A perspective of coronary disease seen through the arteries of living man*

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"A LONG DISPUTE," Voltaire (himself an incorrigible disputant) was fond of saying, "means both parties are wrong." Cardiology's longest debate concerns the pathogenesis of acute coronary disease. Today the resolution seems at hand: thrombus is once again the cause of acute infarction and thrombolysis is its cure. We do not wish to say, as Voltaire might, that this consensus is wrong, but it is incomplete because it leaves unanswered a crucial set of pathophysiologic questions: What events precede coronary thrombosis? After formation of thrombus begins, are there fates other than infarction? At what points can the evolution of any of the acute (or chronic) coronary syndromes be arrested? Our Perspective proposes a systematic description—a paradigm—of the pathophysiologic mechanisms of acute and chronic coronary artery disease in man that deals specifically with these three questions.

In the past year we have taken a metaphoric voyage through the coronary arteries of living man, using fiberoptic angioscopes. Through this exploration, we have seen the coronary endothelial surface in both acute and chronic coronary syndromes. Our unanticipated discovery has been that each of the common clinical presentations seems to have a specific, identifiable endothelial pathology. We will first describe these fundamental relationships between clinical symptoms and the appearance of the coronary endothelium and will then correlate our findings with the known postmortem histologic appearance of similar lesions. Finally, in the spirit of a Perspective, we will conclude by proposing a paradigm that brings together acute and chronic coronary artery disease as a single pathophysiologic entity.

Historical perspective: the dispute over the role of coronary thrombosis. A century ago, pathologists first began carefully examining the hearts of people who clutched their chests and died; they found thrombus and concluded that coronary thrombosis caused sudden death. James Herrick expanded this view in 1912 when he proposed that not everyone with thrombus died, in other words, that thrombus also caused myocardial infarction.1 But as research continued, it seemed that Herrick was "wrong." In 1939, Charles Friedberg and his colleagues reported that about one-third of patients with the clinical diagnosis of acute myocardial infarction had no demonstrable coronary thrombi at autopsy.2 A year later, H. L. Blumgart, Paul Zoll, and others began to report the complementary finding, coronary thrombosis without infarction,3 which "clearly established that thrombotic occlusion can occur with or without infarction."4 The "long dispute" ignited. Over the next three decades, while the nation waged periodic wars, leading cardiologists and pathologists did likewise. Meyer Friedman and Bleakley Chandler, who saw thrombus in well over 90% of cases of transmural myocardial infarction, found it impossible to believe there was other than a direct cause-effect relationship.4,5 David Spain found thrombosis in only 54% of his cases of acute infarction and maintained it was a secondary event.6 This finding of thrombus in only half of the autopsied cases of acute infarction was confirmed by others.7 Somebody's observations, it seemed, must be "wrong." Accordingly, in 1973, the
National Heart, Lung, and Blood Institute convened a Workshop on Coronary Thrombosis in the Pathogenesis of Acute Myocardial Infarction in Washington, DC. The 36 international authorities who attended clearly understood the problem: “At one extreme, the entire concept of coronary thrombi causing infarcts has been challenged... at the other extreme some investigators have continued strongly to maintain [its] essential etiologic role.” Alas their two conclusions would have been a Voltairian feast: “The idea that coronary thrombosis is a secondary event following infarction is provocative and deserves serious consideration” was followed by “myocardial infarction can result from acute ischemia produced by thrombotic occlusion of a coronary artery.”

Today some will say the debate has been resolved, that the “errors” of the past are corrected. In 1980, DeWood et al. reported that coronary angiography performed within 4 hr of the onset of symptoms revealed that 90% of patients with acute infarction had complete coronary occlusion. In a small percentage of these patients, the cardiac surgeon removed fresh thrombi from the coronary arteries during bypass surgery. Soon thereafter intracoronary infusion of streptokinase was reported as therapy in acute myocardial infarction; in 90% of cases angiographers saw completely obstructed coronary arteries become patent within 30 min. Coronary thrombosis is now widely accepted as the predominant cause of acute transmural myocardial infarction. The wide discrepancy in autopsy prevalence of coronary thrombosis reported in the preceding four decades had been caused by the perverse and unrecognized tendency of thrombi to lyse. In cardiology’s long dispute no one, and everyone, was “wrong.”

Coronary atherosclerosis: a modern paradigm. Our purpose is to chart the remaining areas of uncertainty about coronary thrombosis—to look at phenomena before and after the occlusive thrombus and thereby to include the full spectrum of acute and chronic coronary disease. We will propose that coronary disease is a continually repeating cycle of clinical stability interrupted by acute syndromes. Our central idea is that this clinical cycle is driven by two unrecognized cycles at the endothelial surface, which determine the patient’s specific symptom presentation (figure 1).

The first histopathologic cycle is stable atheroma—endothelial ulceration—platelet adhesion—ulcer healing. We believe that each of these states has a related clinical syndrome. The coronary arteries in stable angina have smooth, yellow-white atheroma on the endothelial surface. When the atheroma develops an endothelial ulceration, the clinical presentation becomes accelerated angina (increased frequency of angina without rest pain). If platelet aggregates that form on the ulceration embolize, either sudden death or ischemic cardiomyopathy result. When the ulcer heals there is rapid progression of the coronary stenosis at that site, but the clinical state returns to chronic stable angina.

The second cycle is endothelial ulceration—partial thrombosis—thrombus evolution—thrombus incorporation—stable atheroma. This cycle also has related clinical states. When a partially occlusive thrombosis develops on the endothelial ulceration, the patient experiences unstable rest angina. If the thrombosis proceeds to complete occlusion, acute myocardial infarction results. Coronary thrombi may lyse or may be incorporated into the vessel wall. When the thrombus is incorporated, it causes rapid progression of coronary

![Diagram](https://example.com/coronary_cycle_diagram.png)

**FIGURE 1.** The ulceration-thrombosis cycle of coronary disease.
stenosis. After lysis or incorporation, there is return to chronic stable angina. The cycles then repeat.

Events preceding coronary thrombosis: clinical-histologic features of the first cycle. The basis of our paradigm is the correlation between symptoms and the details of endothelial surface we see in living patients. Because our angioscopic observations correspond directly to gross autopsy description, however, we also can infer the histologic appearance of these lesions. The first cycle consists of stable atheroma, endothelial ulceration, platelet adhesion, and healing with atheroma progression.

Stable atheroma. Figure 2, A, is an illustrative angioscopic image from the left circumflex coronary artery of a 65-year-old woman with a 2 year history of stable angina pectoris. 2.5 mm horizontal ST segment depression during exercise, a strongly positive thallium test consistent with multivessel disease, and greater than 90% stenosis in all three major coronary arteries. There is a smooth, crescent shaped yellow-white atheroma protruding into the coronary lumen. Angioscopy of the left anterior descending coronary artery revealed similar smooth atheroma.

Figure 2, B, shows a large, mature atheroma. The lumen has been markedly narrowed by a huge, fibrous plaque. To the right of the lumen there is an area of necrosis. Although most of the necrotic core was lost in preparation, macrophages still line the wall of the abscess.

This lesion is typical of the atheroma we have seen by angioscopy in patients with stable atherosclerotic disease. The earliest nonobstructive lesions are oblong and oriented along the axis of flow; obstructive lesions have no regular shape and are usually eccentric. Histologically these stable atheroma exhibit several stages of development that correspond to our angioscopic observations. The small nonocclusive oblong protrusions are fatty streaks, which are composed predominantly of lipid-laden macrophages. As the lesion enlarges and becomes partially obstructive, smooth muscle cells are found to have migrated from the media into the subendothelium, and the lipid-laden macrophages are covered by a fibrous cap. Thus in stable exercise-induced angina, the normal endothelial cells have been replaced by a heavier fibrous cap, but the endothelial surface itself remains intact. Although there is no doubt that the pathophyslogic basis of pain in stable angina is a transient increase in oxygen demand that exceeds the artery’s capacity to deliver flow, we now believe that stable angina is the only syndrome in which this mechanism is the dominating factor.

Endothelial ulceration. In contrast to stable angina, when the clinical presentation is an unstable syndrome, we see changes in the endothelial surface. The least severe of the unstable coronary syndromes is accelerated angina (increasing frequency of angina without rest pain).

Figure 3 shows the endothelial surface of the left anterior descending coronary artery in a 75-year-old man with a 7 year history of stable angina and a 3 week period of accelerated angina pectoris. The accelerated syndrome was only partially responsive to nitrates and \( \beta \)-blockers. At angiography he was found to have an 80% to 90% stenosis in the left circumflex coronary artery. The endothelial surface is disrupted and there is subintimal hemorrhage. There is, however, no thrombus attached to the endothelial surface. Microscopically, serial sections of ulcerations show progressive thinning of the fibrous cap as the point of rupture is approached.4

The distinguishing feature between acute and stable coronary disease at angioscopy is this endothelial ulcer: thus far, all but one of our patients with accelerated angina have had endothelial disruption.11 Furthermore, the acute lesion invariably lies in the coronary artery identified by electrocardiography as the one responsible for acute ischemic symptoms.12 Although the cause of endothelial ulceration is not definitely established, a strong inferential case exists for erosion from within. Atheromas almost always lie beneath the ulceration, and the evolution of ulceration bears a histologic resemblance to rupture from within induced by an inflammatory foreign body response.4 The mechanism by which ulceration causes angina may be through release of vasoconstrictive compounds such as thromboxane A\(_2\) from platelets that aggregate at the site.13

Platelet aggregation. Despite the fact that endothelial disruption causes platelet aggregation, we do not always see a thrombus attached to the ulceration either at angioscopy or at autopsy. This suggests that platelet embolization, documented in the constricted canine coronary artery,\(^14\) also occurs in man. Evidence of microemboli distal to coronary thrombus has been found in 73% of sudden ischemic cardiac deaths\(^15\) suggesting that microemboli trigger fatal ventricular arrhythmias in man. This is not to imply that sudden death is always caused by emboli, since people who die instantaneously (within 30 sec) rarely have any type of acute coronary lesion.\(^16\) The important point is that sudden death, like the other acute coronary syndromes, has more than one cause. Nevertheless, we believe that microemboli are an important cause of sudden ischemic cardiac death.

Coronary embolization is not necessarily fatal, and its frequency is probably much higher than we recognize. Since microemboli are not found in autopsies of patients with chronic coronary disease, they probably disappear by endogenous lysis. The alternative clinical outcome of endothelial ulceration with platelet microemboli, therefore, is another example of the chronic-acute-chronic cycle, in this case heart failure without history of infarction, in the presence of nonoc-
FIGURE 2 to 7. For legends see opposite page.
exclusive coronary disease. We believe that microemboli that lyse are an important cause of ischemic cardiomyopathy.

Healing with progression of stenosis. The ultimate evolution of endothelial ulceration is healing. Animal studies in our laboratory and others have demonstrated that experimentally induced endothelial disruption heals rapidly. After attachment of platelets, endothelial cells grow inward from the margins of the damaged surface, covering the platelet-fibrin mass. Simultaneously the platelets and fibrin are rapidly replaced by macrophages, smooth muscle cells, and fibrous tissue so that at 4 weeks the site of prior endothelial damage is often not readily identifiable. In man, this is probably the most common outcome: Duncan et al. found that 81% of 251 patients with new or worsening angina had returned to full-time work at 6 months; only 16% went on to have acute myocardial infarction. We believe that healing of the endothelial ulcer leads to stabilization of the acute coronary syndrome.

Reendothelization of an ulceration over a ruptured atheroma, however, invokes an important permutation of the normal healing process. In the animal preparation, endothelial injury in the presence of hyperlipidemia results in accelerated development of atheroma. We believe that precisely the same process occurs in human coronary disease, with or without clinical hyperlipidemia. This view conforms to clinical reality: 75% of patients with unstable angina exhibit rapid localized progression of stenosis when coronary angiography is performed soon after the acute episode.

This pathogenetic mechanism, we believe, also occurs in stable angina. A critical insight from our angiographic experience is that coronary endothelial ulceration can occur in the absence of a recognized change in symptom pattern; at coronary angiography, ulceration or thrombus also is reported in a small percentage of patients with stable angina. Serial angiography clearly establishes the phenomenon of episodic localized progression. For instance, Singh found that only 34 of 105 (33%) of coronary stenoses exhibited progression at 4 year follow-up (7.8%/year). Rapid progression typically occurred with the abrupt development of new symptoms and frequently involved previously normal segments. We believe that endothelial ulceration without symptoms is the major (but unrecognized) cause of rapid localized atheroma progression in coronary heart disease.

The restenosis rate after percutaneous transluminal coronary angioplasty is 30%. Our angiographic experience in vivo has demonstrated that substantial endothelial disruption, undetectable by angiography, can be induced by balloon angioplasty in patients who are initially thought to have had a successful therapeutic procedure (figure 4). We also believe that this same process—endothelial disruption, platelet aggregation, and accelerated fibroproliferative response—is the cause of restenosis after percutaneous transluminal coronary angioplasty.

In summary, the first cycle—ulceration, platelet aggregation, and healing—has several potential acute and chronic disease outcomes: accelerated angina, microembolization producing either sudden death or chronic heart failure, and healing with return to stable angina, often accompanied by accelerated progression of coronary stenosis.

FIGURE 2A. A stable atheroma in the left descending coronary anterior of a patient with stable angina pectoris.

FIGURE 2B. An atheroma with a necrotic core covered by a fibrous cap. (Reproduced from Am J Pathol 48: 19, 1966, with permission.)

FIGURE 3. An endothelial ulceration in the left descending coronary artery of a patient with accelerated angina.

FIGURE 4. The true and false lumina of a coronary dissection after percutaneous transluminal coronary angioplasty.

FIGURE 5A. A fresh partially occluded coronary thrombosis in a patient with unstable rest angina pectoris.

FIGURE 5B. A partially occlusive coronary thrombosis attached to an endothelial ulceration (courtesy Dr. Meyer Friedman).

FIGURE 6A. A completely occlusive coronary thrombosis in the left anterior descending coronary artery.

FIGURE 6B. A coronary thrombosis containing fragments of the endothelial surface and cholesterol clefts in a patient who died soon after the onset of an acute myocardial infarction. (Reproduced from Am J Pathol 48: 19, 1966, with permission.)

FIGURE 7A. Absence of a coronary thrombosis in a patient 2 weeks after a transmural myocardial infarction.

FIGURE 7B. Incorporation of a coronary thrombosis as seen in three serial sections of the coronary artery. (Reproduced from Br J Exp Pathol 47: 553, 1966, with permission.)
When the coronary thrombus forms: the second cycle.
The second cycle consists of ulceration, partial thrombosis, thrombotic occlusion, and lysis or incorporation with atheroma progression.

Partial coronary thrombosis. Figure 5, A, is from a 70-year-old man with new-onset, unstable rest angina (increasing frequency with rest pain). He had an inadequate in-hospital response to nitrates, β-blockers, calcium-channel blockers, and heparin. The electrocardiograms showed transient inverted T waves in the anteroseptal leads, but there was no creatine kinase elevation. His coronary angiogram revealed a 95% left anterior descending coronary stenosis. The angioscopic image was recorded just distal to the stenosis. There is a bright red partially occlusive thrombus just distal to the stenosis. The thrombus surface undulated during infusion of the clear viewing solution but was not dislodged from the endothelial surface by vigorous flushing.

Figure 5, B, shows a coronary artery with a partially occlusive intraluminal thrombus. There is rupture of the fibrous cap that covered an atheroma cavity, and at the point of rupture there is thrombus formation. Beneath the point of rupture lies an atheroma, whose necrotic content has been partially removed during fixation.

Partially occlusive thrombus is typical of this clinical syndrome: 87% of our patients with unstable rest angina have had a thrombus; in contrast, we have not yet seen thrombus in stable coronary disease. Furthermore, when an intracoronary thrombus is removed at autopsy, it is attached to an ulcerated endothelial surface in over 90% of cases. We believe that the continuum of clinical severity from accelerated angina to unstable rest angina has a pathologic parallel: that from endothelial ulceration to partially occlusive thrombosis.

Like the endothelial ulceration, the partially occlusive thrombus is also biologically unstable—its two short-term potential fates are lysis or progression to occlusion. The frequency of remission of unstable rest angina with supportive medical therapy suggests that spontaneous lysis is common. The angiographic literature also suggests that endogenous lysis can occur fairly rapidly with supportive therapy. In patients with acute infarction, Rentrop et al. found a 90% prevalence of total obstruction in the first several hours, but after 14 days of conventional therapy it was only 33%. We believe that spontaneous lysis is a common outcome of both partial and totally occlusive coronary thrombosis.

Coronary occlusion. The alternative to lysis for the partially occlusive thrombus is progression to total occlusion, represented by the clinical syndrome of acute myocardial infarction. Both clinical and pathologic data support the hypothesis that partially occlusive thrombi can progress to occlusion over a period of days or weeks. In his review of the world literature, Fulton found that 13% to 40% of patients with unstable angina progressed to myocardial infarction within 3 months, many within the first few days or weeks. Conversely, in patients with acute infarction there was a prodrome of unstable angina in 30% to 65% of patients. Autopsy confirmation is provided by the identification of two or more thrombus layers, attributed to episodic growth over time, in 81% of thrombi from patients who die with unstable angina. We believe that some coronary thrombi progress slowly to occlusion and that acute myocardial infarction in this group should be almost entirely preventable.

Nonetheless, the more common presentation of myocardial infarction is sudden onset of chest pain, suggesting that in the majority of infarctions progression to total occlusion is rapid.

Figure 6, A, is from a 66-year-old man with a 1 year history of stable angina who had the sudden onset of severe chest pain that waxed and waned over several hours. During hospitalization, the pain recurred and an ECG revealed ST segment elevation in the inferior leads. He immediately received heparin and intravenous tissue-type plasminogen activator and experienced complete relief of pain within 30 min, but soon thereafter symptoms recurred. At angiography, he had total left circumflex coronary artery occlusion. The figure shows the left circumflex coronary artery at the site of angiographic occlusion. There is a coronary thrombus obstructing approximately 90% of the lumen.

Figure 6, B, shows a portion of a thrombosed segment of the left anterior descending coronary artery of a patient who died 90 min after the onset of symptoms. A large atheroma cavity has ruptured into the lumen. The red-staining lipid content of the cavity, containing some cholesterol clefts (arrows), constitutes the upper third of the thrombus, which occludes the lumen. The remaining two-thirds of the thrombus consists chiefly of platelets, with an outer fringe composed chiefly of erythrocytes. In the atheroma cavity there are many cholesterol clefts, and an area of calcification lies in direct contact with the cavity.

In our paradigm, there are two competing forces that determine whether a thrombus completely obstructs the coronary artery: the mass of thrombus required to produce occlusion and the efficiency of endogenous lysis. Complete thrombotic occlusion is common (79%) when the preexisting stenosis is greater than 75% of the lumen but uncommon (3%) when the preexisting stenosis is less than 75%. Recurrence of occlusion after therapeutic thrombolysis is also clearly related to the magnitude of preexisting coronary stenosis. This principle also applies to balloon angioplasty, atherectomy, and laser angioplasty. It appears that even extensive endothelial disruption can heal without thrombotic occlusion when the residual stenosis is not severe. We believe that the magnitude of stenosis at the time of endothelial disruption determines whether the vessel remains patent or occludes.

Prognosis in stable coronary disease, therefore, is the product of two independent factors: percent stenosis and the phase of atheroma cycle. This explains the
relative inaccuracy of prognostication based solely on “percent coronary stenosis” and “stress-induced ischemic abnormalities”: one of the two factors determining prognosis is not assessed. Whether an ulceration and thrombus develop is determined by the atheroma cycle; the clinical outcome is determined by percent stenosis when this occurs. We believe that clinical prognosis is determined by both percent stenosis and the atheroma cycle; the unseen phase of the atheroma cycle is the “hidden factor” in coronary disease.

**Thrombus incorporation.** The thrombus cycle is completed by either endogenous lysis or incorporation of the thrombus into the vessel wall.

Figure 7, A, shows the endothelial surface of a left anterior descending coronary artery in a 64-year-old man 2 weeks after transmural anterior myocardial infarction. Assuming that the transmural myocardial infarction was caused by an occlusive coronary thrombus, it has apparently undergone lysis. The endothelial surface is ulcerated, but there is no evidence of thrombus.

Figure 7, B, shows the alternative fate of coronary thrombus. The thrombus has been covered by a thin layer of endothelium, and the platelet-fibrin mass is being replaced by macrophages and fibrous tissue.

In several more weeks, if the evolution of this thrombus parallels that in the animal, the lesion will be indistinguishable from the chronic stable atheroma. We believe that both thrombus incorporation and endothelial healing cause rapid progression of coronary stenosis.

In summary, the second cycle—partial thrombosis, progression to occlusion, and lysis or incorporation—has several potential clinical outcomes: unstable rest angina, myocardial infarction, embolization producing sudden death or chronic heart failure, and healing with rapid progression of coronary stenosis. Like the first cycle, it also returns to the starting point: a stable atheroma with stable angina pectoris.

**The coronary artery disease paradigm and its therapeutic implications.** Our paradigm of coronary disease consists of linked histopathologic cycles based on endothelial ulceration and coronary thrombosis. Within each cycle there are specific endothelial conditions, each of which is responsible for the clinical syndromes we identify at the bedside. Our paradigm implies that between each transition there may be a brief opportunity for an intervention that can break the cycle. In principle, the intervention should be specific for the endothelial condition, and it can be inferred from the clinical presentation (figure 8).

We need interventions that induce these four specific effects: prevent ulceration, inhibit platelet aggregation, lyse thrombus, and promote endothelial healing. We have no known interventions that cause the first or last effect. Ironically, these are the two classes of interventions are the most likely to interrupt the rapid progression of stable coronary atheroma. We suspect that erosion of the fibrous cap is caused by macrophages, which are known to cause both free radical formation and to produce enzymes capable of destroying collagen and elastin. Therefore we believe that antioxidants and anti-inflammatory agents deserve immediate investigation as drugs that can impede atheroma rupture and/or promote ulcer healing.

In patients with endothelial ulceration, we need agents to inhibit platelet aggregation. If effective, these agents could reduce the rate of sudden death or development of ischemic cardiomyopathy from emboli and impede progression of thrombus to total occlusion and myocardial infarction. Some of these effects have been established by the Veterans Administration Cooperative Study in 1266 men with unstable angina who were randomly assigned to treatment with buffered aspirin or placebo. There was a 51% lower cardiac event rate at 3 months in the aspirin-treated group. These results have been recently confirmed by the Canadian Multicenter trial. We believe additional antiplatelet agents (e.g., prostaglandin derivatives) deserve trial in the full range of clinical disorders secondary to endothelial disruption (e.g., after angioplasty).

In patients with unstable rest angina caused by partial thrombosis, arrest of progression to total occlusion by thrombolytic therapy requires investigation. As yet the data are limited. Lawrence et al. found a large and statistically significant reduction in cardiac event rate at 3 months when patients with unstable angina received 24 hr treatment with intravenous streptokinase during hospitalization. We believe that with attention
to risk vs benefit, thrombolytic agents deserve trial in unstable rest angina; however, the rate of bleeding complications must be reduced well below that reported in acute infarction.

In summary, we see coronary disease as two interlocking cycles. The first consists of a stable atheroma that progresses to endothelial ulceration, platelet aggregation, and ulcer healing. The second cycle, which begins with the endothelial ulceration, progresses through partial thrombosis, complete occlusion, lysis, and thrombus incorporation. Each phase of the two cycles results in a clinical syndrome, and each may benefit from specific therapy. This paradigm links basic science to clinical practice, offers testable hypotheses, and suggests that there is an opportunity for considerable advancement in the medical therapy of coronary heart disease.

If by this paradigm we can redirect the debate on coronary thrombus, it is because where others have seen resolution, we see lack of information. Although the new information from our first angioscopic explorations is limited, we believe that the missing link in our understanding of human coronary disease has been our inability to perceive its evolution. We know our paradigm may be "wrong": it is based on observations in selected patients, so ill that they required bypass surgery. But if it is in error, we will not mind being wrong. As Lewis Thomas says in The Wonderful Mistake, "'...Biological needs a better word than 'error' for its driving force. ... Or maybe error will do after all, when you remember that it came from an old root meaning to wander about, looking for something.'"

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