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EDITORIAL COMMENT

Plaque Vulnerability

Pathologic Form and Patient Fate*

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Atherosclerosis is a disease of success and excess. The success is our ability to invent the means to provide a vast excess of daily calories and master both the art of French cooking (1) and the production of fast food (2). The excess is our inability to curb the appetites for either, after natural selection favored those who could store up for lean times (3) and the industrial revolution provided the leisure moments to do a lot of storage. Oh, gimme those tallow-drenched fries!

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Atherosclerotic coronary artery disease threatens to become the leading cause of death in the world only 250 years after Heberden (4) first noted the curious clinical expression of its presence but some 250,000 years since "Mitochondrial Eve" (5) lived in East Africa. Heberden's paper to the Royal College of Physicians was given in 1768, the same year that the modern circus was invented in London (6), placing it well after the development of leisure time. Heberden thought there had never been a prior description of angina pectoris and associated sudden death (4), and more ancient texts speak little of coronary plaque. So, the study of the disease is relatively young, but there are paradoxical leaps along the way. We naives who trained in the beginning of the latter half of the twentieth century learned that myocardial infarction was of unknown cause, and the mainstay of therapy was a comforting presence at the bedside. We remember the near physical wave of astonishment when DeWood et al. (7) published their proof that infarction was due to thrombosis in the coronaries. But this observation had been made by Herrick (8) in 1912 in a very interesting context with respect to the current article by Kramer et al. (9). Despite a lack of immediate interest, Herrick was right, DeWood was right, and the new dogma was very satisfying: atherosclerotic plaque and luminal narrowing created a local thrombogenic diathesis, a clot formed and limited or stopped blood flow, and death of myocardium in the downstream watershed followed. Subsequently, plaque rupture or erosion was identified as the diathesis (10), and the story was compelling. Something triggered disruption of the plaque; the clot formed over it; and depending on location and severity, a heart attack or sudden death or both ensued.

Herrick's paper and its follow-up in 1919 (11) were not actually about clotting in the coronaries. Rather, they were about his observation that coronary thrombosis did not necessarily lead to sudden death, that there was a broad spectrum of symptoms and consequences of this accident. In this issue of the *Journal*, Kramer et al. (9) refine this concept, relate it to whether the plaque has undergone erosion or rupture, relate those distinct architectural disruptions to clinical expression and pathological description, and prove Herrick's belief.

Beginning with 345 recent sequential Medical Examiner cases of sudden coronary death referred to the authors' laboratory, the authors studied the pathology and associated demographic data of 111 cases of coronary thrombosis in which the thrombi were the cause of death. Unlike the late 20th century illusion described in the preceding text, sudden death did not follow suddenly upon thrombus formation. The majority of thrombi (79 of 115, 69%) were "late," at least 1 day old, and the majority of those were in the "infiltrating" or "healing" categories, at least 4 days old. Plaque ruptures were more common in the older subset of a relatively young cohort, and plaque erosions were more common in women. The severity of stenosis, the area bounded by the internal elastic lamina, the area of plaque, the necrotic core size, and the total plaque burden were all greater in the ruptured than in the eroded group. Erosions tended to have older, healing thrombi compared to ruptures. The differences impressed the authors enough that they suggest that we think about the possibility that erosions and ruptures be treated differently, another application of the developing principles of personalized medicine in which better pathophysiologic understanding—whether genomic or pathologic—allows the therapeutic targeting of subsets rather than the whole set. These are very interesting observations and confirmations of reports that used other methods of study.

The state of knowledge about atherosclerosis and its complications (12), their relationship to inflammation (12–14), and genetic predisposition (15) and even a schema for classification (10,16) are well developed. Yet, the manifestations of atherosclerotic coronary artery disease remain even more complicated than the current dogma suggests. This relates, at least in part, to the interplay between the biologic and the physical, to the system of arterial plumbing where the disease is expressed. The authors noted a nonsignificant trend in this young population of more hypertension in ruptured versus eroded plaques (9) and site their earlier work where this was indeed the case (17). The coronaries live with stresses that no other arterial bed

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endures. They are tacked onto the epicardial surface of an ellipsoid body that rhythmically reduces its volume and deforms the arteries 100,000 times/day. This motion curls, stretches, lengthens, shortens, and compresses the arteries with each cardiac cycle. The presence of the plaque alters surface shear stress, and the bulge of plaque, a wing in the hemic wind, pulls endothelial cells off the surface (18). The plaque itself presents physical discontinuities as sites for increased stress and the pulse rate actually alters the stiffness of the fibrous cap (19). Therefore, it is not surprising that high blood pressure in this system might result in plaque rupture (9,17).

Similarly, it is not surprising that erosion and rupture might arise from different profiles of artery, system, and patient and, in turn, that the nature of the disruptions might yield different fates. The idea that sudden death in complex coronary arterial disease might be a late complication of thrombosis related to distal microembolization is intriguing. However, as the authors point out, this is not a representative population. The average age of patients in this study with sudden death due to a coronary thrombosis secondary to erosion or secondary to rupture was 43 and 52 years, respectively (9), whereas the average age of patients having a first myocardial infarction is reported as 64.5 years for men and 70.3 years for women (20). Furthermore, the study is limited of necessity to those patients referred by a medical examiner because of sudden death and might not represent the findings in a population of patients with more chronic coronary disease. Nonetheless, the authors are in good company in their confirmation of Herrick (11), and future therapeutic options for coronary accidents suggested by their detailed post-mortem observations await the arrival of new in vivo techniques in the age of personalized medicine.

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