Special Report

Homage to James B. Herrick: A Contemporary Look at Myocardial Infarction and at Sickle-Cell Heart Disease
The 32nd Annual Herrick Lecture of the Council on Clinical Cardiology of the American Heart Association

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For a clinical cardiologist, I know of no award more appreciated than selection for the Herrick Lecture. I express my personal gratitude to the Council on Clinical Cardiology for adding me to a long list of distinguished predecessors, among whom I realized to my amazement that every individual, living and dead, is one I have cherished as a personal friend. There are too few advantages to growing old, but realizations such as this are surely to be treasured. Ptolemy, who lived near the beginning of the millennium that we are now about to close, wrote, “As material fortune is associated with the properties of the body, so honor belongs to those of the soul.”

James B. Herrick has become a revered figure not only in cardiology, but also in hematology. In fact, of his 2 historic contributions in medicine, the first came in 1910, when he described the unusual sickle-shaped erythrocytes found in a blood smear from an anemic young black Caribbean dental student in Chicago. His more familiar (to us) landmark article about myocardial infarction came 2 years later, in 1912. In it, he reported that myocardial infarction was not an inescapable tocsin of doom, but that it was often survived, sometimes with little lasting damage. Even today, there is too little appreciation that the complex causes of fatal myocardial infarction include many factors other than simply the occlusion of a coronary artery.

Both his sickle-cell article and the one on myocardial infarction were essentially “case reports,” a category today too often greeted by editors with rejection and by readers with disdain. But what case reports Herrick’s were! In his sickle-cell article, he imaginatively considered every conceivable cause or explanation for the unusual sickle-shaped erythrocytes he saw and, with astonishing acumen, concluded that the explanation must lie in some abnormal intracellular factor that we now know to be a biochemical alteration of the hemoglobin molecule. The one case of myocardial infarction that he reported was autopsied by Herrick’s colleague and friend, Ludwig Hektoen, but to those findings, Herrick added numerous personal experiences with similar but surviving patients from his own clinical practice, combined with a comprehensive review and critique of virtually all of the published literature on the subject. Both articles were written in matchless style and have proven to be of continuing value for nearly 100 years.

Few clinical scientists have been remembered for not 1 but 2 signal contributions to medical knowledge, and Herrick’s achievement in this regard has captured the imagination of clinical scientists ever since. This seemingly surprising accomplishment in 2 segments of medicine now seldom practiced together must be considered in the context of today’s medical specialization. In Herrick’s day, cardiology and hematology were not thought of as separate fields, and internal medicine itself was not yet established as a professional discipline. As a general physician, Herrick was fascinated early on with the diagnostic value of careful microscopic study of blood smears taken from his patients, which provided important information about anemia, infection, or leukemia, for example. Similarly, it was only after long cogitation about his own observations on myocardial infarction that he summoned the considerable courage to dispute the long-prevailing concept espoused by Cohnheim and others, ie, that myocardial infarction was always fatal. In retrospect, it is disappointing to read that neither the sickle cell nor the myocardial infarction article attracted the immediate attention they both deserved. This may be the reason why Herrick did not continue investigation into what we now know as sickle-cell anemia. However, the initial disinterest of his peers did not dissuade him from a lifelong and imaginatively productive interest in myocardial infarction.

Having been elected a member of the American Society of Hematology in 1960, exactly 50 years after Herrick’s sickle-cell article was published, and a member of our Council on Clinical Cardiology in 1963, 51 years after Herrick’s publication on myocardial infarction, I have faithfully retained an active professional and research interest in both hematology and cardiology. It thus appealed to me as a subject for this Herrick Lecture to take a contemporary look at both sickle-cell anemia and myocardial infarction. On examining what I knew and could find about the knowledge of the 2 subjects...
during Herrick’s professional life, it was quickly apparent that there was much more information and active interest in myocardial infarction than in sickle-cell anemia. Even today, there is far more research on myocardial infarction than on sickle-cell anemia, but knowledge about both conditions has grown immensely since early this century. This opportunity to discuss both conditions may be seen as a harmonizing framework resembling Herrick’s own contributions. Accordingly, I will discuss myocardial infarction first and at more length than I will sickle-cell heart disease.

A Contemporary Look at Myocardial Infarction

In my half-century of continuing interest in this subject, I have been fascinated with the evolution and successful application of knowledge obtained by an immense cadre of investigators. Two contemporary subjects very intensively studied are the use of serum markers for diagnosis and ischemic preconditioning (with the related conditions of hibernation or stunning). Both subjects have proven to be important in all levels of ischemic heart disease (or, as also lamentably known, “acute coronary syndromes”). It is my growing belief that much more could be understood about both serum marker diagnosis and ischemic preconditioning if greater attention was directed at the role of apoptosis, rather than almost exclusively on necrosis. These 2 very different forms of cell death are found in all biological tissues and clearly play a role in many aspects of normal and abnormal processes in the human heart, including myocardial infarction.

Apoptosis and Necrosis in Acute Myocardial Infarction

It is now clear that in experimental as well as clinical circumstances, both apoptosis and necrosis participate and each has vast and vastly different influence on the evolution of acute myocardial infarction. Although apoptosis has been aggressively studied by gastroenterologists, hematologists, oncologists, immunologists, developmental biologists, and others now for over a quarter of this century, it is only in the past very few years that much attention has been directed at apoptosis by cardiologists, and the term and concept remain vague for most. For too many generations of pathologists, the presence or absence of necrosis formed the ground rules for saying whether myocardial infarction was or was not present. This rigid dogma mystified and misled too many investigators until it was recognized that a second and quite different form of cell death in the myocardium was due to apoptosis, and this recognition affected the diagnosis of human myocardial infarction.

Apoptosis (sometimes referred to as programmed cell death) is a genetically determined form of cell death often serving as an essential component of normal postnatal morphogenesis in the human heart, but it also can be triggered by noxious stimuli or become uncontrolled after having begun normally, and then it has pathological consequences. Apoptosis is an impressively rapid process, often completed in seconds or minutes when studied in vitro preparations. Cytological characteristics (again studied especially in vitro) include a lack of swelling or even shrinkage of cell size, blebbing of the plasmalemma, a distinctive clumping and then cleaving of the nucleus, early disappearance of the nucleolus, and generally a morphological preservation of intracellular organelles, such as mitochondria or sarcoplasmic reticulum, but perhaps most importantly, preservation of an intact plasmalemma. By contrast, necrotic cells swell in size, their mitochondria and sarcoplasmic reticulum quickly disintegrate, the nucleus deteriorates nonspecifically, and the plasma membrane typically ruptures to release all intracellular contents into the interstitial space.

The noxious local effect of necrotic myocardial debris is further compounded by the harmful effects of neutrophils themselves, thus jeopardizing the viability of other local myocytes that may have escaped the hypoxic effect of coronary occlusion. As an apoptotic cell dies, there is rapid movement of normally intracellular phosphatidylserine molecules to the external surface of the cell, thereby signaling macrophages for phagocytosis. If there is a delay in this phagocytosis, the apoptotic cell (especially its nucleus) breaks into numerous individual apoptotic bodies, each still bound by an intact membrane. In most areas of myocardial apoptosis, the phagocytosis remains effective, creating the histological appearance of an orderly process. However, if (for whatever reason) phagocytosis signals fail or the phagocytic capacity simply becomes overwhelmed, the apoptotic cells and apoptotic bodies then break down and become indistinguishable from necrotic ones.

At the light microscopic level, one can readily distinguish myocardial apoptosis from necrosis in human cases of infarction (Figures 1 to 3) and, although they may be distinctly separate foci, they are frequently either contiguous or even intermingled. The separate apoptotic foci are sharply demarcated (Figures 1, 2, 4, and 5) and have a relatively homogeneous appearance, with a mixture of both apoptotic and nonapoptotic myocytes, as well as numerous macrophages containing phagocytosed apoptotic bodies (Figures 5B and 6A). In areas where phagocytic capacity has been exceeded, free pools or sheets of apoptotic bodies can be seen (Figure 6B). By contrast, the boundaries of necrotic foci are seldom sharply demarcated and, within such foci, there is a mixture of broken myocytes and numerous neutrophils and lymphocytes (Figure 3). Hemorrhage is often seen within necrotic foci but is rare in apoptosis. Late in necrosis, there is sometimes a loss of all identifiable myocytes and the creation of areas of “liquefaction necrosis,” which is never seen in apoptosis.

Many of the original criteria for the morphological diagnosis of apoptosis were based on electron microscopic studies of in vitro preparations. With the later development of an immunohistochemical (TUNEL) method for staining broken strands of DNA within nuclei from paraffin-embedded tissue, a new opportunity was presented for accurate recognition of apoptotic cells in situ (Figures 1B, 2B, 4B, and 6A). Other diagnostic methods are available for gel electrophoretic examination and analysis by flow cytometry, but these are not the usual components of most human autopsy studies. In addition to the TUNEL method, which has proved especially useful in my own laboratory, several other histochemical
methods (some involving fluorescence) are available to stain apoptotic nuclei. There is also a rapidly growing array of special stains to identify either promoters or inhibitors of apoptosis, but there are now so many of these, it is difficult to decide whether the presence or absence of any one or a few of them is functionally significant in a given human case.

There is a useful “experiment of nature” for a comparison with human acute myocardial infarction, the multifocal myocardial degeneration found in fatal cases of thrombotic thrombocytopenic purpura (TTP). These numerous foci include not only the working myocardium, but also any component of the cardiac conduction system (where the foci sometimes cause sudden death due to heart block). Every focus of myocardial degeneration in TTP is due to apoptosis (Figures 7 and 8), and I have never seen necrosis in TTP hearts. The histological appearance of apoptotic foci in TTP (Figure 7A) and in acute myocardial infarction (Figures 1A and 2A) is virtually identical. The ubiquity of apoptosis in the focal myocardial degeneration of TTP may be logically attributed to the smaller areas of ischemia produced by the episodic occlusion of capillaries or small arterioles that is typical of TTP and the better opportunity for macrophages to deal with the dead apoptotic myocytes. Acute myocardial infarction causes much larger areas of ischemia, and necrosis is one of the results.

Serum Marker Diagnosis
Approximately 50 years ago, it was proposed that certain serum enzymes could be measured as a useful reflection of the presence, and even magnitude, of myocardial infarction in human subjects. This measurement would be based on the release of these normally intracellular enzymes during the necrotic death of cardiac myocytes. One of the earliest serum enzymes measured was glutamic oxaloacetic transaminase and, less often, either glutamic pyruvic transaminase or lactic dehydrogenase. The subsequent surge of interest initially focused on the first of these, but it then began to wane because glutamic oxaloacetic transaminase was also released by injured skeletal muscle and the liver. The later parade of candidate enzymes, now more correctly termed markers, included myoglobin, creatine kinase and its subforms and, more recently, 2 forms (T and I) of troponin. The most notable common characteristic of all these markers is that they are normally intracellular substances and they are only released in amounts useful for diagnosis when cardiac myo-
cytes break down. Cardiac myocytes typically rupture during necrosis but not apoptosis, although death by either process leaves the myocytes equally dead.

In tandem with the growing national and worldwide focus on myocardial infarction and the unsurprising growth of several multibillion-dollar industries dealing with the need for its more accurate, early, and consistent diagnosis, there has been a persistent expressed skepticism for every proposed serum marker diagnostic approach. One probable reason for this recurring skepticism has received too little attention, and that is the fact that both apoptosis and necrosis participate importantly in cell death during every myocardial infarction. Furthermore, the major form of death early in murine experimental myocardial infarction is overwhelmingly apoptotic (it is calculated to be 6 times that due to necrosis). Accordingly, the reason for recurring disenchantment with serum marker diagnosis may not be, as popularly believed, that the previously hailed serum marker was not sufficiently specific for myocardial cells, but that no intracellular enzyme is released during apoptotic cell death because the plasmalemma characteristically remains intact until the cell is removed by phagocytosis.

Regarding the experimental evidence that the earliest form of death of cardiac myocytes after murine coronary ligation is overwhelmingly due to apoptosis, a recent clinical study is especially germane. Schuchert et al measured troponin levels as possible early diagnostic markers in patients with acute coronary syndromes who were first encountered and who had blood samples drawn during emergency ambulance contact. They found that these early measurements of troponin levels failed to make the correct diagnosis in 90% of patients who were later determined to have ischemic heart disease. Conversely, the same study found that those few cases with significant troponin elevations early in their clinical course had much poorer prognoses, raising the possibility that necrosis found that early was already preceded by apoptosis. These same caveats may be addressed to the consideration of so-called infarctlets found during surgical or invasive medical procedures and the probability that those same circumstances are also when apoptosis may be maximal but undetectable by serum marker diagnosis.

The sequential fate of apoptotic cells and apoptotic bodies helps explain 2 other aspects of acute myocardial infarction. (1) The roles of apoptosis and necrosis in every human...
myocardial infarction need not be functionally independent or unrelated. It is plausible to consider that acute myocardial infarction in human subjects always begins with apoptotic cell death, as it does in experimental murine acute myocardial infarction, and that any and all necrosis takes place only when the local phagocytic capacity to remove dead apoptotic cells is exceeded (Figure 6B). This may be explained mathematically as too few macrophages available (for whatever reason) or biochemically as the chemotactic signals from the apoptotic cells failed to be generated or were received by the macrophages but, for some reason, misinterpreted. (2) Although the histological appearance of focal apoptosis in human myocardial infarctions is often remarkably discreet and not mixed with necrosis, frequently the apoptotic and necrotic components adjoin or even intermingle. This is unsurprising, especially if one thinks of these as 2 sequential rather than totally independent forms of cell death. Given the variable intermingling of apoptosis and necrosis in every human myocardial infarction, it is then to be expected that some apoptotic cells can be recognized within areas of predominant necrosis. This is sometimes proposed as a criticism of histochemical methods that identify DNA strand breakage as unreliable indicators of apoptosis rather than necrosis, but the criticism loses validity if there is often a mixture of the 2 death processes.

Finally, in comparative considerations between data from murine experiments and observations in human subjects with ischemic heart disease, it is important to remember certain time constraints. It is simple to time the events after the ligation of a rat coronary artery, but it is now increasingly appreciated that the human events are far more complex, giving rise to the useful description of a “stuttering onset.” Some of the obvious sources for this human variability include the waxing and waning of coronary spasm, the clumping and then disintegration of platelet aggregates, the morphology of the obstructing atheroma and especially any hinge-like action from it, and also the extracardiac influences at play, such as hypertension or hypotension, respiratory

**Figure 5.** This additional apoptotic focus of myocardial infarction is shown from the same heart as in Figure 1, with sharp margins (2 black arrows in A) seen at higher magnification. Cells from this apoptotic focus are depicted in B using TUNEL stain; 2 macrophages packed with phagocytosed apoptotic bodies are marked with black arrows, and a nonapoptotic blue nucleus (open arrow) of a myocyte has a myriad of ingested brown juxtanuclear apoptotic bodies. Myocytes can phagocytose nearby apoptotic cells or bodies, but macrophages are "professional" phagocytes.

**Figure 6.** Different stages of phagocytosis of apoptotic bodies by macrophages during acute myocardial infarction are shown here in A, from same heart as in Figures 1 and 5, and in B, from same heart as in Figure 3. Figures 3A and 3B showed an area of necrosis, whereas B here depicts a separate focus of apoptosis from the same heart, with many free apoptotic bodies lying in the intercellular space. In A, 4 macrophages are marked with open arrows; the nonapoptotic (blue) nuclei are visible, combined with varying degrees of packing with brown apoptotic bodies. A mass of brown juxtanuclear apoptotic bodies within a cardiac myocyte is marked with a short black arrow, and 2 non-apoptotic nuclei of cardiac myocytes are marked with thinner black arrows. TUNEL stain was used in both A and B.
problems, emotional and reflex neural influences, and a wide assortment of pharmacological agents affecting the heart in different ways. Thus, the precisely timed events in the rat experiments serve as a useful frame of reference relative to human events with myocardial ischemia, but it cannot be surprising that the procession of events in humans is seldom so predictable and is sometimes seemingly contradictory.

Ischemic Preconditioning
In 1918, Fred Smith heeded the suggestion of his mentor, James B. Herrick, and conducted a series of excellent experiments recording the electrocardiographic effects of ligating a coronary artery in anesthetized dogs. It was the most comprehensive and definitive study of its type at that time, and Smith has received too little credit for that work. In addition to anatomical and electrocardiographic correlations, Smith wrote that he was particularly impressed with the special ischemia produced in the posterior papillary muscle of the left ventricle when the left circumflex artery was ligated. Later examination of this same phenomenon by Jennings and colleagues has contributed enormously to our current knowledge of the metabolic, biochemical, and anatomic dimensions of acute myocardial infarction.

In a landmark study by Murry et al., one that should still be the “gold standard” to which virtually any subsequent study of preconditioning must be compared, there were four 5-minute periods of ischemia produced by temporarily occluding the proximal portion of the canine left circumflex coronary artery, each separated by 5 minutes of reperfusion. The surprising discovery was that a later infarct produced (by prolonged occlusion of the left circumflex artery) after such “preconditioning” was only one-quarter the size of an infarct produced without preconditioning. Their provocative conclusion, which quickly caught the attention of others, was their stated suggestion that in humans, multiple episodes of angina may delay cell death and thus allow the salvage of jeopardized myocardium by reperfusion.

Regrettably, neither Smith nor Jennings et al. described certain relevant anatomic features of the normal canine left circumflex coronary artery and the subsequent ischemia produced by its occlusion. In the canine heart, the left circumflex artery is the primary blood supply to the atrioventricular (AV) node and, combined with the terminal branches of the large single septal branch of the canine left anterior descending artery, provides the blood supply to the canine His bundle and proximal bundle branches. As a consequence, some (possibly major) alteration of AV conduction is
to be anticipated when the dog’s left circumflex artery is ligated. This is in considerable contrast to human coronary anatomy, where the predominant blood supply to the AV node and His bundle is from the right coronary artery. Specifically, the coronary sinus, from which the dominant venous drainage from the heart returns, is in the canine heart supplied entirely by the left circumflex artery. This artery is proximally occluded, variable but often copious dilation collateral flow will come to it by this transatrial route. Why is it that the left circumflex artery is the major source of collateral circulation left after it is occluded when the canine sinus node artery, located >95% from the distal portion of the right coronary artery, is cannulated and ligated for experimental selective perfusion of the sinus node? It has such copious collateral blood flow from atrial branches of the left circumflex artery that the experiments so conducted can be continued for many hours without any apparent impairment of sinus node function. In fact, in >15% of such canine experiments, the retrograde collateral blood flow into the occluded sinus node artery produces a pulsatile pressure equal to central aortic pressure. It is apparent that substantial collateral circulation exists in the canine heart connecting the left circumflex and right coronary arteries and that when the left circumflex artery is proximally occluded, variable but often copious collateral flow will come to it by this transatrial route. Why this does not more often prevent or at least modulate intense ischemia in the dog’s left ventricular posterior papillary muscle (consistently found by both Smith and Jennings et al) is puzzling. However, in studies such as those characteristic of experimental ischemic preconditioning by intermittent occlusion and release of the left circumflex coronary artery, transatrial anastomotic flow could be a source of error. It is my expectation that it will be unwelcome news to say that alternating ischemia and reperfusion may not actually reduce the volume of myocardium later lost with sustained or long-duration occlusion of the canine left circumflex artery, but that it may reduce only the volume of recognizable (histologically or biochemically) necrosis. Perhaps each of the previous 5-minute periods of occlusion and/or the intervening similar periods of reperfusion had themselves neatly eliminated segments of myocardium by apoptosis. It is already known that brief periods of various forms of injury (ie, hypoxia, irradiation, thermal injury) in a variety of tissues typically produce apoptosis, whereas the same type of injury in the same experimental preparation, presented more intensely or for longer periods of time, leads entirely to necrosis. Similar experiments have been conducted in the kidneys with precisely the same alternating ischemia and reperfusion protocols as in the heart, and they produced apoptosis.

A different but also comprehensive review of ischemic preconditioning suggested that the most direct evidence that the human myocardium can be preconditioned comes from studies performed in isolated, cultured human cardiomyocytes subjected to simulated ischemia and reperfusion. However, closer examination of that work reveals that the human cardiomyocytes were obtained from biopsies of the right ventricular outflow tract during surgery to repair cases of tetralogy of Fallot, circumstances that could be interpreted as hardly normal myocardium. Furthermore, the following methodological details are especially relevant. The necessary dispersal of biopsied myocytes to be cultured introduces inescapable distortion of these myocytes, including damage to intercellular junctions with various degrees of healing, the necessary elimination of the normal collagenous framework within which normal myocytes function, and the required use of collagenase and trypsin to produce this separation. The culture medium contained bovine serum to which had been added penicillin, streptomycin, and betamercaptoethanol. Ischemia was simulated by placing cells in an acrylic chamber flushed with 100% nitrogen, followed by exposure to low-volume anoxic perfusion (hypoxia, not ischemia), and then 100% nitrogen to reduce the PCO2, with pH adjusted to 7.4 and osmolality corrected with sodium hydroxide and hydrochloric acid. Many of these actions are standard components of certain cell-culture methods, but they are hardly reassuring...
about the comparability of these in vitro circumstances to either viable or infarcting myocardium. The experimental simulation of canine myocardial ischemia is far more difficult than some may want to think.

Two observations on the entire concept of ischemic preconditioning as a putatively beneficial exercise raise some concern about the validity of the original deductions, although one must admire the cautious choice of the term preconditioning in the original work, rather than a more implicit or even explicit claim of benefit. (1) Despite the immense amount of research into the subject of ischemic preconditioning by investigators of great talent from many different venues, no one has yet found the elusive responsible substance that might mediate preconditioning. (2) In a recent comprehensive and very informative review by investigators especially knowledgeable on the subject, the title emphasized the paradox inherent in ischemic preconditioning. There has been, despite frequent claims of widespread confirmation of the original work by a myriad of investigative teams, little or no examination of the possibility that the penultimate infarction after the preconditioned dog’s sustained occlusion of its left circumflex artery did not actually mean that a reduction in the total volume of myocardium lost had occurred, but only that the amount recognizable lost by necrosis had been reduced.

There are both old and recent studies that support the idea that apoptosis must play a role in the events described in the original work that launched the concept of ischemic preconditioning. In a historic report of the effects of coronary occlusion published in 1935 by Tennant and Wiggers, it was observed and documented that myocardial contraction ceased instantaneously distal to a point of left anterior descending coronary occlusion in anesthetized dogs, which was followed in <1 minute by a measurable bulge of the ischemic myocardium. Bulging myocardium must be stretched, and recent murine experiments have demonstrated that myocardial stretch causes apoptosis in the stretched area. Furthermore, Olivetti et al demonstrated apoptosis at the margins of fatal human myocardial infarction, a finding that they attributed to local stress, most likely the same as the canine myocardial bulges. Taken together, these observations raise an important question about how much local bulging and stretch (and probably apoptosis) may attend the classic experiments using proximal occlusion of the canine left circumflex coronary artery. Certainly the time frame of the Tennant and Wiggers observations would suggest that 5 minutes of coronary occlusion must be associated with myocardial bulging and stretch, whereas the 2 more recent studies cited indicate that local apoptotic cell death must be anticipated. In fact, both ischemia and stretch, either separately or together, are themselves powerful causes of myocardial apoptosis. Neither could be reflected by the measurement of serum markers.

However, the production of ischemia and myocardial stretch or bulging comprises only half of the sequential events included in the classic experiments of ischemic preconditioning. The other half is a matching interspersion of similar periods of reperfusion (the occluding ligature released). There are at least 3 considerations associated with this reperfusion. (1) Oxygen and other beneficial substances are provided to the surviving ischemic myocardium, (2) the originally recognized removal of catabolites must include dead apoptotic myocytes, and (3) reperfusion can replenish monocyte macrophages to assure continued efficiency of phagocytosis and removal of apoptotic debris during each succeeding period of ischemia.

Suppose that each of the 5-minute episodes of transient ischemia caused multifocal myocardial apoptosis and that each intervening 5-minute period of reperfusion did each of the 3 things just described. This is not simply a fanciful improbability, but a plausible interpretation of what actually happens. If this scenario is correct, then the explanation of the “smaller” infarct (always defined as necrosis) after preconditioning may simply be because repeated earlier production of apoptosis left fewer myocytes available later to be killed by necrosis. Ischemic preconditioning may then be an example of myocardial infarction on the installment plan, and there may be some advantages to that compared with a situation in which there is more necrosis immediately or very soon. Apoptotic areas, characteristically devoid of an inflammatory reaction by neutrophils (always seen with necrosis), would escape the numerous harmful effects always encountered as a consequence of an inflammatory milieu, eg, tissue acidosis. Support for this line of reasoning is provided by the conclusions of Kajstura et al from murine experiments. They conclude, in contrast to general opinion, that apoptosis is both the initial and principal determinant of infarct size.

In fact, we are woefully ignorant about just how the viable myocardium responds to an area of apoptosis compared with an area of necrosis. For example, it is generally thought today that the initiating event for angina pectoris is an acidic stimulation of sensory neural terminals in the heart. In apoptotic myocardial death, does this mean that angina is either avoided or less severe? Would cardiogenic reflexes be less likely with apoptosis than necrosis? There is already evidence that ischemic preconditioning is associated with fewer late electrophysiological problems than those observed when such preconditioning is not employed. Does this mean that ventricular myocardial apoptosis is less arrhythmogenic than necrosis? Or were all the discarded fatal experiments actually examples of lethal arrhythmogenesis? Of course, when apoptosis destroys significant foci of the conduction system of the heart, different concerns apply, as has been illustrated in fatal cases of TTP. Along the same line of reasoning, multifocal apoptosis in the myocardium could be at least a partial explanation of so-called silent angina pectoris or even silent myocardial infarction, and the same thoughts are pertinent in hibernation or stunning in the heart. Some beneficial advantages associated with ischemic preconditioning may in truth be real, but for a different reason than having a smaller ultimate volume of myocardial necrosis.

Another, and perhaps more woeful, area of ignorance is our minimal understanding of the probable powerful effect of many widely used pharmaceutical agents in the treatment of almost all facets of acute myocardial infarction or even lesser forms of ischemic heart disease. Although there is growing knowledge of the inotropic, chronotropic, and dromotropic...
actions of most of these agents on the myocardium, as well as their effects on systemic and coronary vascular tone, almost nothing is known of how they either inhibit or promote apoptosis and, equally important, whether they either inhibit or promote the effectiveness of phagocytosis, particularly as it would relate to apoptotic cell death. Both the speed of onset to the completion of apoptosis and the similarly rapid process of subsequent phagocytosis of apoptotic cells and apoptotic bodies by macrophages could be either facilitated, retarded, or even blocked by currently unknown effects of any or most of our therapeutic armamentarium.

As we enter a new millennium, there is good reason for optimism about the further improvement of our understanding of all facets of myocardial infarction, including both the value and limitations of serum marker diagnosis, as well as a different interpretation of how ischemic preconditioning works. It is unlikely that the active pursuit for explanations in these enormously popular research subjects will soon ebb, but I hope that an increased attention to roles for apoptosis will be more widely applied. Paramount in such evolutionary changes must be a serious and active concern for finding some means of detecting and measuring the presence of apoptosis in vivo, especially during human myocardial infarction, although I doubt that the discovery will be some new serum marker, given that apoptotic myocytes do not lose their plasmalemmal integrity. In this context, recent efforts to measure apoptosis in vivo are encouraging.

Near the beginning of the past century, James B. Herrick radically changed our thinking about myocardial infarction as a tocsin of doom, leading to a century-long parade of investigations of myocardial infarction in all its fascinating facets. As we begin the 21st century, I hope and believe that a wider appreciation of all aspects of apoptosis in myocardial infarction will substantially increase and improve our understanding of this terribly important subject.

A Contemporary Look at Sickle-Cell Heart Disease

After Herrick first described sickle-shaped erythrocytes in the blood smear from a young black dental student, there was limited further attention by others to this surprising observation for a long time, even by Herrick himself. In fact, most of our current understanding of sickle-cell anemia has come in the past few decades, and it now commendably seems to be an increasing area of productive research. My reason for choosing sickle-cell heart disease is not because it per se was any interest of Herrick’s, but because there is already clear evidence of how clinically important it is to recognize that sickle-cell anemia affects the heart in more ways than simply the consequence of the anemia itself.

There is understandable emotional and intellectual sensitivity by individuals who either have or may be subject to sickle-cell anemia, because there are harsh and punitive possibilities stemming from the misuse of such information about its cardiac effects. However, it is both medically and ethically unwise to ignore or evade the growing scientific evidence that such an association exists and is clinically important. In fact, there are sizeable opportunities for understanding many other aspects of cardiac disease from a better understanding of sickle-cell heart disease. Furthermore, there is substantial hazard for patients with sickle-cell heart disease if they and their physicians ignore this evidence.

As has previously been reported, patients with either homozygous or heterozygous forms of sickle-cell anemia can have cardiac problems, including the occurrence of sudden, unexpected death. Regarding sudden death, there are especially significant morphological abnormalities found in the cardiac conduction system of such individuals, including the sinus node and the AV node (Figures 9 to 11). There are, of course, numerous contributing factors underlying the cardiac changes in sickle-cell patients, including the effects of anemia, the morphological and biochemical effects of the sickle cells themselves, and platelet abnormalities, independent of whether they are a primary or secondary abnormality. Sickled erythrocytes are known to stack and to agglutinate into obstructive masses within small arteries, capillaries, and venules. Once there, they become enmeshed with circulating platelets to form obstructive masses. The enmeshed platelets...
compound the obstructive problem with adherent and enmeshed fibrin. There is also evidence that platelets may have an intrinsic or primary abnormality in sickle-cell anemia, independent of the results of their simply being caught “in flight,” so to speak, by the stacked erythrocytes.65,66

In addition to the widely known influence of adherent platelets on the endothelium and other components of the vascular wall, there is also evidence of a mitogenic effect by sickled erythrocytes themselves.67 Thus, these secondary effects (in addition to the direct consequence of arresting the flow of blood) may help explain the surprising prevalence of both endothelial proliferation and fibromuscular dysplastic sites among many small coronary arteries (Figures 9 to 11). These additional vascular obstructive lesions also account for the focal degeneration and later focal fibrosis throughout both the ventricular or atrial working myocardium, as well as the conduction system.

Just as was discussed in the comparison of cardiac disease in TTP with examples of acute myocardial infarction, similar comparative lessons are available for sickle-cell heart disease. I have previously written of the importance of abnormalities in the small coronary arteries in atherosclerotic heart disease and myocardial infarction,68,69 and I emphasized that the histological character of many of these small coronary abnormalities was primarily narrowing due to focal fibromuscular dysplasia, rather than atherosclerosis.70 The clinical consequences of these lesions in regard to arrhythmogenesis, the generalized prevalence of focal myocardial destruction, and the probable impairment of at least some potential routes of development of coronary collateral circulation are similar for myocardial infarction and for both TTP and sickle-cell heart disease. It should be added and emphasized that one major difference is that acute myocardial infarction is rarely found in either TTP or sickle-cell heart disease. It should be added and emphasized that one major difference is that acute myocardial infarction is rarely found in either TTP or sickle-cell heart disease for the simple reason that abnormalities of the epicardial large coronary arteries are seldom present in those 2 hematological diseases. However, multifocal myocardial degenerative and/or fibrotic lesions are common to all 3 conditions.

In both TTP and sickle-cell anemia, there are characteristically widespread vascular occlusions involving virtually every organ of the body, including the heart. In patients with acute myocardial infarction, there are sometimes atherosclerotic lesions in the circulation perfusing the brain or the kidneys, but we do not usually consider acute myocardial
infarction as a multiorgan problem. However, in all 3 conditions, apoptosis plays a prominent role in the patterns of cell death encountered. Those patterns have already been discussed for myocardial infarction and for TTP. I will now describe some similarities and major differences for the situation in sickle-cell heart disease.

Whereas acute myocardial infarction always involves both apoptotic and necrotic cell death and, in TTP, virtually all the focal myocardial cell death is apoptotic and not necrotic, the pattern of myocardial cell death is less distinct in sickle-cell heart disease. There are certainly foci of apoptotic degeneration in sickle-cell heart disease (Figure 12), and the distribution and episodic occurrence of multifocal narrowing in small coronary arteries are similar to TTP, but the nature of the arterial lesions in sickle-cell heart disease is quite different. In this disease, the small coronary lesions are a mixture of both endothelial proliferation and fibromuscular dysplasia, with some examples being purely one or the other but, more often, both types of lesion will coexist. One reason for this arterial morphological difference may lie in the absence of sickled erythrocytes in TTP and the mitogenic effect of such erythrocytes in sickle-cell heart disease. Additionally, the cytological composition of the intravascular obstructive masses differ. In TTP, these are primarily platelet aggregations, with variable but only a small admixture of fibrin, whereas in sickle-cell heart disease, the major role of the abnormal red blood cells is paramount and the platelet contribution, although significant, is the lesser contributor.

Differences in the pathogenesis of small coronary lesions between myocardial infarction, TTP, and sickle-cell heart disease can be countered by one situation common to these 3 diseases (and one that is too seldom examined), circulating endothelial cells. These have not only been demonstrated in both angina pectoris and acute myocardial infarction, but also in sickle-cell anemia. In all 3 conditions, I have seen small masses of endothelial cells included in embolic debris within small coronary arteries. This is important not only for what it tells about the arterial occlusion, but also for what is implied about the source of such endothelial fragmentation. In fact, in the coronary lesions associated with fatal cases of the toxic oil syndrome, the embolic obstruction of even the epicardial coronary arteries is sometimes composed entirely of sloughed masses of endothelium. But however the multiple examples of small coronary narrowing in sickle-cell heart disease may be explained, there can be little doubt that these lesions take time to develop and must represent old or recurring processes, not the events just preceding death.

There is one final consideration linking the pathophysiological consequences of platelet aggregations and small coronary occlusions found in acute myocardial infarction, TTP, and sickle-cell heart disease, the racemose histological anatomy of the coronary chemoreceptor, which abounds in a myriad of interwoven small arteries and capillaries. Evidence has previously been presented that severe bouts of new hypertension associated with either angina pectoris or early acute myocardial infarction may be mediated by the release of serotonin from platelets clumped within this chemoreceptor of the heart. The arrhythmogenic effect of such acute hypertension, which is sometimes double the level of resting blood pressure, could cause lethal electrical instability in the heart, whether in the usual forms of myocardial infarction or as in TTP or sickle-cell heart disease. Conversely, there is some evidence that pathological obliteration or pharmacological blockade of this coronary chemoreceptor may disrupt the afferent pathways mediating angina pectoris, providing an alternative explanation (to that of apoptosis) for the pathogenesis of silent angina pectoris or silent myocardial infarction.

Neither Herrick nor many investigators since have directed much attention to the cardiac involvement of sickle-cell anemia. This is unfortunate because sudden death is not uncommon in sickle-cell anemia and chronic cardiac insufficiency is also a clinical problem in some patients. Actually, Herrick did describe cardiac insufficiency in his patient, but in addition to his anemia, that patient had recurring multiple types of infections prevalent both in the American and Caribbean public of the time. Chest pain in patients with sickle-cell crises has attracted considerable attention and has been variously attributed to pulmonary vascular lesions or to small infarctions within the bone marrow of the ribs or the sternum and still other areas of the thorax. Surprisingly, little attention has been aimed at the heart, although most episodes of chest pain in sickle-cell anemia occur during crises, and the painful crises have been demonstrated to be associated with documented disturbances in the electrical activity of the heart. One probable explanation for this inattention to the heart may be because chest pain crises in sickle-cell anemia.

Figure 12. With TUNEL stain, apoptotic degeneration in both sinus node (SN) and AV node (AVN) is illustrated from case of sickle-cell heart disease also shown in Figures 10 and 11. Examples of brown apoptotic myocytes are marked with black arrows and blue nonapoptotic myocytes with open arrows.
so often are seen in childhood or adolescence, although adults also are affected. Chest pain is too seldom suspected to be cardiac in young patients.

To revert to my initial point that Herrick brilliantly recognized sickle cells in the blood smear of his patient but rarely thought or wrote further about them, in contrast to his continued and enormously useful contributions in myocardial infarction, I have presented a comparable disparity of comments on these 2 subjects, ending with this relatively brief discussion of sickle-cell heart disease.

Closing Thoughts About James B. Herrick

We are now at a special and immensely thought-provoking time in history, as not only one century but an entire millennium has come to a close during the past few weeks. Herrick’s life and accomplishments we unabashedly admire and extol, but one lesson must not escape our attention. This concerns the continuing, growing, and worrisome decline in the numbers of young physicians choosing to become clinical scientists, a problem that has frequently been addressed by previous Herrick lecturers. Few would quarrel with the thought of James B. Herrick as an exemplary model of the physician-scientist. Some would quickly add that yes, but he lived in a different time and societal culture. To that I would counter that his impeccable professional principles and his dedicated personal concern for patients are timeless. The vast majority of medical students of all times enter medical school honestly believing that these are their principles as well. What happens to change this noble beginning?

We can take one Herrick example to illustrate his character and the valuable model it provides. After his original proposal that myocardial infarction was not a universal tocsin of doom, a logical “scientific” question was how the ECG could be useful in its diagnosis. After all, it was not only already available for a decade by 1912, but Einthoven had demonstrated that its signals could even be transmitted by telephone. Sir Thomas Lewis, for inexplicable reasons, did not combine his remarkable work on clinical electrocardiography with Herrick’s subject of myocardial infarction, but that may be because Lewis was obsessed with cardiac rhythm and conduction (particularly atrial fibrillation) and by the 1920s, naively announced that there were no more scientific questions warranting investigation with electrocardiography. Early on, Frank Wilson urged Herrick to take advantage of electrocardiographic observations in relation to myocardial infarction, a subject that Wilson and his colleagues revolutionized with their later introduction of precordial leads at a time when Herrick was still busily involved in some research and much patient care.

Herrick fully understood the growing importance of technology in medicine but was never distracted from his clinical focus. What Herrick did was to advise his protégé Fred Smith to examine the electrocardiographic effects of experimental myocardial infarction in anesthetized dogs, an assignment that Smith generously acknowledges in his landmark contribution, which Herrick could have, but refrained from, shared authorship. Herrick not only prospered intellectually and in the admiring tributes of his peers, but he remained at heart a physician.

Rather than thinking of Herrick as some sort of antediluvian illusion, I submit that the mental and emotional image that attracts most young medical students to their career remains much closer to Herrick than to many of us today. Perhaps we are too concerned with the didactic teaching of principles of research, often ending with one or more additional degrees, than with what made Herrick special. As more and more young cardiologists now strive for their next grant from the National Institutes of Health and for lecturing and posturing before like-minded audiences, we forget the image that this presents to our intellectual heirs. We collectively present a façade of “science” so transparent and so devoid of love for patient care that students and house staff not only see through it, but vote with their feet, so to speak, and stay away from us in droves. That will change only when they again see more examples of the model epitomized by James B. Herrick: certainly seeking new knowledge, but centered on the immutable principle of a proper physician recognizing that caring for the patient is based especially on caring about the patient. As for despairing that there are no more questions worthy of research by true physicians, remember how Alexander the Great wept because there were no more opportunities for conquest. There are and always will be new problems and new questions in medicine, and there will probably be more in the future than in the past.

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References


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