A nimal models of disease get a bad press, none more so than models of atherosclerosis. Rodents do not get atherosclerosis, and rabbits and pigs get minimal disease; only a limited range of primates gets significant atherosclerosis that resembles human lesions. The development of genetically engineered mice with disorders of lipid metabolism, such as apolipoprotein E (apoE) and LDL receptor knockout mice, was therefore a major step forward in animal models of atherosclerosis (reviewed by Smith and Breslow\textsuperscript{1}). These mice develop atherosclerosis spontaneously, albeit variable between mouse strains,\textsuperscript{2} which can be accelerated on a high cholesterol diet. The plaques that develop are widespread and reproducible and have some architectural features reminiscent of human lesions. These mice have formed the basis for a plethora of studies identifying specific molecules critical to atherosclerosis, in particular, those regulating monocyte adherence/chemotaxis and macrophage differentiation/foam cell development. Still the critics carp. The major dissent has been that lesions occur at sites very different from human lesions—the aortic root and thoracic aorta for instance. Lesions in the aortic root are also foam cell–rich, rather than smooth muscle cell–rich, may not have a single definable fibrous cap, and represent xanthomata rather than clinically important advanced lesions. Most important of all, these mice are models of atherogenesis, not advanced atherosclerosis, and they do not exhibit the single most important event in human atherosclerosis, that of plaque rupture leading to vessel occlusion.

It now appears that the mouse may get the last laugh. In recent years, there has been increasing evidence of spontaneous plaque rupture in mouse atherosclerotic plaques.\textsuperscript{3–5} Evidence includes loss of fibrous cap continuity, intraplaque hemorrhage and fibrin deposition, evidence of buried (ruptured) fibrous caps, thrombi extending to a necrotic core, blood-filled channels within lesions (suggesting recanalization of healed plaques), and deep ruptures extending to the necrotic core. These features of rupture have been demonstrated in both aortic and brachiocephalic lesions, the latter being a site of the most advanced and reproducible lesions. Brachiocephalic plaques are also associated with vessel stenosis and perivascular inflammation,\textsuperscript{6} both features seen in advanced human lesions. Although these studies represented a major advance in our modeling of plaque rupture, in most cases rupture did not cause vessel occlusion and could not be indicted in the animal’s death.

In this issue of 	extit{Arteriosclerosis, Thrombosis, and Vascular Biology}, Williams et al\textsuperscript{7} extend these observations further. Nearly 100 apoE knockout mice on a mixed C57BL6/129SvJ background were fed a high-fat diet. Approximately two thirds died suddenly, and one third were euthanized in a 60-week period; plaque morphology in the brachiocephalic arteries was examined in all mice. The major finding was a significant increase in the number of buried caps in ruptured versus unruptured lesions, indicating previous rupture in the same plaque. However, Williams et al\textsuperscript{7} also quantified the composition of lesions that demonstrated previous rupture compared with those that did not. Plaque size, lipid core fraction, and luminal stenosis were significantly greater in ruptured versus unruptured plaques, whereas fibrous cap thickness was smaller in ruptured plaques.

The critical question that arises from this and other studies is “Do we now have a mouse model of plaque rupture that reproduces human lesions?” The answer to this must be a qualified “Yes.” We have known for many years the characteristics of vulnerable plaques in humans, those associated with myocardial infarction and death. Such plaques exhibit high lipid volumes, high inflammatory cell and low smooth muscle cell contents, with a relatively thin fibrous cap.\textsuperscript{8} The observations of Williams et al\textsuperscript{7} on plaques showing previous rupture reproduce these characteristics most closely. Evidence of repeated plaque ruptures and repair leading to plaque growth has also been demonstrated in human lesions.\textsuperscript{9} The study by Williams et al\textsuperscript{7} argues strongly that sudden plaque growth in the mouse occurs by repeated rounds of rupture and repair and that most ruptures are silent.

We should also note areas in which these mouse studies do not reproduce the behavior of human plaques. In particular, sudden death in these mice was not correlated with plaque rupture, nor with any specific plaque parameter; this means that, although these mouse lesions model plaque rupture, they do not model death associated with plaque rupture. There may be many reasons for this; such as a superior mouse Circle of Willis (preventing major stroke) and a lack of involvement (or different behavior) of coronary arteries.\textsuperscript{5} In addition, local thrombosis in the plaque may not translate to vessel occlusion due to species-specific rheological factors or regulation of blood coagulation.

In addition, although the appearance of buried caps suggests previous plaque rupture as a cause of plaque growth,
there are also other possible explanations for these appearances. In particular, the presence of multiple buried fibrous cap-like structures in human and mouse arteries does not necessarily prove that such structures occur by plaque rupture and repair. Such appearances could also occur by episodes of rapid lipid deposition, macrophage efflux, and smooth muscle cell recruitment without invoking fibrous cap rupture and repair. Episodes of thrombus formation in association with previously ruptured plaques were very rare in the study by Williams et al,7 emphasizing the possibility of this alternative explanation.

Accepting these minor caveats, studies such as those by Williams et al7 herald a new age of study of manipulations that affect plaque rupture and composition, rather than just plaque burden or development. A number of animal and more limited human studies have identified agents that change plaque composition rather than plaque load or size, predicting effects that would promote plaque stability.10–12 Indeed, this is one proposed mechanism for the beneficial effects of HMG-CoA reductase inhibitors in humans in the absence of significant plaque regression. However, neither animal nor human studies have definitively proven an effect of a therapeutic manipulation on plaque rupture; rather, this has been implied by the reduction in clinical events. In contrast, these mouse models may provide the ability to measure plaque ruptures directly, allowing direct testing of agents against this phenomenon.

Such studies will require the ability to induce rupture in advanced lesions. To date, plaque rupture has mostly been seen in older mice (>42 weeks old in the study by Rosenfeld et al5) or 9 to 20 months in the study by Calara et al.5 Ruptures have been clinically silent, only detectable retrospectively at histology, and are seen at various stages of plaque repair, indicating an asynchronous occurrence. Testing of interventions to reduce rupture ideally would be performed in a model of acute, synchronous, and reproducible rupture in a large proportion of animals. Preliminary studies with pressor agents and acute induction of cell death in mouse lesions have shown that such manipulations can cause plaque rupture and thrombosis in a large proportion of animals, occurring in a short time frame (hours to days).13 Thus, the combination of advanced atherosclerotic plaques in defined anatomical locations in genetically modified mice with an acute stimulus may be the new testing ground for therapeutics that inhibit plaque rupture.

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Breaking the Plaque: Evidence for Plaque Rupture in Animal Models of Atherosclerosis
Martin R. Bennett

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