Editorials

Circulation Research

The Impact of a Journal and Its Editor on a Career in Experimental Cardiology

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In the early 1950s, the leadership of the American Heart Association recognized that much more fundamental knowledge of basic cardiovascular function was required if one was going to improve the treatment and diagnosis of heart disease. They believed that a journal dedicated to basic research on the circulation would foster an increased understanding of the cardiovascular system and founded Circulation Research. In 1953, when volume 1 of Circulation Research was published, the basic sciences relevant to cardiovascular research such as physiology, biochemistry, pharmacology, and pathology all had journals that were devoted to these disciplines in which there were scattered studies on the heart and circulation. However, these studies were not always read by basic scientists in other disciplines, and the field lacked a journal devoted primarily to understanding how the cardiovascular system worked in health and disease. Circulation Research provided a forum where studies on the heart and cardiovascular system could be published and has been eminently successful in fostering the application of the basic medical sciences to understanding the function of the cardiovascular system.

At the time the journal was founded, basic research support was beginning to be available from the National Institutes of Health, and basic knowledge of biology was being developed at an enormous rate, but from meager foundations. Mitochondria had moved from objects difficult to discern by histological techniques to organelles of considerable interest to biochemists. Moreover, methods of isolating them from heart and studying their metabolism were under development. Energy metabolism in general, the use of electron microscopy to establish the ultrastructure of cardiac muscle, the isolation of contractile and other proteins along with determination of their structure and composition, DNA and RNA metabolism, all were under intensive study, but the application of this knowledge to the cardiovascular system was diffuse and unfocused until Circulation Research came on the scene.

The founding editor of Circulation Research was Carl J. Wiggers, the leading cardiovascular physiologist of his time. He had very clear ideas about how a journal should be run and these ideas had a significant impact on me in the early phase of my career. I thought that I would recount a bit of ancient history about the role of this journal and its editor on my career as a sidelight on the 50th anniversary of the founding of Circulation Research.

Although Wiggers’ chief interest was in hemodynamics, he accepted articles on virtually all aspects of cardiovascular function and disease. However, he followed a strange editorial rule or at least a rule not followed by most editors. This was that no more than three authors could be listed on a paper published in Circulation Research. He believed that each author listed on a paper should have made a substantial intellectual contribution to the paper and that three scientists were the maximum number that could make such an intellectual contribution. I ran afoul of this rule when I finished up a research project begun by William B. Wartman, my chief at the Northwestern University Medical School, with the help of two postdoctoral fellows, Linn A. Campbell and Robert L. Craig. On July 1, 1953, I joined the faculty of Northwestern as an instructor in pathology at the same time that Campbell and Craig returned to the clinics. My first assignment was to finish the experiments required to complete the study. Unfortunately, although I had made a significant intellectual contribution, I ended up on the title page with the strange designation “with the collaboration of Robert B. Jennings, MD.” This was unfortunate and seemed unfair. However, nothing could be done about it and I went on to other experiments. By the way, this was one of the first studies designed to ascertain if a therapy, in this case ACTH, could reduce the size of a myocardial infarct. It, like many other proposed treatments, had no effect.

However, a few years later, Wiggers had a much more profound effect on my career. I had begun studies designed to learn the event or series of events that led myocytes to die as a consequence of ischemia. Based on the loss of glycogen from frozen-dried tissue sections, I suspected that they began to die after about 1 hour of ischemia had elapsed and perhaps before. However, there was no easy way to verify this hypothesis because precise sampling of the damaged myocardium was difficult simply because the myocardium remained grossly and microscopically normal for many hours after the artery was occluded. We solved the problem of identifying tissue that was both ischemic and destined to die as a consequence of ischemia by showing that permanent occlusion of the circumflex artery in the open-chest anesthetized dog heart resulted in homogeneous fatal injury to the posterior papillary muscle of the circumflex bed. This provided us with a uniformly injured, readily identified site of injury, which we could use to establish the timing of myocyte injury.
death. This was done by exposing the myocardium to episodes of ischemia followed by restoration of arterial flow to eliminate the ischemia. Using this technique, we showed that less than 15 minutes of ischemia resulted in no myocyte death. We defined this state as “reversible injury.” A few myocytes died after 20 to 25 minutes of ischemia and virtually all of the myocytes in the subendocardium of the circumflex bed were dead after 60 minutes of ischemia. We termed this state “irreversible injury” and hypothesized that the biological change or changes that killed the ischemic myocytes developed late in the phase of reversible injury.

Using this knowledge, we tested whether normal-appearing myocytes, which we had defined as being irreversibly injured, exhibited any metabolic defects with respect to the metabolism of glucose to CO₂ and H₂O. Homogenates were prepared after both 60 and 120 minutes of ischemia, times that we knew were associated with a large proportion of irreversibly injured cells in the posterior papillary muscle. Tissue from the subendocardium of the anterior descending bed was used as control. We found that the irreversibly injured tissue could not metabolize glucose to CO₂ and H₂O with nearly the efficiency of control tissue and discussed these findings in terms of reversible and irreversible injury in a paper submitted to Circulation Research in 1959.1 The first reference in this paper was to our unpublished studies of reversible and irreversible injury. Wiggers accepted the paper as long as we published reference number one. Unfortunately, although the experiments were complete and the results known, there was no reference number one.

Since I really wanted the metabolism paper published, I was forced to create reference number one from the data on reversible and irreversible injury that we had in-house. It was published in 1960.² This study had a much bigger impact on experimental cardiology than did the metabolism study because it showed that one could salvage ischemic myocardium by reperfusion, which is the critical feature of thrombolysis therapy of acute myocardial infarction in humans. Since I already knew the answer about the timing of irreversible injury, I doubt that I would ever have published this paper had not Wiggers required that it be in press before he would accept the metabolism paper. Thus, I owe a great debt to him for forcing me to write up reference number one.

This personal reminiscence of the term of the first editor of Circulation Research, and the impact that he had on me, has been fun to recall. The next 44 years has seen Circulation Research become the premier journal of cardiovascular research. Eduardo Marbán is the 10th in a series of distinguished editors and continues to foster the publication of solid science relevant to understanding how the cardiovascular system works in health and disease. May the next 50 years be as successful as the first 50.

References

Key Words: fiftieth anniversary ■ impact factor ■ clinical cardiology ■ American Heart Association ■ irreversible injury
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