

ingly run up against the historical reluctance of American voters to allocate much more than 18 percent of the GDP to federal spending. Since 1946 the federal government's share of the GDP has stayed remarkably close to 18 percent, going below 16 percent in only 2 of the 57 years and above 20 percent in only 1.

One response, of course, is to ignore this *de facto* ceiling on federal revenues and assume that an increasingly graying society will want to spend a greater share of its money on pensions and health care for the elderly. But Medicare and Social Security both rely on a substantial component of payroll-tax financing, the burden of which falls primarily on nonelderly workers. Although many of these workers have elderly parents and are anticipating their own age of eligibility, it is unclear whether there would be political support for such a large transfer of resources from the nonelderly to the elderly.

The late Senator Daniel P. Moynihan (D-N.Y.) famously characterized Social Security as the third rail of American politics. Since he made that remark, the dollars spent on both Social Security and Medicare have increased, raising that third rail's voltage. As a result, an enormous amount of polit-

ical capital is required to address the issue of long-term financing, making it highly tempting for the next administration simply to leave the matter to its successors. Unfortunately, deferring the issue will only exacerbate the problem for future administrations and taxpayers.

Dr. Newhouse reports serving on the board of directors of and holding equity in Aetna.

From the Department of Health Care Policy, Harvard Medical School; and the Department of Health Policy and Management, Harvard School of Public Health — both in Boston; and the Kennedy School of Government, Harvard University, Cambridge, Mass.

1. CBO's March baseline projections. In: CBO's current budget projections. Washington, D.C.: Congressional Budget Office, March 2004. (Accessed October 1, 2004, at <http://www.cbo.gov/showdoc.cfm?index=1944&sequence=0#table1>.)
2. Blendon RJ, Benson JM, Brodie M, et al. Voters and health care in the 1996 election. *JAMA* 1997;277:1253-8.
3. Jamieson A, Shin HB, Day J. Voting and registration in the election of November 2000. Current population reports. P20-542. Washington, D.C.: Census Bureau, February 2002.
4. Congressional Budget Office. The budget and economic outlook, September 2004. (Accessed October 1, 2004, at <http://www.cbo.gov/showdoc.cfm?index=5773&sequence=2>.)
5. Organisation for Economic Co-operation and Development. Health data 2000. (Accessed October 1, 2004, at http://www.oecd.org/document/30/0,2340,en_2649_33929_12968734_119656_1_1_1,00.html.)

Triggering Myocardial Infarction

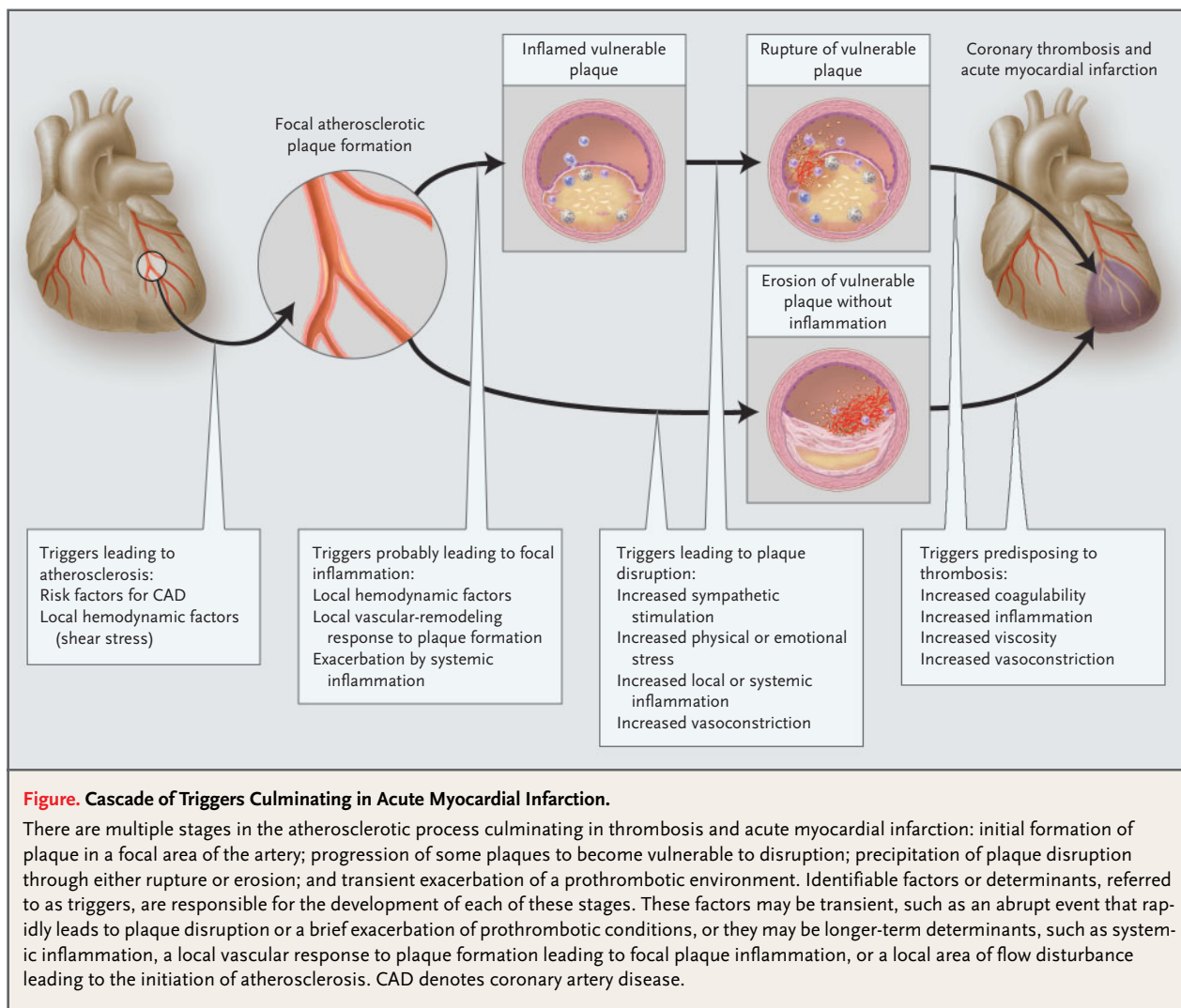
Peter H. Stone, M.D.

Related article, page 1721

Enormous progress made during the past few decades has dramatically enhanced our understanding of the pathobiology and pathophysiology responsible for acute myocardial infarction. Investigations in vascular biology have elucidated the critical role of growth factors, the proliferation of smooth-muscle cells, and the central role of inflammation in the initiation and progression of atherosclerosis.¹ Research has also focused on the initiating events or "triggers" that qualitatively alter the stable or quiescent phase of coronary atherosclerosis and initiate a cascade of events that culminates in acute myocardial infarction. Some triggering phenomena may exert a single, transient effect on the pathophysiologic process, such as a surge of sympathetic activity, whereas others exert a more varied and pervasive effect, amplifying risk at multiple points and over a longer period. In this issue of the

Journal, Peters et al. (pages 1721–1730) provide compelling epidemiologic evidence that particulate air pollution from traffic may trigger the abrupt onset of acute myocardial infarction. An understanding of air pollution in the larger context of triggering of the entire process of atherosclerosis suggests, in addition, that air pollution plays a more complex and multifaceted role in the development of cardiovascular disease over the longer term.

As initially described 15 years ago, the triggering of acute myocardial infarction typically begins with the so-called vulnerable or high-risk coronary atherosclerotic plaque, a focal lesion in jeopardy of plaque disruption.² The vulnerable plaque is usually an inflamed, thin-cap fibroatheroma, characterized by a lipid-rich, atheromatous core with cholesterol crystals and necrotic debris, a thin fibrous cap with an infiltration of macrophages and lymphocytes,



and decreased smooth-muscle-cell content, and associated with expansive remodeling of the outer vessel wall.³ The inflammatory cells associated with this type of high-risk plaque express a variety of cytokines and chemokines that contribute to inflammation and oxidative stress, as well as matrix metalloproteinases that can degrade the extracellular matrix, thereby weakening the plaque's fibrous cap and rendering it prone to rupture. Other, less common, coronary plaques that are prone to disruption may be characterized by extensive proliferation of smooth-muscle cells in a proteoglycan-rich matrix without the accompanying intense inflammation and thin fibrous cap; in such cases, a thrombus may form from a superficial erosion of the endothelial surface.

In persons with such a pathobiologic substrate

of vulnerable plaque, the initiating event or trigger that may lead to the disruption of the plaque is often an external activity associated with increased sympathetic stimulation, such as physical or emotional stress or vasoconstriction. This trigger may lead very rapidly to the rupture of the vulnerable plaque, exposing the bloodstream to the thrombogenic contents of the plaque or the denuded endothelial surface, leading to rapid thrombus formation and, consequently, acute myocardial infarction. An additional trigger or initiating process, such as a transient increase in coagulability, inflammation, viscosity, or vasoconstriction, may further predispose to the formation of a thrombus.

Recently, it has been suggested that the sites at which triggers contribute to the development of acute myocardial infarction can be extended proxi-

mally in the pathophysiologic process⁴ (see Figure). Although atherosclerosis may affect the coronary tree diffusely, the principal manifestations of coronary plaque are highly focal. In a susceptible person with an adverse risk-factor profile, local hemodynamic disturbances, such as small areas of disturbed coronary blood flow and low shear stress, constitute the initiating event or trigger leading to focal atherosclerotic plaque formation and progression, which may continue for years. Although there may be many such areas of intimal thickening in early stages of atherosclerosis, only a subgroup, and perhaps a very small subgroup, of these coronary plaques become inflamed or vulnerable at any one time. Other plaques may acquire characteristics of fibrosis and scarring, and still others may remain quiescent.

The triggering factors that determine which of those early plaques will progress and become inflamed are unknown, but it is likely that local hemodynamic factors, local vascular-remodeling responses, and the degree of systemic inflammation all contribute. Plaques that are inflamed and prone to rupture are those in which there is expansive or outward remodeling of the arterial wall, whereas those that are more fibrotic and scarred, without active inflammation, are associated with constrictive or inward remodeling. The divergent vascular-remodeling characteristics most likely reflect the balance in the dynamic regulation of collagen synthesis and breakdown.

Epidemiologic studies have long demonstrated the increased cardiac morbidity and mortality associated with particulate air pollution, and recent investigations have focused on the mechanistic role of air pollution in cardiovascular disease.⁵ Inhalation of particulate air pollution into the lungs leads to both pulmonary and systemic inflammation, with induction of cytokines and chemokines and generation of oxidative species. These injurious molecules create and exacerbate inflammation and oxidative stress, which lead to direct vascular injury, atherosclerosis, and autonomic dysfunction. Particulate air pollution also rapidly leads to a significant increase in fibrinogen, plasma viscosity, and platelet activation, as well as the release of endothelins, a

family of potent vasoconstrictor molecules. Studies in animals have clearly documented the short- and long-term adverse effects of particulate air pollution on each step of the triggering cascade of coronary disease culminating in acute myocardial infarction: accelerated atherosclerosis, vasoconstriction, and increased thrombogenesis.

The association between exposure to traffic and the abrupt onset of myocardial infarction described by Peters et al. suggests that particulate air pollution from traffic may have led to abrupt plaque disruption and perhaps to the exacerbation of a thrombogenic environment. Transient, intense inflammation, vasoconstriction, and increased coagulability, alone or in combination, are potential culprits in this process.

In addition to these extremely short-term effects of particulate air pollution, its deleterious longer-term effects on the entire gamut of atherosclerotic triggers cannot be overemphasized. Decades of epidemiologic evidence underscore the cardiovascular morbidity and mortality related to air pollution. The proinflammatory, proatherosclerotic, and prothrombotic effects of particulate air pollution are compelling. As both epidemiologic and now mechanistic evidence mounts, there is greater urgency to accelerate our efforts to reduce particulate air pollution and to improve cardiovascular health.

Dr. Stone reports having received grant support from Boston Scientific and Pfizer.

From the Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston.

1. Libby P. Inflammation in atherosclerosis. *Nature* 2002;420:868-74.
2. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989;79:733-43.
3. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000;20:1262-75.
4. Stone PH, Coskun AU, Yeghiazarians Y, et al. Prediction of sites of coronary atherosclerosis progression: in vivo profiling of endothelial shear stress, lumen, and outer vessel wall characteristics to predict vascular behavior. *Curr Opin Cardiol* 2003;18:458-70.
5. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 2004;109:2655-71.