13. Plaque Toxins and Clinical Coronary Syndromes

"...Different morphologic patterns of myocardial necrosis suggest that various pathogenetic mechanisms with different biochemical derangements may interact in the natural history of the coronary heart disease."
G Baroldi [251]

The Pathogenesis of Angina Pectoris Pain

The pathogenesis of the pain of angina pectoris remains in doubt [217,226]. Lewis advanced the theory that the "P" (pain) factor, a chemical agent derived from ischemic cells, stimulates sympathetic nerves, producing the pains of angina pectoris [227]. The specific chemical agent(s) were not identified. Lewis attemped to explain the wide variety of anginal pains on the basis of one mechanism, myocardial ischemia. He did not consider the possibility that two different mechanisms might produce the pains. Many investigators, including Lewis, believe cardiac sympathetic nerves within the myocardium are stimulated by chemical metabolites derived from ischemic myocardium [217,227], but this does not explain many features of angina pectoris.

We hypothesize the pain of angina pectoris is caused by the stimulation of cardiac sympathetic nerves by two different, broad classes of chemical agents, derived by two separate and distinct mechanisms. Chemical agents derived by the first mechanism are those metabolites produced by ischemic cells and stimulate intramyocardial sympathetic nerves, producing typical anginal chest pain. These metabolites, localized to the area of myocardial ischemia, are subsequently neutralized and/or removed by flowing blood (227), and do not reach the adventitia of the epicardial arteries. Chemical agents derived by the second mechanism are chemical toxins discharged from UPs (discussed above), and circulate to all distal cardiac structures, including the adventitial nerves distal to the UP.

These two different mechanisms, each associated with different chemical agents that stimulate sympathetic nerves in different locations, both producing anginal-type pains, could explain some of the chest pain variations in angina pectoris. For example, direct stimulation of adventitial sympathetic nerves by plaque toxins may produce different anginal pains from ischemic metabolites that stimulate intramyocardial sympathetic nerves. Similarly, stimulation of adventitial nerves by plaque toxins in the right coronary artery may produce a different type and distribution of chest pains than the same toxic stimulation of adventitial nerves in the left coronary artery. The same reasoning applies to the toxic stimulation of adventitial nerves in the proximal compared with the distal portion of the artery [216].

If this hypothesis is correct, it may be possible to distinguish these two different mechanisms clinically. For example, the anginal pains produced by ischemic metabolites from myocardial cells may produce the typical substernal tightness, heaviness, and pressure associated with stable angina pectoris. Chest pains of this type are commonly precipitated by exertion, relieved by rest, and are frequently associated with one or more significant, fixed, coronary stenoses. The relationship between exertion and the chest pain provides strong evidence in favor of ischemia. These chest pains, which are usually gradual, not sudden or dramatic in onset, and which are directly related to the amount

of exertion, suggest it takes time for cells to become sufficiently ischemic to produce the metabolites that ultimately stimulate the nerves and produce the chest pain.

The anginal pains produced by chemical toxins discharged from UPs may be expected to be sudden in onset when the toxin, discharged from the UPs, strikes distal sympathetic nerves [202]. Chest pains produced by this second mechanism would be expected to come on at any time, at rest or during sleep, without exertion or other obvious precipitating cause, whenever the plaque ulcerates and the discharge of toxins occurs.

These two mechanisms may also be distinguished by the mode of relief. Chest pain caused by the first is relieved by rest, presumably because the production of ischemic metabolites ceases when exercise stops. The administration of vasodilators, such as nitroglycerin, may assist in neutralizing or removing these metabolites through increased blood flow (227). Chest pains produced by the second mechanism are similar to those described for unstable angina, often subsiding spontaneously without specific treatment, suggesting that the offending chemical toxin is no longer present, presumably neutralized or removed by flowing blood. Such spontaneous relief of chest pains suggests coronary blood flow was not significantly obstructed by a fixed stenosis.

The third possible way the two mechanisms could be distinguished is by the overall character, somatic distribution, and reproducibility of the anginal chest pain. We would expect anginal chest pains associated with the first mechanism to be reproducible, non-progressive, and localized to the same somatic distribution with each episode. The character and distribution of the chest pains produced by the second mechanism would be expected to vary in intensity, distribution, and duration, depending on

the amount, potency, and speed of release of the toxin, and the specific nerves stimulated. The second mechanism would be expected to produce a wide range and variety of chest pains because there are so many variable precipitating factors.

The possibility that two different broad classes of chemical agents with different chemical characteristics, originated by two mechanisms that stimulate different sympathetic nerves differently, must be considered in the pathogenesis of the pain of angina pectoris (228).

Variant (Prinzmetals) Angina (VA)

The VA syndrome is the prototype we will use to illustrate how plaque toxins and embolic plaque contents may be involved in the pathogenesis of the initial symptoms in ACSs. In patients with VA, the sudden onset of severe anginal chest pain, S-T segment elevation, cardiac arrhythmias, and myocardial perfusion defects, all developing simultaneously, are consistent with spontaneous PU and discharge of plaque toxins into the coronary circulation. The quick reversal of these symptoms and signs, with the exception of the myocardial perfusion defects [229–231], is consistent with prompt neutralization, dilution, and/or washout of these same toxins. Prompt reversal of the entire syndrome is also consistent with unobstructed coronary flow.

Many investigators attribute VA to acute ischemia caused by reversible coronary vasospasm [229,231]. The triggering agent responsible for producing this spasm has not been identified [69,232,233]. Until it is, it cannot be stated with certainty that VA is caused by coronary vasospasm because the triggering agent may have a number of effects including, but not limited to, coronary spasm.

Angiographic, intravascular ultrasound, and post-mortem examinations of the area of coronary spasm commonly show the presence of atherosclerotic plaques and, in a few cases, the presence of acute lesions [69,229,234–237]. The triggering agent that precipitates spasm appears to be related in some way to active atherosclerotic disease, possibly an acute lesion at or near the site of spasm [229]. Our pathologic studies of patients who died as a result of ACD show the presence of one or more UPs, many of them unrecognized on angiography [57,147]. Because patients with VA are at risk of developing acute coronary events, we postulate that patients with VA also have one or more unrecognized, chronic UPs in their coronary tree. If this is correct, patients with VA have a source of plaque toxins and plaque contents with the potential to discharge plaque toxins into the coronary circulation and produce, directly or indirectly, the VA syndrome. Plaque toxins may be the "local factor" mentioned by Maseri as playing a role in coronary spasm and the VA syndrome [234].

The development of myocardial perfusion defects following an episode of VA indicates some type of myocardial injury has occurred [229–231]. Recovery of myocardial perfusion can occur in a matter of hours or can be prolonged and require several days, indicating the injury was temporary but was severe enough to cause ventricular dysfunction [229–231]. Had myocardial injury been caused solely by vasoconstriction or spasm, we would expect the spasm to subside with the symptoms, and the ventricular dysfunction to reverse in a matter of minutes. Prolonged ventricular dysfunction suggests additional factors, over and above spasm of the epicardial artery or the myocardial arterioles, caused the perfusion defects. We believe those additional factors are primarily plaque toxins originating from UPs that supply that segment of myocardium. Embolic material [64,128,212–216], as discussed above, would add to and aggravate the effect of the toxins. This direct toxic suppression of ventricular function could explain why some VA episodes are prolonged and unresponsive to treatment [231].

Figure 8 illustrates several UPs discharging plaque contents into the lumen. We have suggested the plaque contents from plaques such as these are intermittently "milked" into the lumen by pulsatile arterial pressure. The intermittent discharge of embolic plaque contents and toxins may be expected to produce intermittent symptoms. The VA syndrome could be caused by the discharge of toxins from plaques with this configuration, triggering not only intermittent coronary spasm, but also injury or dysfunction of the distal myocardium and/or the conduction system. Although the prognosis is generally good for patients with VA, an sudden cardiac death rate of 3.6% and an AMI rate of 6.5% indicate VA is not a benign condition but is another manifestation of active, ulcerative, coronary disease [231].

The presence of one or more chronic UPs that intermittently discharge plaque toxins could explain many of the following observations and findings in the patient with VA. For example, the increase in heart rate following an episode of VA [231] could be due to the release of catecholamines secondary to toxic stimulation and/or injury of the myocardium. Multiple sites of coronary spasm [238] could be due to the presence of multiple, actively discharging UPs [57]. The coronary spasm associated with PTCA [203,239] could be caused by the release of plaque toxins when the plaque is split by balloon inflation, its contents discharged. The S-T elevation characterizing an episode of VA, mimicking AMI, and with associated perfusion defects [231], can be explained by the release of a large amount of highly potent toxins that cause temporary transmural dysfunction, similar to that of a transmural infarction.

We believe coronary spasm is not the cause, but is one of many components of the VA syndrome triggered by plaque toxins.

Sudden Cardiac Death (SCD)

We hypothesize that SCD, an ACS whose initial symptom is a sudden lethal arrhythmia, is caused by the sudden dramatic arrest or disruption of cardiac conduction by plaque toxins, not by acute ischemia. SCD, as discussed here, refers to those patients with apparently normal hearts, and no symptoms of coronary heart disease, who collapse and die suddenly without warning [240]. The majority of these patients have unrecognized coronary atherosclerosis. The clinical and pathologic evidence supporting this hypothesis are as follows:

First, SCD in these patients occurs much too rapidly to be caused by acute myocardial or conduction system ischemia [207,218]. Ischemic injury and occlusive thrombosis take time to develop [241]. Even acute total occlusion of a coronary artery, as with a balloon during PTCA, does not produce sudden lethal arrhythmias [219].

Second, Holter monitor recordings of patients taken at the time of SCD, frequently do not show S-T changes to support a sudden onset of acute ischemia, certainly not the massive ischemia, to be expected if that was the cause [242,243]. Holter recordings do, however, often show an increase in heart rate, plus the development of complex ventricular ectopy just before the onset of the lethal arrhythmia [242,243]. The increase in heart rate may be due to the release of catecholamines by plaque toxins (244), postulated earlier regarding the VA patient. Complex arrhythmias indicate a serious disturbance of the conduction system.

Third, careful pathologic studies show the majority of SCD patients have one or more UPs in their coronary arteries and, therefore, have the lesions that could serve as a source of plaque toxins [57,64,150,156,245–247]. In addition, immediate coronary angiograms of SCD patients who are successfully resuscitated show the presence of complex UPs similar to those seen on postmortem examination [247–249]. Thus, the majority of SCD patients have acute structural abnormalities in the coronary arteries, along with the sudden, lethal, disruption of cardiac rhythm [57,139,156]. Abnormal structure correlates with abnormal function.

Fourth, contraction bands or myofibrillar degeneration, an early histologic sign of injury, have been found in the myocardium and in the conduction system of many SCD patients [250–252]. Contraction bands in the conduction system suggest injury occurred at approximately the same time as the onset of the lethal arrhythmia (Figures 24 and 25). The effect of plaque toxins on the myocardium and the conduction system may be quite similar to the immediate effects of absolute alcohol [210,211]. We propose that plaque toxins caused the contraction bands in the conduction system and are responsible for causing the lethal arrhythmia through sudden, direct injury to the conduction system [252].

Fifth, the lethal arrhythmia causing SCD is potentially reversible. Successful defibrillation and resuscitation of the SCD patient are not necessarily followed by an immediate recurrence of the original episode, indicating the triggering agent is transiently present. This observation, not consistent with a fixed coronary obstruction or an occlusive thrombus causing severe ischemia, is consistent with rapid washout of a plaque toxin. Furthermore, SCD survivors do not necessarily go on to develop occlusive thrombosis and/or AMI, so the arrhythmia was not a precursor to these events [245,248,253]. AMI is found in a minority of SCD patients, providing addi-

tional evidence the arrhythmia was not related to a prior, unrecognized, or silent AMI [57,240,244,253–255]. Our pathologic studies of 26 SCD patients without AMI showed 59 UPs, but only 23 (39%) were associated with luminal thrombosis. Of these only 9 thrombi (39%) were totally occlusive [57].

Sixth, infarction of the conduction system is rarely found at post-mortem examination, even with large trans-mural infarctions. The conduction system appears to be relatively resistant to ischemia and, presumably, relatively resistant to developing lethal arrhythmias caused by ischemia [252,256]. This inherent resistance is probably related to the rich collateral and anastomotic blood supply to the conduction system [257], and the rich and preferential blood supply to the peripheral conduction system via the left ventricular subendocardium [258]. In addition, since conducting fibers do not contract and may not have the same energy requirement as regular myocardium, they may be able to tolerate ischemia without serious injury or malfunction [252]. A serious insult is required to injure the conduction system, and to disrupt normal cardiac conduction, and to produce lethal arrhythmias.

Seventh, such interventions as coronary artery bypass surgery, PTCA with or without stents, aimed at relieving presumed myocardial ischemia in SCD survivors, have been generally unsuccessful [249], providing further evidence the lethal arrhythmia may not be caused by ischemia. We believe ischemia is an infrequent and remote pathogenetic factor in precipitating the lethal arrhythmia responsible for SCD.

Figures 24 and 25 show the pathologic findings in a 39-year-old white male who died SCD outside the hospital, shortly after complaining of chest pains. The patient had no prior history of heart disease, and the postmortem examination showed no evidence of AMI. Luminal stenosis, subsequently

determined to be approximately 80% of the cross-sectional area, was evident on the post-mortem angiogram (Figure 24A). Gross and microscopic examination of the stenotic area showed a shelled out plaque, with a small false channel (Figures 24B, C), but no evidence of thrombosis. No other acute coronary lesions were present in this patient.

Large amounts of plaque contents were present in the lumen distal to the UP (Figure 25A), as well as microemboli in the vasa vasorum (Figure 24D), and in the microcirculation of the distal myocardium (Figure 25B). Contraction bands were found in the myocardium and in the peripheral conduction system (Figures 25C,D), indicating recent injury. The clinical history plus the histologic evidence are consistent with sudden PU, the discharge of a large amount of plaque contents and plaque toxins, causing direct injury to the conduction system and the adjacent myocardium. The findings in this patient illustrate a common mechanism that could be responsible for SCD.

Unstable Angina (UA) and Non S-T Segment Elevation Myocardial Infarction (NSTEMI)

The prevailing opinion is that the UA syndrome and closely related NSTEMI are caused by acute myocardial ischemia secondary to plaque rupture [69], thrombus formation, and reduced coronary flow [259]. The diagnosis of myocardial ischemia is based on anginal chest pain, S-T segment depression, and, when present, the elevation of cardiac enzymes [69]. However, angiographic and pathologic studies often show one or more acute lesions, in the form of complex UPs, in the coronary arteries [57,69], but not necessarily thrombus formation or obstruction to coronary flow. Therefore, the UA patient, like the patient with SCD, has UPs that could serve as a source of plaque toxins. If VA and SCD are caused by plaque toxins, not by ischemia,

it is reasonable to postulate UA and NSTEMI are also produced by the same mechanism. What evidence supports this hypothesis?

The sudden onset of rest angina, nocturnal angina, or new onset severe angina [259], like SCD, occurs too rapidly for either thrombosis or ischemia to develop and precipitate these symptoms [241]. Moreover, anginal-type chest pain and S-T depression are not specific for ischemia and can be produced by other agents, particularly by toxic chemicals [210,211]. Anginal chest pain and S-T depression represent presumptive evidence, not proof, of ishemia. Thrombolytic drugs, intended to relieve ischemia, have not only failed to help the patient, they have led to an increase in fatal and nonfatal AMI [69]. As a result, these drugs are no longer recommended for the treatment of UA and NSTEMI [69]. There is reason to question ischemia in the pathogenesis of UA and NSTEMI syndromes.

If plaque toxins can stimulate sympathetic nerves in the heart to produce angina pectoris and are sufficiently potent to cause S-T changes and myocardial injury, then toxic injury mimics, and is indistinguishable, from ischemic injury. We hypothesize UA and NSTEMI syndromes are not due to ischemia at all, but are caused primarily by plaque toxins. Furthermore we believe that plaque toxins are sufficiently potent in themselves to cause myocardial injury and NSTEMI, without implicating ischemia, thrombosis, or obstruction of coronary flow. The subsequent development of thrombotic occlusion, ischemia, and S-T Elevation Myocardial Infarction (STEMI) in some UA or NSTEMI patients does not nullify our hypothesis. Once thrombotic occlusion develops, ischemic injury becomes superimposed on toxic injury, and an entirely different syndrome is present. This hypothesis could explain why thrombolytic drugs are contraindicated in the patient with UA and NSTEMI and sheds light on the mechanisms involved.

Many of the multiple, chronic UPs found in patients with ACD contain intraintimal and mural thrombi, with plaque contents incorporated into the body of the thrombus (Figure 26) [198]. An intraintimal thrombus acts to seal the UP [148] and to prevent the discharge of plaque contents and plaque toxins. A thrombolytic drug, by causing lysis of intraintimal thrombus, reverses the normal repair responses (Chapter 9), and reopens what is essentially a sealed UP [148,260]. Multiple UPs may be present in all 3 major coronary arteries [57], and may be reopened by these drugs and discharge plaque toxins to the entire myocardium. This could result in global myocardial dysfunction in spite of adequate coronary blood flow [222,261]. In addition to reopening the core, the lysis of thrombus also releases any plaque contents and toxins contained within the body of the thrombus, adding to the toxins liberated from the reopened core itself. Microembolic obstruction of the microcirculation could also contribute to toxic injury by obstructing antegrade, collateral, and anastomotic flow, as discussed above [128].

The lysis of intraintimal thrombus also allows blood to re-enter the now empty, or partially empty, necrotic core [262]. This reentry may change the dynamics within the core. For example, the reentry of blood could lead to dissection of blood along cleavage planes (Figure 7, Chapter 4), the formation of blind pockets (Figure 20), or the disruption and/or dislodging of the fibrous cap to form an occluding flap of tissue (Figure 20). Administering a thrombolytic drug is also associated with the activation of platelets [263,264]. Activation of platelets may lead to the formation of a new intraintimal thrombus in a newly reopened necrotic core, and lead to an occlusive thrombus and acute events. Therefore, thrombolytic drugs may convert a relatively stable UP into an unstable UP, resulting in fatal and non-fatal AMI. The mechanisms described

here could explain adverse clinical events, and the paradoxical response that follows thrombolysis in patients with UA and NSTEMI [264].

Aiming therapy at ischemia and thrombosis with thrombolytic drugs in patients with UA and NSTEMI fail [69] because ischemia and thrombosis are the wrong targets. The target is the UP and the associated discharge of plaque contents and plaque toxins. Therapeutic efforts should be aimed at the identification and elimination of the culprit UP responsible for discharging the plaque toxins and other material. How is this best accomplished?

At the present time, the approach offering the best chance of eliminating an actively draining UP is to intervene with a cardiac catheterization, identify the culprit UP, perform PTCA and place a stent in the area (Chapter 4). This approach would stabilize the UP by doing two things. First, the plaque would be completely drained by splitting the fibrous cap with a balloon, allowing coronary blood flow to carry away any remaining plaque contents and toxins. Second, the placement of a stent would stabilize the plaque by occluding any cleavage planes, would close any blind pockets, tack up any loose fragments of fibrous cap, and would produce unobstructed coronary flow across the lesion. Any complications, such as spasm or sudden ventricular arrhythmias resulting from the liberation of toxins during PTCA could be handled at the catheterization table. This view is supported by clinical studies that show early intervention in the patient with UA and NSTEMI results in a decrease of recurrent events and improvement in the long-term prognosis [265–268]. This approach would not disturb or affect intraintimal thrombi in UP elsewhere in the coronary tree or create more unstable lesions.

We believe UA and NSTEMI syndromes are caused by plaque toxins released from chronic UPs, not by ischemia secondary to thrombotic obstruction.

Thrombolytic drugs are contraindicated because they dissolve intraintimal thrombus, reopen sealed UPs (Figure 26), and lead to the discharge of more plaque toxins, and activate platelets leading to acute events. Therapeutic efforts aimed at stabilizing the UP and neutralizing plaque toxins would focus on the right target, in the right patient, for the right reasons.

S-T Elevation Myocardial Infarction (STEMI)

Why are thrombolytic drugs recommended for the treatment of STEMI [122,269], but not for UA and NSTEMI [69], if all have the same pathologic substrate in terms of UPs and the same overall plaque burden? The major difference is STEMI IS caused by ischemia secondary to acute obstruction of coronary flow, commonly by occlusive thrombosis, but UA and NSTEMI are not. The administration of a thrombolytic drug to the patient with STEMI is appropriate because this treatment is aimed at the right target, occlusive thrombosis, for the right reason, to restore coronary blood flow. Relieving the thrombotic occlusion with a thrombolytic agent relieves the ischemia, reduces the size of the infarction, and improves the prognosis [122,269].

Since the majority of occlusive thrombi are superimposed on a UP, we assume plaque toxins are discharged from the core prior to the formation of the thrombus [262], producing injury, initial enzyme elevation, and symptoms, before thrombosis and ischemia develops (Figure 8). After the formation of the occlusive thrombus, subsequent enzyme elevation is due to ischemic injury and infarction, superimposed on the initial toxic myocardial injury or infarction. These two different mechanisms for producing STEMI could explain the two different histologic types of myocardial infarction described by

Baroldi [251]. It is possible that we are dealing with two entirely different mechanisms in the pathogenesis of STEMI.

If two mechanisms are present, one ischemic and one toxic, they might offer an explanation of some of the observations, clinical findings, and complications following the administration of thrombolytic agents to the patient with STEMI [222]. The most important observation is that thrombolytic drugs are not 100% effective in opening acutely occluded coronary arteries, as might be expected if the occlusion were pure thrombus. We believe that the failure of thrombolytic agents to reperfuse an acute occlusion is due to the presence of a blind pocket and/or a flap of fibrous cap that do not respond to the lytic agent (Figure 20). Perforating this blind pocket or flap with a guide wire may be all that is necessary for the thrombolytic drug to perfuse the artery and lyse any associated thrombus [123].

Reperfusion of an obstructed artery with a thrombolytic agent or with PTCA may be followed by reperfusion injury, manifested by failure of the injured myocardium to recover contractility despite adequate coronary flow, the no-reflow phenomena [222]. It is our theory that reperfusion injury and the no-reflow phenomena are caused by plaque toxins liberated from UPs, both before the thrombotic occlusion and then again after reperfusion. Thrombolysis restores coronary flow, but it also liberates any toxins contained within the thrombus, reopens the necrotic core, and releases more plaque toxins.

No-reflow is believed to be due to severe injury to the microcirculation, particularly the endothelial lining of these vessels, obstructing flow. Toxic injury to the microcirculation may be so severe that angiographic dye leaks into the myocardium and results in the myocardial staining or blush often observed at angiography [222]. Further, these toxins may circulate to the peri-infarction zone, not only enlarging

the infarction, but also causing post-infarction angina despite adequate coronary flow [222]. Toxins may also injure the peri-infarction tissue, causing re-entrant arrhythmias, and/or they may directly injure the conduction system and precipitate the various arrhythmias often observed following thrombolysis [270,271]. These observations may explain why a bigger, more wide open artery is not necessarily better if this flow brings with it more toxins or more emboli [222]. These toxins may be the “untreated factor” or unrecognized factor responsible for the no-reflow phenomena referred to by Gibson [126].

Thrombosis versus Plaque Toxins

Although thrombolytic drugs relieve thrombotic occlusion and improve survival in patients with STEMI, it is becoming increasingly apparent that thrombosis and resultant ischemia are not the primary cause nor the primary pathologic lesion in many other ACSs. In other words, “Ischemic Heart Disease” may not be ischemic at all, in many patients, but “Toxin Induced Heart Disease.” It is a mistake to attempt to explain all the facets of ACD on the basis of ischemia and/or occlusive thrombosis. If the fundamental lesion underlying all ACS is the UP, and UPs discharge plaque toxins capable of causing direct injury to cardiac tissues, then it is reasonable to consider plaque toxins as a major additional etiologic factor in the pathogenesis of ACD. Thrombosis is but one of the many components, reactions, and responses that characterize ACD. Thrombosis is not inherently pathogenic, but becomes pathologic only in certain circumstances (Chapter 9). Therefore, preventing or treating thrombogenic responses per se is not appropriate for all ACSs and correcting thrombosis corrects only one component of ACD. There are many other components to consider.

Myocardial Rupture and Thrombolytic Drugs

Myocardial rupture is a well-recognized complication of thrombolytic therapy for STEMI, occurring much more frequently in these patients than in patients not receiving a thrombolytic drug [272–274]. Myocardial rupture occurs only in patients with transmural infarctions [273] and appears to be related to excessive softening and liquefaction of infarcted tissue, beyond what is observed in the majority of transmural infarctions. Infarction and necrosis are not synonymous terms [200] because fully necrotic tissue has no structure while infarcted myocardium still has many structural elements intact. Therefore, when the infarcted tissue becomes excessively necrotic and is without any residual fibrous structure, it is prone to rupture.

What is the pathogenesis of myocardial rupture in general, and after thrombolysis in particular? Why does excessive liquefaction occur, and why does it occur more frequently in the patient receiving thrombolytic drugs? Myocardial rupture has been attributed to a lack of collateral and/or anastomotic blood flow to the infarcted area [275]. Embolic obstruction of these alternate channels could occur as a result of emboli originating from the culprit occlusive thrombus as it undergoes lysis, or from emboli originating from mural or intraintimal thrombi in UPs in uninvolved coronary arteries [64] that supply collateral flow to the obstructed, culprit artery. Lack of well developed collateral flow in patients who develop their first infarction may also be a factor in rupture as well [275].

We hypothesize the liquefaction of infarcted myocardium is caused primarily by excess plaque toxins that become trapped or localized in the infarcted area. Obstruction of antegrade flow and embolic obstruction of collateral or anastomotic flow may delay or prevent neutralization or washout of

these toxins. The trapped toxin could cause excessive softening, liquefaction, and, if not neutralized, rupture of the myocardium. This could explain myocardial rupture in patients with small infarctions involving secondary branches [276], probably with limited collateral and/or anastomotic flow where a toxin could be highly concentrated.

The use of primary PTCA and stents without thrombolytic drugs for the treatment of STEMI has resulted in a decrease in myocardial rupture compared with results following the use of thrombolytic drugs [277]. The reduction of myocardial rupture following PTCA may be explained by the removal of the obstructing luminal thrombus, restoring blood flow without disturbing intraintimal thrombus, not reopening sealed UPs, and the washout of any retained toxins by restored blood flow.

Stunned Myocardium

Stunned myocardium is defined as viable but dysfunctional, akinetic, dyskinetic, noncontractile myocardium in the presence of adequate coronary blood flow. Myocardial stunning is usually a temporary phenomenon, lasting only hours to days, often associated with ACSs including VA, SCD, UA and NSTEMI [278,279]. Most investigators believe stunning is related in some way to ischemia produced by obstruction or partial obstruction of blood flow, sufficient to cause cellular dysfunction and loss of contractility, but not of viability [201,279]. However, stunned myocardium is non-contractile, yet it has normal perfusion on thallium scintigraphy, resulting in a “perfusion-contraction” mismatch [279]. If the stunning were due to ischemia, the perfusion scan should show a decreased uptake of thallium to go along with the proposed decrease in coronary flow. The failure to establish the presence of ischemia by this objective method is strong evidence stunning is not caused by ischemia.

We believe myocardial stunning is another ACS, which could be explained on the basis of plaque toxins liberated from unrecognized UPs. Myocardial injury caused by a plaque toxin may be temporary and reversible, depending upon the amount of toxin discharged from the necrotic core and the speed with which it is neutralized or washed away by flowing blood. If stunning is caused primarily by plaque toxins and not by obstructed blood flow, this could explain the quick reversal of stunning after an episode of VA, UA, or focal myocardial dysfunction in patients with unobstructed coronary arteries [280,281]. The discharge of plaque toxins from a non-obstructive UP during exercise could also explain stunning associated with exercise testing and its quick reversal in the post-exercise period [280]. Furthermore, stunning is attenuated by the use of superoxide dismutase, an enzyme that tends to neutralize free radicals, which offers further evidence that stunning may be related to toxic injury [201,282,283]. It is interesting that Kloner, et al., concluded that myocardial stunning consists of two components, an ischemic component and a toxic component caused by reactive oxygen species, with the toxic component appearing to be larger than the ischemic component [201]. We believe stunned myocardium is caused primarily by plaque toxins from UPs, quickly washed away before permanent injury or infarction can occur, not by ischemia.

Silent Ischemia (SI)

SI may not be caused by ischemia at all, but by the recurrent release of subclinical amounts of plaque toxins, discharged from asymptomatic, unrecognized chronic UPs (Figure 8). The diagnosis of SI is commonly based on S-T segment depression on a Holter monitor recording or during exercise testing [284,285]. S-T depression is not specific for ischemia and could be caused by plaque toxins, as already discussed. The prompt reversal of S-T depression in the patient with SI is consistent with

temporary injury caused by toxins and quick washout of these toxins by circulating blood, as in myocardial stunning [284]. We hypothesize that patients with SI develop ACSs because the plaque discharging the toxins develops a larger ulceration and discharges sufficient toxins to produce clinical syndromes, such as UA or NSTEMI, or proceed on to develop coronary thrombosis and STEMI [286,287]. If this is correct, identifying patients with silent and reversible S-T depression on Holter monitors may identify patients with active, open, unstable UPs in whom an intervention could prevent an acute event. Our hypothesis is supported by recent studies confirming early intervention with PTCA and stent placement reduces the acute event rate in SI patients [287].

Oral IIB/IIIA Inhibitors

Oral IIB/IIIA inhibitors have been dropped from clinical testing because of an unexplained increase in adverse clinical events, including bleeding and fatal and non-fatal AMI [141,288,289]. The oral IIB/IIIA inhibitors were given on the assumption that acute coronary syndromes such as UA and NSTEMI, were caused by ischemia related to thrombus formation. As discussed above, we hypothesize these ACSs are NOT caused by thrombosis or ischemia, and this explains why the IIB/IIIA inhibitors did not benefit these patients. We believe the oral IIB/IIIA inhibitors were given to the wrong patients for the wrong reasons, causing harm rather than benefit [141].

The failure of the oral IIB/IIIA inhibitors is the same as that postulated for thrombolytic drugs. These agents cause excessive bleeding and fail to prevent ACSs in unstable coronary syndromes because they unseal UPs and prevent the normal hemostatic responses required for repair. IIB/IIIA inhibitors, like

thrombolytic agents, transform stable UPs into unstable plaques, leading to the discharge plaque toxins that initiate acute coronary events.

Why are intravenous IIB/IIIA inhibitors successful in preventing many of the complications associated with coronary interventions, including stent placement in patients with STEMI, NSTEMI, and UA [290]? In our view the difference lies in the duration of treatment. The intravenous IIB/IIIA inhibitors are given for a very short period of time. They do not significantly disturb intraintimal thrombus in UPs, but they prevent new thrombus formation at the site of the PTCA and/or stent. In contrast oral agents are given for long periods of time and prevent normal hemostatic responses of UPs, essential to control bleeding and resolution of injury. It is the prevention of these normal hemostatic responses that results in bleeding into the plaque core, swelling of the core, the creation of an unstable lesion, and the production of acute coronary events.

Aspirin (ASA), UPs, and Plaque Toxins

Why is ASA, a platelet inhibitor, successful in preventing primary and secondary acute coronary events [291] when oral IIB/IIIA inhibitors, powerful anti-platelet agents, precipitate acute coronary events? What does ASA actually do, and what is involved in the prevention of acute coronary events? ASA has no known effect on either the formation or prevention of PU, but appears to have significant effect on those developments that take place after PU [291,292]. We hypothesize ASA acts by preventing the growth of thrombus, but has little or no effect on thrombus that is already present, whether occlusive, mural, or intraintimal thrombus. If this is correct, ASA prevents acute events by NOT disturbing the normal hemostatic and thrombogenic responses aimed at injury repair, but prevents the tendency for a thrombus to grow above and beyond what is

required for injury repair (Chapter 9). As a consequence, the UPs are not reopened, plaque toxins are not released, an unstable lesion is avoided, and resolution and repair of an UP can occur. ASA may also prevent the platelet aggregation response associated with the release of thrombogenic plaque contents [207], in this way preventing or reducing the number and size of platelet microemboli passing into the distal circulation during acute plaque rupture.

Conclusions

We believe, based on the foregoing evidence, that atherosclerosis is caused by a single infectious agent, or by multiple infectious agents through molecular mimicry, which enter the artery wall at any breach of endothelial integrity and establish a focus of infection. This organism then grows and expands, causing first a proliferation of diseased fibrous tissue, then destruction of this tissue to form atheromas. The organism grows and expands by direct contiguity in both circumferential and longitudinal directions, fusing with adjacent atheromas. The organism grows and expands by subverting normal defensive responses to its own purposes. Lipid is retained in all plaques because the organism requires oxidized LDL, or some variant thereof, as a source of energy to fuel replication and expansion.

Control of risk factors, particularly the reduction of cholesterol and other lipids, may cause the organism revert to a dormant state for an indefinite period. A chronic inflammatory response develops because the IA is a foreign organism, and inflammatory defenses mobilize against it. Calcification, which occurs quickly on degenerated tissue and uses normal bone-forming mechanisms, is effective in delaying the growth and expansion of the infectious organism. Adventitial tissue is inherently resistant to the infectious agent, thickening to pre-

vent outward expansion into the pericardial space and confining the organism to the intimal layer. The only outlet for an expanding atheroma is to ulcerate and drain into the lumen of the coronary artery. Although the organism is usually most active deep within the intimal layer, it may also localize to the endothelial surface and spread, erysipelas-like, in all directions from a central focus.

The natural course of events for any necrotic focus is to spontaneously rupture and drain into a body cavity, to the external surface of the body, or to be replaced by fibrous tissue. We believe most atheromas ulcerate and drain at some time during their existence, usually when the plaque is relatively small.

UPs frequently persist as chronic, indolent, festering, gradually progressive, inflammatory lesions, are asymptomatic, but provide the substrate for rapid progression leading to acute coronary events. UPs are the fundamental lesion underlying all ACSs, and the variety of ulcerations is what gives rise to the many different ACSs.

The atheromatous core contains many plaque toxins. These toxins, when discharged from an UP, stimulate and/ or injure all cardiac structures. The effect of these toxins depends on the amount released, their potency, the structures affected and how quickly the toxins are removed by circulating blood. We believe the release of plaque toxins is primarily responsible for VA, SCD, UA, and NSTEMI, myocardial rupture after AMI, myocardial stunning, and silent ischemia.

Future Directions

If atherosclerosis is found to be caused by an infectious organism, we assume an antibiotic or antiviral method will be developed to treat the organism in order to eliminate the disease. If this approach is successful and we are able to eradicate the infectious organism, would this remove the necessity to stop smoking, reduce cholesterol, blood pressure, and other risk factors? Would preventive measures go by the board in favor of antibiotics, taken whenever the organism becomes active?

We visualize that current preventive measures will continue to be necessary, even if an infectious organism is identified and we have a specific antibiotic or a vaccine. We know organisms that give rise to chronic infectious diseases may become resistant to antibiotics and emerge in even more resistant forms, as with tuberculosis. AIDS is treated with drugs whose aim is to force the virus into remission, rather than an attempt to eradicate the organism from the body. The same may be true of atherosclerosis. If we can identify patients who are carriers of the organism, then we may be able to institute specific measures to prevent transmission. Identifying the organism may allow us to institute measures that keep it in a state of remission, even if not eradicated. Adding an antibiotic or antiviral treatment to risk factor modification may accelerate a remission, forcing the organism into a dormant state. This would have the same effect as eradication if the organism could be kept dormant indefinitely.

Based on the observations put forth in these chapters, particularly the infectious organisms ability to subvert normal defense mechanisms, we believe it may be difficult to eradicate and will present a continuing challenge in the future. As with tuberculosis, the fight requires ongoing vigilance to diagnose, treat and limit the growth of this organism.