ty is weak; published estimates of within-subject variability (*15–17*) indicate that CRP measurement could differ by 71 to 84% from an earlier reading. (iii) The likelihood of beneficial intervention is unknown. We don't know how to intervene (we don't understand the mechanisms underlying the observed associations), and we don't know if intervention alters outcomes. Taken together, these considerations argue in favor of caution before plunging ahead.

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Atherosclerosis and Inflammation

IS ATHEROSCLEROSIS AN INFLAMMATORY disease that can occur even in the presence of "low" or "healthy" plasma concentrations of cholesterol, as Gary Taubes' article "Does inflammation cut to the heart of the matter?" (News Focus, 12 April, p. 242) implies? The answer lies in what those terms actually mean. We have argued that labeling a pathophysiologic process "inflammatory" can be misleading, because inflammation always has an underlying cause (*1*). For example, even though the lung is full of inflammatory cells in Pneumococcal pneumonia, the disease is considered infectious—the root cause—but with an important, secondary inflammatory reaction. Regarding atherosclerosis, a large body of experimental evidence supports the "response to retention" hypothesis of early atherogenesis: Retained or trapped low-density lipoprotein (LDL) particles within the vessel wall become enzymatically and oxidatively modified, thereby provoking, among

other things, an influx of inflammatory cells that accelerate LDL retention, early lesion development, and ultimately the progression to life-threatening plaques [reviewed in (*2*–*6*)]. In an important, recent validation of this hypothesis, LDL that was genetically engineered to be poorly retained was found to be nearly incapable of producing early atherosclerotic lesions in vivo (*7*).

This brings us to the question of what is a "low" or "healthy" plasma cholesterol level. Human atherosclerosis is vanishingly rare when LDL concentrations are below 80 mg/dl, regardless of other risk factors (*2*), and no widely accepted animal models of atherosclerosis exist that arise from either genetic derangements of immunity or distal sites of chronic inflammation in the absence of plasma lipoprotein abnormalities. Although the cholesterol levels referred to in Taubes' article may seem low or healthy compared with the very high average values in Westerners, they are still above 80 and therefore merit serious concern.

Therapies directed at both lipoprotein retention and the responses—including inflammation—to retained material will have the greatest chance for continued successes against atherosclerosis. We must not neglect either the primary or secondary processes in this deadly disease.

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CORRECTIONS AND CLARIFICATIONS

PERSPECTIVES: "Flood basalts—bigger and badder," by P. R. Renne (7 Jun., p. 1812). In describing the flood volcanism occurring during the last several hundred million years, the wrong units were used to describe the implied magma production rate. It should have read "on the order of 1 km^3/year."

NEWS FOCUS: "How devastating would a smallpox attack really be?" (31 May, p. 1592). A sidebar to the story about smallpox models incorrectly stated that about 1250 in every million people vaccinated against smallpox in the past suffered from serious side effects. That number, taken from a 2001 report by the Advisory Committee on Immunization Practices (ACIP), also included mild side effects and adverse reactions. For adverse reactions the ACIP classified as "moderate to severe," the number is only 293.9 per million persons vaccinated. These include generalized vaccine (241.5 per million), eczema vaccinatum (38.5), progressive vaccinia (1.5), and postvaccinial encephalitis (12.3).

Letters to the Editor

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