Response

I HAVE ALWAYS OBTAINED PERMISSION TO collect materials wherever I have gone. In addition, I acquire all necessary permits from the U.S. Department of Agriculture to bring disease-free samples into the United States. The arrangement generally is that if an organism proves valuable, then the supporting organization and I will discuss the disposition of financial benefits that the local community may derive. This plan is laid out at the outset. One of the main goals of the program is to help scientists in developing countries improve their scientific infrastructure. This is accomplished in a multitude of ways, including giving investigators opportunities to work in my lab for advanced training. In addition, local investigators are invited to become involved directly in the research. This has been true with scientists from Nepal, China, Morocco, Venezuela, Israel, Papua New Guinea, India, and Korea, to name a few countries with which I have been involved. Many people do not understand that to find a successful drug is difficult and expensive, and therefore a lot of time cannot be spent discussing matters of income where income may not ever exist. Discovery is the least expensive of all of the steps required in drug discovery. Ultimate drug development may cost up to $300 million. Compounds fail for many technical reasons, including toxicity, availability, side effects, and inability to reach the appropriate site. Nevertheless, it is absolutely critical to me that local people get energized about the novel and important biological prospects that exist in the forests around them and be encouraged to study them and learn about their promise and potential. It is also essential that more efforts be made to save these important biological resources before they disappear forever.

GARY STROBEL
Department of Plant Sciences, 206 Ag BioSciences Building, Montana State University, Bozeman, MT 59717, USA. E-mail: uplgs@montana.edu

C-Reactive Protein and Atherosclerosis

THERE IS A CREDIBLE ALTERNATIVE HYPOTHESIS that may explain the challenging observation that many states not heretofore regarded as inflammatory are associated with minimal C-reactive protein (CRP) elevation, discussed in Gary Taubes' article "Does inflammation cut to the heart of the matter?" (News Focus, 12 April, p. 242). Many other noninflammatory factors (demographic, genetic, life-style, and medical) can be added to those cited in the article, including depression, chronic fatigue, poor physical conditioning, high-protein diet, hypertension, insulin resistance, and albuminuria. Many of these conditions indicate suboptimal physical status and may reflect tissue injury. CRP has long been used clinically to evaluate the presence and degree of inflammation (*1*), classically defined as the response to tissue injury. I propose that tissue injury itself causes CRP elevation, even when no inflammatory response is apparent. Minor CRP elevation would thus identify individuals who bear an increased burden of tissue damage, resulting from a variety of causes (*2*). It is highly likely that among these is cumulative oxidative stress, which is strongly implicated in the pathogenesis of aging (*3*). Such biologically older individuals have a greater likelihood of manifesting diseases associated with aging or of dying (*4*).

Inappropriate use of screening tests can be harmful (*5*), and many have concluded that routine use of CRP testing is premature (*6–12*). CRP testing does not meet three major criteria for an effective screening test (*13*): (i) Accuracy is uncertain; we have no idea of how many individuals are incorrectly identified as high risk (*14*). (ii) Reliabili-

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.

IRVING KUSHNER

MetroHealth Campus, Case Western Reserve University, 2500 MetroHealth Drive, Cleveland, OH 44109, USA. E-mail: ikushner@metrohealth.org

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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