Two Ways to Make Great Contributions

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This commentary is about 2 investigators, Robert Furchgott and Stanton Glantz, who have written some of the most highly cited articles in Circulation Research. Furchgott and Glantz changed our scientific world and our society.

As I read the list of most highly cited articles in the 60 years of publication of Circulation Research, 2 stories came to mind. The first story is of a great discovery, and the second is of a great contribution to reduction of cardiovascular disease.

First is Robert Furchgott’s finding that endothelium is critical in normal vasomotor function of arteries. His finding was followed by a series of studies that demonstrated the importance of endothelial dysfunction in atherosclerosis, hypertension, and other diseases. Second is a story about Stanton Glantz, who made major contributions to our understanding of ventricular diastolic function, which foreshadowed our understanding of diastolic heart failure. However, for me, the truly inspiring story is how Glantz successfully challenged the tobacco industry, with enormous consequences for cardiovascular health.

Endothelial Function

Furchgott’s Brief Review, which is the article in Circulation Research with the third greatest number of citations, begins in his modest, understated manner: “A few years ago, we discovered that the relaxation by acetylcholine of isolated preparations of arteries is strictly dependent on the presence of endothelial cells.” Several years before the Brief Review was published, Paul Vanhoutte had invited Furchgott to a small meeting to talk about his finding, which had been presented as an abstract. I talked with Furchgott, and thought that his finding was interesting, but not likely to be of great importance. I reasoned that there is not much acetylcholine in blood vessels, or in blood to which endothelium is exposed and, therefore, it was not likely that this vasorelaxing effect of acetylcholine in the aorta ex vivo was of much functional importance. The editors of Nature had more insight, and published his work.2

Francois Abboud, Michael Brody, Allyn Mark, and I were editors of Circulation Research, and we invited Furchgott to write the Brief Review. He described a series of studies that characterized effects of endothelium-derived relaxing factor (EDRF) in several physiological and disease states. He said “it is still too early to evaluate the physiological significance of relaxation of blood vessels that is endothelium-dependent and not mediated by prostaglandins.”

The importance of EDRF evolved in a series of studies in Circulation Research and other journals. Based on the finding that serotonin produces relaxation when endothelium is present, but contraction when endothelium is absent,3 we tested the hypothesis that atherosclerosis augments vasoconstrictor responses.4 We found that arterial vasoconstrictor responses to serotonin are greatly potentiated by atherosclerosis. Soon after, Freiman et al5 demonstrated that endothelium-dependent relaxation is impaired in atherosclerotic primates, and that endothelium-independent responses to nitroglycerin are normal. Verbeuren et al6 also reported that, when atherosclerosis develops, endothelium-dependent relaxation is impaired.

During the next few years, many studies demonstrated that atherosclerotic arteries generate excess superoxide, and that superoxide inactivates NO. Mügge et al7 found that chronic treatment with polyethylene-glycolated superoxide dismutase improves endothelium-dependent relaxation. It was known that endothelium generates high levels of superoxide in atherosclerotic arteries, but a surprise was that arterial media also is an important source of oxidative stress in atherosclerotic arteries.8

In his Brief Review, Furchgott1 said “the goal of chemically identifying EDRF that is released by Ach from endothelial cells will probably be difficult to achieve.” My view of Furchgott’s work is that the initial discovery of EDRF, which was the sine qua non of this area of research and his Nobel Prize, was serendipitous. For me, his brilliant work was to identify NO as EDRF. He first described a variety of EDRF preparations of arteries is strictly dependent on the presence of endothelial cells.” Several years before the Brief Review was published, Paul Vanhoutte had invited Furchgott to a small meeting to talk about his finding, which had been presented as an abstract. I talked with Furchgott, and thought that his finding was interesting, but not likely to be of great importance. I reasoned that there is not much acetylcholine in blood vessels, or in blood to which endothelium is exposed and, therefore, it was not likely that this vasorelaxing effect of acetylcholine in the aorta ex vivo was of much functional importance. The editors of Nature had more insight, and published his work.2

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of characteristics and potential sources of EDRF. Then, in 1986, Furchgott and Louis Ignarro independently presented evidence that NO is EDRF. I admire their ability to move beyond mediators that seemed more likely, and to identify a gas (truly amazing at the time) as EDRF. When Ferid Murad demonstrated the role of cGMP in response to NO, the pathway was complete.

I have previously quoted the presentation speech at the award of the Nobel Prize in Physiology or Medicine, to Furchgott, Ignarro, and Murad in 1998: “the hunt for Furchgott’s endothelial factor came to an end during a scientific meeting...in the summer of 1986. At the meeting Furchgott concluded...that the factor was identical with NO. Ignarro supported this at the same meeting...[and] went one step further... The hunt was over. The riddle concerning the endothelial factor was finally solved.”

## Science and Society

Stanton Glantz published a series of highly cited articles about ventricular mechanics. He pointed out “the diastolic pressure-volume curve’s ability to change can produce shifts in systolic performance.” Much later, we realized the importance of heart failure with normal systolic function, or diastolic heart failure.

Research is Glantz’ profession. He is also an activist, who is dedicated to studying and publicizing the health hazards of passive smoking. In 1994, presumably because of his activism, Glantz received a box of papers in the mail, with a return address “Mr. Butts.” I can only imagine the thrill when he opened the box to find a 4-foot pile of papers that implicated Brown and Williamson (B&W), the third-largest tobacco company, in a 30-year cover-up of effects of cigarettes smoking. Most of the information in this article about EDRF is a summary of a Web source from PBS.org.

What should Glantz have done with these papers that B&W said were stolen, and sued for their return? Glantz gave them to the University of California San Francisco Library, which made them available to the public, first scanned onto CDROM (high tech for the time) and then posted them on the Internet (even more high tech). I think this was a brilliant decision, although Glantz has a more modest explanation for the decision. When B&W declared that the articles were stolen, Glantz said “that resolved questions we had about the authenticity of the materials.”

Key aspects of the B&W documents were that the tobacco industry had known for 30 years that cigarette smoking caused cancer and was addictive, and that they hid that information. The CEOs of the 7 largest tobacco companies had just sworn to state and federal litigation against the tobacco companies, to the B&W documents, and Francois Abboud, David Harrison, and Michael Welsh for their suggestions.

Each of the articles was reviewed by 8 reviewers. The articles went beyond health effects of smoking, and described ways that B&W managed research and publications. One of the articles indicated that B&W suppressed its own research, which indicated that smoking causes cancer, by sending the material to its legal department. B&W lawyers claimed that the material was protected by attorney-client privilege, and did not need to be disclosed.

An editorial that accompanied the articles in JAMA said that tobacco companies have “managed to remain highly profitable from the sale of a substance long known by scientists and physicians to be lethal.” The editorial was unique because it was cowritten, and cosigned, by the editors and the board of trustees, president, and president-elect of the AMA. Release of the B&W documents and the subsequent scholarship had a profound effect on the debate over tobacco, and contributed to state and federal litigation against the tobacco companies, ultimate enactment of legislation granting the Food and Drug Administration authority over tobacco, and contributed to passage of the first global public health treaty, the World Health Organization Framework Convention on Tobacco Control.

The online collection at the UCSF Library (http://legacy.library.ucsf.edu), which is now >83 million pages of documents, has formed the basis for >800 peer reviewed scientific articles and other publications about the tobacco industry (http://legacy.library.ucsf.edu/tobacco/docsbiblio).

In the articles in JAMA, and in his book The Cigarette Papers, Glantz acknowledged grant support from the National Cancer Institute (NCI). The grant was in response to an NCI solicitation to “evaluate the effect of advocacy in the development of tobacco control policy.” In response to a public relations and lobbying campaign by the tobacco industry, the House Appropriations Committee attached a rider to the NCI appropriation defunding the last year of Glantz’ grant. A subcommittee report indicated that the grant did “not properly fall within the boundaries of the NCI portfolio.”

Finally, there is a relationship between the 2 short stories in this commentary. The year that JAMA published the articles related to the B&W documents, it was demonstrated that cigarette smoking is a risk factor for endothelial dysfunction (eg). Since then, many articles have confirmed and extended the finding. Tan and Glantz have suggested that reduction in passive smoking may have contributed to the rapid decrease in acute myocardial infarction that followed implementation of smoke free laws.

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