Revisiting the Historical Origins of Clinically Meaningful Coronary Artery Obstruction

To the Editor: As part of a recent informative editorial on the significance of nonobstructive coronary artery disease, Rumberger[1] reviewed the historical origins of the 50% coronary stenosis standard for the definition of myocardial ischemia and the relationship of percentage stenosis to coronary flow reserve and fractional flow reserve. I believe some corrections are warranted.

Rumberger repeated the commonly stated but incorrect assumption that the origin of the 50% stenosis threshold is attributable to the landmark 1974 article by Gould et al.[2] The origin of the 50% coronary stenosis standard antedates the Gould article and was adopted in 1969 as the threshold for intervention by the VA Cooperative Study, the first major randomized trial of bypass surgery.[3] Even before this, in 1966, a 50% or greater diameter stenosis was identified as indicating a "severe" arteriographic narrowing by Sones' group at the Cleveland Clinic and was subsequently used and published as the cutoff value for bypass surgery when introduced by that institution.[4] The original Gould et al[2] article specifically indicated that a stenosis of "45 to 50 percent by diameter probably does not impair coronary flow reserve in man." In the text, they were careful to indicate that coronary flow reserve begins to decline at a 30% stenosis but that a 65% to 95% stenosis is required to cause marked impairment of coronary flow reserve. Nor is the Gould et al[2] article the origin of the 70% stenosis standard, which was adopted by the Coronary Artery Surgical Study in 1973,[5] before the publication of the Gould et al report. The Gould et al[2] article, although transformational for many fields, is not responsible for the adoption of the 50% or 70% stenosis threshold for ischemia.

Rumberger[1] also indicated that a 70% coronary stenosis has become "the de facto stenosis measurement supported by fractional flow reserve data." To the contrary, the major lesson of coronary flow reserve and fractional flow reserve research is that it is not possible to determine the functional significance of a coronary stenosis on the basis of percentage stenosis. Only one-third of narrowings within a stenosis range of 50% to 70% display provokable myocardial ischemia by fractional flow reserve.[6]

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In Reply—Revisiting the Historical Origins of Clinically Meaningful Coronary Artery Obstruction

To the Editor: First, I sincerely thank Rosenthal[1] for his correspondence letter regarding my prior editorial.[2] We all continue to learn, and as a student of medical history I am embarrassed that I was not aware of his excellent 2015 commentary on "The 50% Stenosis."[3] In that article, Rosenthal acknowledged the commonly held physiologic studies by Gould et al[4] as one of the original investigations on the severity of percent stenosis and coronary hemodynamics; I now stand corrected on the true origins of the clinical use of the 50% stenosis threshold. However, as also noted in my editorial, I suspect that a lot of the future issues of "percent stenosis" relied on the classic hemodynamic studies done by Katz and Linder[5] in the 1930s.

As the use of 50% or more stenosis as possibly suggesting ischemia became popular in the 1960s and 1970s, much of this concept was fostered, legitimized, and perpetuated by studies looking at stress testing, where the sensitivity and specificity values for potential "ischemia" were found to be optimal using the angiographic 50% threshold.

I did not really state *my opinion* about the current use of a 70% stenosis as more likely being the standard for fractional flow reserve; on the contrary, I stated the current "expert consensus" using a percent stenosis threshold for "revascularization." The latest Appropriateness Criteria for Coronary Revascularization in patients with stable ischemic heart disease uses either (1) 70% or more luminal diameter narrowing, by visual assessment, of an epicardial stenosis measured in the "worse view" angiographic projection and/or (2) a fractional flow reserve of 0.80 or less consistent with downstream inducible ischemia.[6]

I still get asked questions by patients about "percent stenosis" since this vernacular has now escaped into the public realm. We are still bound in the stenosis world in cardiology. Yet, control of microvascular

coronary tone is much more complicated than just looking at the worse narrowing, or percent stenosis, in an epicardial coronary vessel. Thus, it is almost naive to define such a luminal narrowing as exemplifying the nature of coronary blood flow and coronary artery flow reserve. I believe that we need to deal with the physiology of ischemia (whether it is fractional flow reserve determined using computed tomography or traditional fractional flow reserve determined during coronary angiography or just true angina experienced by a patient) and not the anatomy perceived by "stenosis" during visual inspection of an angiogram.

However, the main focus of my editorial was that atherosclerotic plaque disease is a disorder of the arterial wall, and it escapes detection by coronary angiography (or stress testing or perfusion testing) until it has advanced to be a disorder of the lumen. As I had stated, coronary atherosclerotic disease is a continuum and not a threshold.

Again, I thank Dr Rosenthal for his correspondence.

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Zika Virus Meningoencephalitis

To the Editor: In the March 2017 issue of *Mayo Clinic* Proceedings, Schwartzmann et al[1] reported on a single case of Zika virus meningoencephalitis and concluded that, "In this case, central nervous system involvement and ZIKV propagation to other organs in a disseminated pattern is quite similar to that observed in other fatal Flaviviridae viral infections." The patient reported by Schwartzmann et al[1] was immunocompromised at the time of Zika virus infection; however, meningoencephalitis accompanying Zika virus infection has also been reported in apparently immunocompetent patients.[2]

An interesting question is whether the immune status has any relationship to the occurrence of meningoencephalitis. In the similar arbovirus infection, dengue infection, meningoencephalitis can also be seen regardless of immune status.[3] In our setting in Southeast Asia, dengue is highly prevalent and Zika virus infection is also endemic. Nevertheless, Zika virus infection is usually asymptomatic and neurological manifestations are extremely rare. Furthermore, despite an extremely high prevalence of dengue in our area (30-224 cases per 100,000[4]), there has never been a report on meningoencephalitis in dengue patients regardless of immune status.

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In Reply—Zika Virus Meningoencelphalitis

To the Editor: We read with interest the letter from Joob and Wiwanitkit[1] which reinforced our interpretation that immunosuppression predisposes the central nervous system (CNS) to infection by Zika virus.

It is known that some microbial infections of the CNS—such as those caused by toxoplasma, cryptococcus, and cytomegalovirus—can be related to predisposing underlying diseases. In the Brazilian Amazon region, the tropical climate favors the proliferation of large quantities of insect vectors and their vertebrate reservoirs, thus supporting the natural cycles of many arboviruses that can infect humans. In a study done in the state of Amazonas, cerebrospinal fluid (CSF) samples from 110 patients with meningoencephalitis were tested by reverse transcription-polymerase chain reaction (RT-PCR) for *Orthobunyavirus* and *Flavivirus*.[2] Lymphomonocytosis predominated in all CSF cell counts. Sequencing of RT-PCR products obtained from 3 patients identified Oropouche virus (Peribunyaviridae). Two of the 3 patients infected with Oropouche virus, a 54-year-old man and a 37-year-old woman, had underlying diseases that affected the CNS or the immune system (neurocysticercosis and AIDS,