calcific nodules. The origin of this lesion is not precisely known, but it appears to be associated with healed plaques. Interestingly, these lesions are found predominantly in the midright coronary artery, where coronary torsion stress is maximal. It is unclear whether the fibrous cap wears down from physical forces exerted by the nodules themselves, proteases from the surrounding cellular infiltrate, or both.

Thin fibrous cap lesions with eruptive, calcified nodules should not to be confused with fibrocalcific lesions that are not associated with thrombi. The latter, as discussed below, appear to be the end result of fibrosis and calcification and are often associated with a narrowed lumen. Moreover, this entity does not appear to be a variant of rupture with calcification, since the nodules themselves appear in the lumen in the absence of an overt intimal tear.

Histological Features of Thrombi (Figure 1)

**Fresh Occlusion**

Fresh occlusion is identified by a luminal thrombus containing platelet aggregates interspersed with inflammatory cells and a paucity of red blood cells. The thrombus, however, often propagates from its original site, becomes fibrin rich, and contains interspersed red blood cells and leukocytes. In a fresh thrombus, there is no evidence of invasion by endothelial cells and/or smooth muscle cells. Little is known of the mechanism(s) involved in thrombus propagation.

**Old Occlusion**

Old occlusions often show the lumen totally occluded by dense collagen and/or proteoglycan with interspersed capillaries, arterioles, smooth muscle cells, and inflammatory cells. These lesions may also demonstrate earlier phases of organizing thrombi containing fibrin, red blood cells, and granulation tissue, especially in the midportion of a long, occluded arterial segment.

**Lesions Not Necessarily Associated With Thrombi (Figures 1 and 5)**

**Fibrocalcific Lesions**

Some plaques have thick, fibrous caps overlying extensive accumulations of calcium in the intima close to the media. Because the lipid-laden necrotic core, if present, is usually small, we refer to this category of lesion as fibrocalcific rather than atheroma. Of course, as shown in Figure 1, it is possible that the fibrocalcific lesion is the end stage of a process of atheromatous plaque rupture and/or erosion with healing and calcification.
Intraplaque Hemorrhage (Figure 5)
Constantinides originally suggested that hemorrhage into a plaque occurs from cracks or fissures originating from the luminal surface. Davies later defined plaque fissure as an eccentric, intraplaque hemorrhage with fibrin deposition within the necrotic core from “an entry into the plaque from the lumen.” The fissuring of the fibrous cap occurs at its thinnest portion, typically at the shoulder region, thereby allowing the entry of blood into the necrotic core. As Davies suggested, plaque fissures may represent precursors or subtypes of plaque rupture. Nonetheless, plaque fissures are often incidental findings in advanced plaques in deaths not attributed to cardiovascular causes.

Alternatively, Paterson proposed that intraplaque hemorrhage is secondary to rupture of vasa vasorum, a common feature of advanced lesions with plaque rupture and luminal thrombi. In our series of sudden coronary death cases, hemorrhage into a plaque was most frequent in ruptured plaques but was also observed in lesions with only 40% to 50% cross-sectional luminal narrowing.

Healed Ruptures/Erosions (Figure 7)
Healed ruptures are characterized by a disrupted fibrous cap filled in by smooth muscle cells, proteoglycans, and collagen (Figure 7). Healed ruptures are best identified by picrosirius red staining, whereby newly synthesized type III collagen is seen overlying a ruptured fibrous cap consisting primarily of type I collagen. The matrix within the healed fibrous cap defect may consist of a proteoglycan-rich mass or a collagen-rich scar, depending on the phase of healing. Lesions with healed ruptures may exhibit multilayering of lipid and necrotic core, suggestive of previous episodes of thrombosis.

Other healed lesions show no evidence of a preexisting rupture of the fibrous cap, and there is usually no necrotic core. Instead, distinct layers of dense collagen interspersed with smooth muscle cells and proteoglycans often containing fibrin and/or platelets are present; we assume these types of lesions are the result of healed erosions (Figure 7).

Examples of the Application of the Simplified Classification (Figure 8)
The combination of well-defined categories with descriptive adjectives allows us to encompass varying combinations of complex lesions not easily identified by the existing AHA scheme. For example, Figure 8A shows a lesion composed of a healed rupture with a superimposed area of erosion. An example of a complex lesion with multiple, healed plaque ruptures is shown in Figure 8B; we would describe this as a healed rupture of a thin fibrous cap lesion. Other complex
lesions may show multiple areas of extensive calcification and a ruptured thin, fibrous cap containing an acute or resolving luminal thrombus or scar.

**Comparison of AHA Types With the Simplified Classification**

One test of the simplified scheme is the ability of our categories, with appropriate descriptive adjectives, to replace the AHA’s distinctions of type III from types IV, V, and VI lesions and their alphabetic subsets. We would equate the AHA’s roman-numbered terms to the following.

**Type III**
We would classify this type of lesion as a pathological intimal thickening (Figure 3) with a poorly formed fibrous cap (because of the absence of a necrotic core). Typically, these lesions show incompletely coalesced extracellular lipid, most of which is located deep within the plaque, underneath a layer of macrophages and smooth muscle cells. The smooth muscle cells may contain lipid droplets. Electron microscopy or histochemical assays for apoptosis may show evidence of ongoing cell death.

**Type IV**
This category is identical to our fibrous cap atheroma with a well-formed cellular cap overlying a confluent, necrotic, fatty core (Figure 3).

**Type V**
The AHA classifies lesions in which prominent new, fibrous tissue has formed in a plaque containing a lipid core as type Va. Again, rather than a separate category, we would describe type V lesions simply as fibrous cap atheromata with thick cellular caps overlying a largely necrotic, fatty mass. If the plaque contains a lipid core that is calcified, the AHA classifies this as type Vb. When type V lesions show marked fibrosis and little lipid, they are referred to as type Vc. Type V lesions may also show fissures, hemorrhage, and/or thrombi. Type Va lesions often show patterns of multilayering (ie, multiple layers of lipid core separated by fibrous tissue) suggestive of repetitive disruption, thrombosis, and healing. Types Va, Vb, and Vc are easily and clearly defined with our simplified scheme by applying appropriate adjectives to our fibrous cap atheroma category, without recourse to confusing and restrictive numbering schemes.

The AHA scheme claims that type V lesions are more severely narrowed than are those of type IV. The basis for this statement is unclear, and several studies have shown that narrowing does not appear to be directly correlated with plaque mass. Because 20% of sudden coronary deaths occur in the absence of luminal thrombi or a healed myocardial infarct, it is essential that culprit lesions with >75% cross-sectional area luminal narrowing be classified. In addition, patients with stable angina have infrequent (<20%) luminal thrombi but do show >50% diameter reduction by angiography. Therefore, we cannot ignore these severely narrowed lesions, but instead, the pathophysiological processes leading to blood flow reduction must be sought.

**Type VI**
The AHA defines the most “advanced” lesions as type VI. Type VI, in our opinion, is a poorly defined category that includes lesions of both types IV and V. Those plaques with lesions showing disruption of the luminal surface are referred to as type VIa, with hematoma or hemorrhage as type VIb, and with luminal thrombi as type VIc. Type VIabc lesions are those containing features of all 3 types.
We suggest that this category is confusing and unnecessarily implies a clear progression from type IV and V lesions. Again, it is easier to refer to a well-defined category such as "thin fibrous cap atheroma" with the appropriate modifiers. For example, in our experience, most "type VI" lesions would be described as ruptured thin fibrous cap atheromas.

Mechanistic Targets in Advanced Lesions
The proposed scheme, including the processes and descriptive adjectives in Figure 1, suggests specific morphological features that represent the critical events and potential mechanistic targets for animal model development or clinical intervention. These include arterial narrowing, erosion, fibrous cap thinning, plaque rupture, and intramural coagulation (Table 4). The varying level of clinical importance among these targets will not be considered, since there are no data to support stratification.

Narrowing
Stenosis of atherosclerotic vessels is the most common morphological target for therapeutic intervention. Surprisingly, this is the change with the least understood histological basis. Since publication of the article by Glagov et al in 1987, we have known that plaque mass (at least in lesions with <40% cross-sectional luminal narrowing) is not correlated with lumen size in humans. Despite innumerable studies targeting intimal mass or plaque surface area in response to balloon angioplasty, lipid feeding, or genetic alterations, it is unclear whether manipulation of any specific histological feature, other than plaque mass itself, correlates well with vessel size.

There are, however, some mechanistic clues from experimental studies in the apoE-knockout mouse. Clinical studies of restenosis after angioplasty, especially those with serial examinations by intravascular ultrasound, have shown a correlation between luminal narrowing and a decrease in the external elastic lamellar area, rather than any increase in intimal or medial mass. Intriguingly, studies involving 1 of us (S.M.S.) showed a similar phenomenon at certain highly consistent sites of lesion formation in the apoE-knockout mouse. Analysis of our data in these susceptible areas in the mouse showed 2 possible clues as to an underlying mechanism. First, lumen loss was correlated with medial atrophy. This suggests that accommodation of the vessel lumen to an increasing mass of intima may be an active process requiring functional, viable medial smooth muscle. This seems counterintuitive, because medial atrophy is usually associated with aneurysm formation; however, the mechanisms responsible for vessel wall remodeling are essentially unexplored.

Inflammation of the adventitia was the second feature associated with narrowing in the apoE-knockout studies. Similarly, arterial balloon injury models in the rabbit and pig have demonstrated that adventitial fibrosis is a more impor-
tant determinant of lumen loss than is intimal mass. In a report, Katsumata and colleagues demonstrated that chronic application of interleukin-1β to the adventitia alone caused luminal narrowing in pig coronary arteries. Although few autopsy studies have examined the adventitia, our study of adventitial fibrosis and thickness in human atherosclerotic coronary arteries after angioplasty (R.V.) has not been found to be correlated with lumen loss and restenosis.

Finally, the possible role of healing in narrowing is intriguing. There is an extensive literature on wound contraction, and there is no reason to assume that wound healing after arterial thrombosis would not lead to a similar phenomenon. Contraction of intimal “wound” tissue as it heals could overcome the normal capability of the media to dilate in response to an increased intimal mass. In an experiment from one of us (S.M.S.), narrowing of vessels after angioplasty depended on the formation of intramural fibrin, raising the intriguing possibility that fibrin could mediate wound contracture in injured vessels.

An extreme example of the possible role of wound healing could be the fibrocalcific lesions described by Kragel and colleagues. Given the extensive matrix formation in these vessels, it seems likely that a loss of adaptive remodeling would result from highly collagenized intima restricting the ability of the vessel to dilate. This could explain the association of severe narrowing with the fibrocalcific plaque.

Erosion
Currently, we have little understanding of the mechanism(s) of erosion. Besides the thrombus, the most striking aspects of this lesion are the absence of an endothelium and the “activated” appearance of the underlying smooth muscle cells. One might assume that the endothelium has somehow been dislodged. However, animal models of atherosclerosis, contrary to some early speculations about the effects of hyperlipidemia or smoking, have not shown large areas of spontaneous denudation. Moreover, unless active tissue factor is present, it is not obvious that the simple desquamation of endothelium in a high-shear artery would lead to a coagulative and thrombotic process resulting in occlusion.

Thus, “erosion” is a mystery in much need of a model. One possibility is that erosion is a manifestation of vasospasm. Unfortunately, little is known of the sequelae of vasospasm in atherosclerotic vessels.

Fibrous Cap Thinning
The mechanism of fibrous cap thinning is not known. There is, however, evidence for extensive apoptosis of smooth muscle cells within the cap of advanced atherosclerosis, as well as those cultured from plaques. Virchow defined “apoptosis” in the plaque over a century ago: “Thus we have here an active process which really produces new tissues, but then hurries on to destruction in consequence of its own development.” Consistent with Virchow’s prescient point of view, plaque smooth muscle cells, both in vivo and in vitro, show limited ability to replicate, even after angioplasty. Moreover, plaque smooth muscle cells show elevated levels of spontaneous apoptosis, as has been demonstrated both in vivo and in vitro. Intriguingly, Pollman et al. found that antisense to Bax, an antiapoptotic gene, promoted cell death and caused thinning of the neointima formed by injury. A similar process of ongoing programmed cell death combined with replicative senescence occurring in the fibrous cap could be operative in the lesion we call “fibrous cap thinning.”
thin fibrous cap would rupture because of its inability to maintain the cap in the face of, for example, macrophage-derived proteolysis, as discussed in the next section. Intriguingly, we have recently found that the normal intima expresses c-FLIP, another antiapoptotic gene, but that this gene is lost in areas of apoptosis of the fibrous cap.62

**Plaque Rupture**

Plaque rupture is the suspected cause of death in 60% of patients with sudden coronary death and thrombosis, and of these patients, 75% show previous sites of plaque rupture.20 Despite the clinical importance of erosion, rupture remains a critical target for investigation.

The most extensive hypothesis to explain rupture is that proposed by Libby and colleagues, an expansion of the original work described by Henney et al.63 This hypothesis proposes that the critical effects of inflammation are the cytokines that drive the expression of proteases and obstruct the actions of proteolytic inhibitors. Particularly intriguing is the hypothesis of Hansson and colleagues, who suggested that specific antigens elicit a T-cell response and that disease progression may be stimulated by autoimmune responses to oxidized lipoproteins.

The principle limitation of this inflammation/protease hypothesis is that we do not know when the inflammatory or immune process becomes “critical.” That is, in experimental animals, proteolytic activity may be elevated even in early lesions that do not rupture.68 Similarly, although atherosclerotic plaques do show clear evidence of collagenase and elastase activity, the time course of net activity in relationship to rupture will probably remain unknown until we have an animal model for this advanced stage. Libby’s work, however, offers intriguing possibilities. The first is their recent observation that stromelysin-3, a protease that itself is able to digest proteolytic inhibitors, is present only in advanced human lesions, as opposed to xanthomata.71 It is intriguing to imagine that expression of stromelysin-3 or an accumulation of oxidation products that inactivate protease serpins72,73 could tip the proteolytic balance. This could be especially significant when macrophage-produced protease activity is present in a fibrous cap that has lost its smooth muscle cells through apoptosis and senescence, as suggested above.

**Intramural Coagulation**

Although we know that occlusion of the vessel in sudden coronary death in most cases depends on coagulation, surprisingly little is known about the mechanisms promoting procoagulant conditions. Advanced lesions contain smooth muscle cells and macrophages that express tissue factor, and this can be shown to activate the extrinsic pathway of coagulation.74,75 However, to our knowledge, there have not been careful studies of when this critical initiating factor for the extrinsic pathway is first found during the progress of atherosclerotic lesion formation. Even less is known about the natural expression of tissue factor pathway inhibitor or the presence of annexin V, a cytoplasmic molecule released during cell death that binds phosphatidylserine, a critical cofactor for tissue factor. Studies of the time course of tissue factor activation and appearance of procoagulant activity during plaque progression are needed in human tissue as well as in animal models.

**Summary**

In our analysis of lesions from patients after sudden coronary death, we identified plaques that were difficult to categorize by the current AHA classification scheme. Therefore, we have devised a simplified classification that relies on descriptive morphology, with minimal implication of the mechanisms involved. This classification scheme highlights specific morphological events that are appropriate targets for development of animal models or human diagnostic procedures, which will permit us to test hypotheses as to the final stages of the disease. The most important events include erosion, rupture, thinning of the fibrous cap, and development of a procoagulation and thrombotic environment.

Our categorization of the lesions largely depends on the status of the fibrous cap. The critical modulators of these changes in the fibrous cap are, at best, poorly known. The most tenable hypothesis, however, is that fibrous cap thinning results from the proinflammatory activities of macrophages and lymphocytes residing in the plaque.

The final test of whether this classification scheme is useful seems to us to have 3 parts. First, can we describe the range of lesions? Second, can the scheme be used to categorize and stage lesions in nonhuman species? Third, and most important to us, does this scheme highlight specific features of the plaque that require mechanistic study? This last feature is extremely important if we are to understand how plaques progress from clinically benign xanthomata or fibrous cap atheromata to lesions that kill.

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