An important new direction of cardiovascular research—an attempt to identify the mechanisms of acute disease onset—is now emerging. The effort is based in part on the recognition that activities of the patient frequently play a prominent role in triggering the onset of acute cardiovascular disease (1). The acute precipitant may act by causing disruption of a vulnerable coronary artery plaque and occlusive thrombus formation producing acute myocardial infarction and sudden cardiac death. This relatively simple, yet new, insight into a mechanism of disease onset suggests research approaches that may lead to methods for preventing the leading cause of death in the industrialized world.

The relative position of this new field of research on acute risk factors is shown in Figure 1. The narrow column in the center of the figure indicates the onset of coronary thrombosis causing nonfatal myocardial infarction or sudden cardiac death. The four wide columns represent research areas focusing on the different stages of coronary artery disease. Chronic risk factors, acute treatment and long-term management have been areas of intense research interest and considerable progress. In contrast, the events that occur in the hours and minutes before the onset of thrombosis and are the causes of conversion of chronic to acute disease—have received relatively little attention.

**Scientific background for the new field.** The increased prospects for success in this hitherto difficult and relatively unapproachable field of study result from the multiple advances in understanding of acute coronary artery disease achieved during the 1980s. The work of DeWood et al. (2) clearly established that acute thrombosis causes myocardial infarction. Davies and Thomas (3), Falk (4) and others, building on the pioneering studies of Constantinides in the 1960s (5), identified the pathoanatomic role of plaque disruption and thrombosis in sudden death and unstable angina, as well as in myocardial infarction. Puster and colleagues (6) characterized the types of arterial injury likely to produce thrombosis, and Willerson et al. (7) identified interventions capable of modifying conversion of chronic to acute disease in experimental animals. Randomized clinical trials have demonstrated that aspirin (8), beta-adrenergic blocking agents (9), lipid-lowering regimens (10) and, more recently, angiotensin-converting enzyme inhibitors (11) can prevent myocardial infarction, but the mechanisms of the beneficial effects are not fully identified.

Our group (12,13) provided the first objective evidence that infarction onset is more frequent in the hours after awakening, thus identifying triggering of onset by activities of the patient. Plaques that are disrupted and cause disease onset have been found to contain higher concentrations of lipids and macrophages than are found in nondisrupted plaques (14,15). Finally, it is now recognized that the entire sequence of plaque disruption and occlusive thrombosis often begins in lesions previously causing <50% reduction of the diameter of the arterial lumen, as judged by prior angiograms (16) and angiographic assessment, after thrombolysis.

Although these gains in understanding are impressive, the field of triggering remains relatively unexplored, and only a small fraction of its potential benefit has yet been realized. Heart attack, the term for the combined disorders of myo-
cardiac infarction and sudden cardiac death, continues to account for an estimated 500,000 deaths/year in the United States (18). Even the optimal utilization of thrombolytic therapy for myocardial infarction—the advance on which the greatest attention has been focused—could prevent only 25,000 deaths acutely, or 5% of the total, because most deaths occur suddenly before any type of treatment can be initiated (19). A major challenge for the 1990s is to use the advances of the 1980s as starting points to identify, and subsequently block, the acute processes triggering onset of coronary artery disease.

Triggers, acute risk factors and vulnerable plaques. Three important concepts—triggers, acute risk factors and vulnerable plaques—provide an intellectual framework for understanding disease onset. Definitions and the relation among the three concepts are presented in Figure 2.

Figure 3 presents an expanded version of this concept, demonstrating its interaction with the established pathophysiologic features of myocardial infarction and sudden cardiac death.

The process begins with a nonvulnerable atherosclerotic plaque shown on the left. This plaque may become vulnerable to disruption, for reasons that are poorly understood at present but include increases in macrophage and lipid content and inflammatory cell products. At this point, hemodynamic or vasoconstrictive forces generated by a physical or psychologic stress might disrupt the plaque. If the plaque disruption produces a major thrombogenic stimulus such as

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Figure 1. Position of the relatively undeveloped area of research on conversion of chronic to acute disease with respect to the traditional areas of research on coronary artery disease. ASA = aspirin; CABG = coronary artery bypass grafting; EP = electrophysiologic; ETT = exercise treadmill testing; MI = myocardial infarction; PTCA = coronary angioplasty.

Figure 2. Definitions and the relations among triggers, acute risk factors and vulnerable plaques.
a type III lesion with medial injury, an occlusive thrombus forms rapidly leading to myocardial infarction or sudden death. If the plaque disruption produces only a minor thrombogenic stimulus, the patient may be asymptomatic, yet platelet aggregates and thrombin generation may contribute to growth of the plaque or cause unstable angina or non-Q-wave myocardial infarction (20). At this point, other external triggering activities could cause the artery to constrict and the thrombus to become occlusive or could lead to increased coagulability, causing the clot to grow, leading to complete occlusion and myocardial infarction or sudden death.

Disease onset due to triggered disruption of nonstenotic lesions requires an addition to the traditional view of the process through which an atherosclerotic plaque grows and eventually produces clinical symptoms. The traditional teaching has been that atherosclerotic plaques cause disease after passing through the stages of the fatty streak and the fibrous plaque to the stenotic, complicated lesion. The new understanding warrants addition of a significant pathway to clinical disease through disruption of a nonstenotic vulnerable plaque.

Unquestionably, the best approach to prevention of coronary artery disease is primary prevention of atherosclerosis, and extensive research toward this goal must continue. However, a multifaceted approach is warranted and pursuit of the opportunities exposed by this new information is essential. The efforts are complementary and there is a high likelihood that the basic scientific methods developed for study of the fatty streak can be used to identify the mechanisms through which more advanced plaques become vulnerable to disruption.

It is possible to understand much of the success of preventive therapy through interference with various acute processes. For instance, aspirin can prevent infarction by preventing increases in coagulability, whereas beta-blockade could possibly reduce the hemodynamic stresses leading to plaque disruption. The successful reduction of acute coronary events by lipid-lowering therapy demonstrated by Brown et al. (21) may well have been achieved by reducing plaque vulnerability or coagulability, as indicated by the finding that fewer nonstenotic plaques produced coronary events in the groups with the more significant lipid lowering.

As in any new field, there are many unanswered questions. What are the triggers of onset? For what percent of
events can a trigger be identified? How do the triggers operate? What are the acute risk factors produced by the trigger? Is it possible to sever the link between a potential trigger and its pathologic consequence? Can we prospectively identify plaques vulnerable to disruption? Can such vulnerable plaques be treated?

New research opportunities. Recent progress in scientific methods on the epidemiologic, clinical and basic science levels provides the opportunity to address these previously unanswerable questions. On the epidemiologic level, a new technique termed the "case-crossover" analysis has been developed by Maclure and Mittleman (12,22,23) and successfully utilized to analyze triggering of infarction by heavy physical exertion. The method utilizes each patient as his or her own control for the expected frequency of a potential triggering activity in a 1-h hazard period before the onset of the event. This permits comparison of observed to expected frequencies without the confounding encountered in traditional case-control studies. Comparison of triggering in various subgroups of patients can also suggest differences in pathophysiology of onset, as demonstrated by the observation that patients with prior beta-adrenergic blockade do not have the increase in infarction in the hours after awakening observed in those not receiving such therapy (23).

On the clinical level, the response to thrombolytic therapy and the new technology of the catheterization laboratory provide new opportunities to study this process. For instance, with intracoronary angioscopy, it is now possible to visualize in living patients the disrupted lesions causing the acute coronary syndromes (24), rather than relying solely on autopsy studies that are complicated by patient selection and postmortem changes. Angioscopy, with its ability to detect yellow plaques and red versus white thrombus, may aid in the search for surface characteristics of the vulnerable plaque. Intracoronary ultrasound (25), with its ability to penetrate beneath the lumen surface and reveal certain tissue characteristics, may have the potential to detect within the arterial wall lipid-rich plaques that are vulnerable to disruption.

On the basic science level, developments in cellular and molecular biology offer promise of methods to control acute risk factors and treat vulnerable plaques. For instance, once the mechanisms controlling chronic endogenous fibrinolytic activity are sufficiently understood, it might be possible to eliminate the daily decreases in endogenous fibrinolysis that possibly contribute to the occurrence of coronary thrombosis. If the growth factors (26) and chemotactic agents (27) controlling macrophage infiltration of plaques were fully identified, perhaps the development of vulnerable plaques could be prevented. Fortunately, there is an animal model of triggering developed more than 30 years ago by Dr. Paris Constantinides and his colleagues (28) in which these ideas can be explored. The injection of Russell viper venom, a proteolytic procoagulant, into atherosclerotic rabbits triggers localized platelet-rich thrombi remarkably similar to those observed in patients. Reinroduction of this model will permit study on the basic science level of many aspects of the triggering process (29).

Thus, a broad new area of potential research is now apparent, and the tools with which to address its major questions are available. Numerous signs indicate that the area is receiving increased attention. Epidemiology, which has in the past focused on chronic risk factors, has recently devoted increased attention to acute risk factors. Clinical cardiology, which has directed its efforts toward treatment of the disease once it has occurred, is now examining findings during the acute onset of disease to reason backward to the triggering events. Journals are featuring triggering articles, and both the American Heart Association and the American College of Cardiology have created structured sessions for presentation of triggering research. The greatest impetus to the rapid development of this field would be an increase in federal funding. Unfortunately, the limited National Institutes of Health budget has severely curtailed the active pursuit of this and other new scientific opportunities.

Although the rate of research progress may not be optimal, the continued unacceptably high rates of morbidity and mortality from heart attack, and the great potential that could result from understanding triggering, ensure that advances in this field will continue. Conventional attempts to reduce the annual 500,000 deaths from heart attacks must be vigorously pursued, but the reduction of chronic risk factors becomes progressively more difficult, and even as effective a treatment as thrombolysis can prevent only a limited number of heart attack deaths. Insight into triggering and acute risk factors offers a new approach to prevention by identifying and treating the plaques that are vulnerable to rupture, and by finding means to sever the linkage between a potential trigger and its catastrophic consequences. This new approach has great potential to continue and accelerate the decline in cardiovascular disease.

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References


