The delayed diagnosis of myocardial infarction: it took half a century!

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IN 1940 the physiologist Carl Wiggers claimed, "Delayed recognition of important physiological discoveries frequently continues untenable and wrong points of view. . . . Greater mutual efforts ought to be made by clinicians and physiologists for better dissemination, digestion and absorption of important physiological discoveries."1 Although angina pectoris had been described by William Heberden in the 18th century, and some 19th century physicians recognized an association between this symptom and sclerosis of the coronary arteries found at autopsy, the syndrome of acute myocardial infarction was not recognized until the 20th century.2-5 The "wrong point of view" that led to the long delay in the recognition of acute myocardial infarction was the belief that sudden coronary occlusion was invariably fatal. This view predominated until 1912 when James Herrick proposed that myocardial infarction in man was not always fatal and could be recognized during life. Additional factors that contributed to this delay included: (1) the inconstant relationship of symptoms to pathological findings in ischemic heart disease, (2) the excessive reliance on auscultation as an indicator of cardiac disease, (3) the failure to routinely examine the coronary arteries or the myocardium at autopsy, (4) the reluctance or tardiness of clinicians to incorporate new pathophysiologic discoveries into medical practice, (5) a willingness to accept theories of disease without scientific evidence to support them, (6) the preoccupation with the new field of bacteriology, which distracted clinicians and biomedical scientists from the more traditional organ-centered approach to disease, and (7) the lack of any diagnostic techniques with which to objectively identify coronary artery obstruction or its consequences during life. Nevertheless, during the second half of the 19th century many discoveries were made that ultimately led to an understanding of the clinical and pathologic sequelae of coronary occlusion. Most of the important observations were made by individuals who combined extensive experience in pathology with clinical practice.

In the 1840s several British physicians became interested in the coronary circulation. John Erichsen studied the relationship of cardiac arrest and experimental coronary occlusion, Joseph Swan attempted to demonstrate coronary anastomoses using injection techniques, and Richard Quain initiated a detailed study of "fatty diseases of the heart." Quain received his medical training at University College, London, where he studied physiology under William Sharpey, one of the first in Britain to use the microscope in medical teaching. Quain was appointed assistant physician to the Brompton Hospital for diseases of the chest in 1848.6 His thorough scientific training and clinical experience equipped him to investigate the clinical and pathologic features of heart disease. Quain's attention had been drawn to this subject in 1845 "by the sudden death of a gentleman, in whose body no sufficient explanation of that event could be found. A peculiar fatty condition of the heart was observed and recorded during the examination. The occurrence, soon afterwards, of two similar cases, led to the conclusion, that the presence of this fatty matter in the heart's texture bore some important relations to the structure and functions of the organ."7

In 1850 Quain published a comprehensive review on fatty diseases of the heart based on a study he had undertaken with Charles Williams who had reported the association of coronary artery sclerosis with myocardial scars more than a decade earlier. Williams, professor of medicine at University College, had studied under Hope, Magendie, Laennec, and other leaders of the scientific study of heart disease and was later characterized by Quain as " . . . the principal founder of our modern school of Pathology . . . ."8 Quain reviewed the histories and cardiac pathologic findings in
83 patients with fatty disease of the heart he or his colleagues had seen or whose cases had been previously published. He differentiated epicardial fat from the circumstance in which “the muscle fibre itself degenerates into molecular fatty matter,” a condition he denoted “fatty degeneration.” Quain believed this process had been overlooked in the past because the microscope was rarely used in studying the heart at autopsy. He sought to prove “that the molecular fatty matter in the fibre is the result of a chemical or physical change in the composition of the muscular tissue itself independent of those processes which we call vital.” Quain rejected the “vitalism” that had dominated medical and scientific thought for generations and sought to establish scientific truths through accurate observation.9

His study revealed the “close relation which exists between this condition [ossification of the coronary arteries] and fatty degeneration.” In every heart with fatty degeneration examined, Quain found “the coronary arteries were more or less ossified or obstructed. . . . I have seen the coronary artery extremely ossified, going directly to the only part of the heart affected.” Despite these important observations, Quain failed to appreciate the subtleties of the pathophysiology of coronary artery disease. He felt that the “degenerated condition of the heart’s fibres is a very sufficient source in itself of the several phenomena (viz. breathlessness, faintness, and pain), which are recognized under the name of angina pectoris, or syncope anginoso.” In a recent review, the British pathologist A. D. Morgan concluded 52 of Quain’s 83 cases probably represented ischemic heart disease.10 Although Quain’s report was enthusiastically reviewed it had little impact on clinical practice; microscopic examination of the myocardium and careful assessment of the patency of the coronary arteries would not become routine in autopsies for several decades.

Some mid-19th century writers recognized that coronary occlusion could result in fatty degeneration and cardiac rupture. Duben, a Swedish pathologist, reported this in 1859. A decade later the German pathologist Rindfleisch attributed fatty degeneration to “atheromatous degeneration of the coronary arteries with plugging of one of their larger branches by a thrombus . . . in every instance. . . .”11 The American physician Austin Flint accepted Quain’s theory of the causal relationship between coronary occlusion and “fatty degeneration” of the myocardium, but believed that other “general” rather than “local” causes could also account for this pathologic finding.12 Flint recognized the serious nature of fatty degeneration and observed in 1870, “Fatty degeneration is . . . especially attended with notable disorder and danger. . . . It may prove fatal, by leading to rupture. Sudden death is liable to occur in an attack of syncope.” Flint claimed the diagnosis of fatty degeneration “was not difficult” if the symptoms of feebleness, dyspnea on exertion, palpitations, and precordial distress were present “especially if the patient have passed the middle period of life, if his habits have been luxurious and indolent . . . if he have the arcus senilis, or if there be a tendency to obesity.” Although Flint identified several “risk factors” for the development of coronary artery disease, it would be a mistake to credit him with the insight into ischemic heart disease this quotation might suggest. The symptoms he attributed to fatty degeneration of the heart are not specific for coronary artery disease and the antemortem diagnosis of coronary thrombosis had not yet been made.

The first reported case of coronary thrombosis recognized during life was published in 1878 by Adam Hammer. Hammer received his medical training in Germany, but emigrated to America in 1848 and settled in St. Louis where he became a successful practitioner and medical teacher.13 Before his return to Europe in 1877, he discussed his case at a meeting of the German Medical Society of New York, but “. . . even the most learned Dr. [Abraham] Jacobi, who might well be called a walking dictionary of medicine, knew nothing of the disease.”14-16 After his return to Germany Hammer discovered that several prominent physicians, including Adolf Kussmaul, were unaware of a similar case. It is clear from the history and gross pathologic findings (there is no mention of a microscopic examination of the heart) that Hammer’s was not a case of atherosclerotic coronary artery disease. An aortic valve vegetation with an attached thrombus had obstructed the coronary artery. Indeed, Hammer’s explanation of how he reached the antemortem diagnosis of coronary thrombosis, and his brief description of the heart, fail to reveal any true insight into the relationship of acute coronary obstruction to myocardial necrosis. Nevertheless, Hammer hoped his case would stimulate interest among clinicians who might also recognize the condition before the death of the patient and experimental pathologists who “we would also expect . . . to study this matter in the near future.”

Important advances in our understanding of the pathophysiology of ischemic heart disease can be traced to the pathology laboratory of Julius Cohnheim at the University of Leipzig.17 Cohnheim had studied under Rudolf Virchow and continued his mentor’s studies on thrombosis and embolism. William Osler,
after a visit to Cohnheim’s laboratory in 1884, characterized him as an experimental pathologist without rival in Europe. Another pupil of Virchow’s, Carl Weigert, became Cohnheim’s assistant in 1874 and made important contributions to the study of histology of thrombosis and embolism and these Cohnheim incorporated into the second edition of his pathology textbook that appeared in 1882.\textsuperscript{18} When Cohnheim and Weigert arrived at Leipzig from the University of Breslau in 1878, they brought a new perspective according to Adolf Strümpell, assistant in the medical clinic at the time. He claimed, “For the first time the question of the etiology of disease was placed in the foreground.”\textsuperscript{19}

Weigert extended Virchow’s and Cohnheim’s studies on tissue injury and proposed the theory of coagulation necrosis, a term coined by Cohnheim. In an 1880 article Weigert discussed the pathologic appearance of infarcts in several organs including the heart. Based upon more than ten years of experiments, he claimed that passive tissue injury was the fundamental mechanism of cellular proliferation in inflammation. He applied his theory to the poorly understood histologic finding of “chronic myocarditis” and claimed,

... with atheromatous changes of the coronary arteries thrombotic or embolic occlusions of their branches not infrequently occur. If the closures result slowly, or, more important still, in such a way that collateral channels, even though insufficient for nourishment, exist, there ensues a slower atrophy with disappearance of the muscle fibers, but without injury to the connective tissue. These destroyed muscle fibers are then replaced by fibrous tissue, and the so-called chronic myocarditis is nothing else but such a process. If, however, a very sudden complete cutting off of the blood supply occurs in certain parts of the heart, yellow dry masses entirely similar to coagulated fibrin result. Here also, however, microscopic examination reveals almost no fibrous exsudate, but often an apparently quite normal tissue (even the cross-striations of the muscle fibers often recognizable) but all muscle fibers and all connective tissue are devoid of nuclei. A reactive infiltration of round cells and spindle cells is present in the vicinity.\textsuperscript{20, 21}

Two years later, Carl Huber, Weigert’s clinical colleague at Leipzig, published the histories of the patients who were found at autopsy to have had myocardial infarctions. Based upon Weigert’s studies, Huber declared that angina pectoris and myocardial infarction were both manifestations of coronary artery disease.

Weigert’s research led Cohnheim to claim, “It is now known that the very great majority of the myocarditic inductions . . . are due to an advanced sclerosis . . . of the coronary arteries supplying the affected part . . . . Furthermore, most pathologists are probably now unanimous in regarding numerous cases of fatty degeneration as the sequela of severe coronary sclerosis. . . . The degeneration usually affects first the papillary muscles, next the subendocardial layer of muscle fibres, and finally, in extreme cases, the whole thickness of the muscular wall.” Although Cohnheim believed, based on his experiments and those of others, that sudden occlusion of a coronary artery was usually fatal, he acknowledged that death was not inevitable. He wrote in 1882, “The occlusion of a coronary artery — in case it does not prove fatal . . . leads to the destruction of the contractile substance of that portion of the heart which is fed by the affected artery, and afterwards to the formation there of so-called myocarditic indurations.”\textsuperscript{22}

The pathologic observations of the Leipzig group had little impact on medical practice in the 1880s. The clinical event we now call acute myocardial infarction was occasionally described, but it was not distinguished from angina. The pathologic features of myocardial infarction were sometimes discovered at autopsy and were found to be associated with coronary occlusion, but the relationship of symptoms to pathologic findings remained obscure. Skilled diagnosticians still debated the pathophysiology of angina pectoris. An example is provided in the 1880 case report of a 62-year-old obese merchant who for two and a half years had “an oppression and constriction in the carotid regions, with a sense of dread while walking up hill.” Dr. Frederick Winsor, a Harvard graduate, diagnosed “temporary exhaustion of the nervous centres” and advised rest. After a severe episode the patient was seen by the prominent Boston physician Henry Bigelow, who suggested the possibility of angina pectoris. The patient was kept in bed but had a three and one-half hour episode of precordial discomfort associated with irregularity of the pulse and pallor. The patient was treated with amyl nitrite and morphine and was thought to be recovering when, four days later, “he quietly died without pain or distress.” At autopsy an apical aneurysm with cardiac rupture was found and “in the vicinity of the rent . . . the characteristic appearance of the muscle was lost, the muscular fibres being here filled with a granular material and in many places with minute fat drops.” The coronary arteries were atherosclerotic and a thrombus occluded the left anterior descending artery. “The portion of the heart in which the rupture had occurred and in which the fibres were found degenerated corresponded to the territory supplied by the branches of this artery.” Winsor and his consultants were surprised at these findings since they had “detected nothing wrong in the heart or lungs” the day after the severe episode and believed the patient would recover. Winsor observed, “I cannot see . . . how the diagnosis, prognosis, or treatment could...
have been improved on in light of our present knowledge. The case, however, goes to increase one’s distrust of the accuracy of physical examination of the chest.” In discussing the case, Dr. Richard Hodgdon “said that he considered angina pectoris a symptom or group of symptoms, and not a disease . . . and thought it ‘unscientific to dignify with the name of a disease some symptoms which, between 1763 and 1832, received fifteen different names, implying nearly as many different origins of the symptoms.’”

A major factor that made it difficult for physicians to distinguish the various ischemic heart disease syndromes we now recognize was the inconstant relationship of symptoms and pathologic findings. Samuel West, a British physician who had studied in Vienna and Berlin, wrote several articles on coronary artery disease in the 1880s and studied coronary anastomoses using injection techniques. He observed in 1883, “It is very remarkable how large an amount of obstruction there may be to both coronary arteries without any cardiac symptoms during life, or any gross pathologic change recognisable in the muscle of the heart after death.”

Cohnheim also noted the poor correlation of anatomy and symptoms, and wrote, “Now it is quite true, that in individuals who have suffered during life from angina pectoris, or perhaps succumbed to an attack, there has repeatedly been found post mortem a more or less extensive and advanced rigidity and sclerosis of the coronary arteries. Nevertheless, a true causal relationship need not therefore exist, especially as it often happens that no trace of disease is to be found in the coronary arteries of such subjects, and — what is still more common — that a very high degree even of coronary sclerosis is met with in persons who have never had an attack of angina.” Cohnheim anticipated the eventual recognition of coronary artery spasm and spontaneous recanalization of a coronary thrombus when he claimed, “Even if the statistics telling in favour of a connection between both processes were more satisfactory than is really the case, this would be little to the purpose. It would always be open to suppose that the circulation through the coronaries, being already impeded, had been still further impaired by some transient accidental circumstance or other; such a supposition, however, is incapable of proof.”

Cohnheim’s assessment was realistic in an era before electrocardiography and coronary arteriography. Only when techniques became available to objectively identify narrowing of the coronary arteries and myocardial ischemia would it be possible to correlate the symptoms of the various ischemic heart disease syndromes with the underlying anatomic and physiologic abnormalities.

Other Europeans further elucidated the pathophysiology of ischemic heart disease in the 1880s. Ernst Ziegler, a Swiss pathologist, proposed the term “myomalacia cordis” for the pathologic changes that result from coronary occlusion. He described the evolution of histologic changes as the age of the infarction increased and declared that myocardial infarction was not invariably fatal. Ziegler wrote, “When the destructive process has gone a certain length, and death does not ensue, processes of repair are set up.” The British physician Donald MacAllister, who translated Ziegler’s text, claimed, “myomalacia cordis has hitherto received but little attention as an integral process; it has been treated under many and various partial names. Clinical observers generally confound it with myocarditis or with fatty degeneration; though it agrees in strictness with neither. The affection is really anaemic necrosis . . . It is not a rare affection, and when at all extensive it brings about death by failure or rupture of the heart.”

A valuable report that synthesized contemporary concepts of ischemic heart disease was published in 1884 by Ernst von Leyden, a Berlin physician and pathologist. He explained that while the emphasis on physical diagnosis had led to significant advances in the area of valvular heart disease, this approach was of limited value in myocardial disease. He encouraged his readers to pay more attention to the pathologic and physiologic alterations underlying the various ischemic heart disease syndromes. Leyden separated coronary artery sclerosis into four groups based on the pathologic findings and divided the clinical manifestations into acute, subacute, and chronic types.

The Scottish physician and pathologist John Steven had studied with Weigert and Huber and was perplexed that their observations had received so little attention. Speaking of Brym Bramwell’s comprehensive monograph on heart disease published in 1884, Steven remarked, “in the long account of the etiology and pathology of the condition [fibroid degeneration], not a hint is given of the possible direct connexion which this lesion may have with disease of the coronary arteries or obstruction of these vessels.”

Despite Quain’s admonition a generation earlier, the heart was rarely carefully examined at autopsy. Samuel West observed in 1884 that “the coronary arteries are frequently overlooked in making an ordinary post-mortem examination.”

Moreover, localized areas of myocardial scarring were “very likely to be overlooked unless all parts
of the organ are completely sliced up" according to Hilton Fagge, a British physician and pathologist.32 Fagge claimed to "have met with an exceptionally large number of instances of the localized fibroid disease" in the autopsy room of Guy's Hospital, although he claimed, "Clinically, fibroid disease and aneurism of the heart can very seldom, if ever, be diagnosed." These comments support the recent claim of pathologist A. D. Morgan: "Although ischaemic heart disease may have masqueraded in the nineteenth century as angina pectoris, fatty degeneration, rupture of the heart, cardiac aneurysm, fibroid degeneration or chronic myocarditis, there would seem to have been . . . quite a lot of it about."30

The publication of Stevens' review of coronary artery disease and the appearance of English translations of the pathology texts of Ziegler and Cohnheim in the late 1880s provided contemporary clinicians with summaries of the recent scientific observations on the pathophysiology of ischemic heart disease. The concept of myocardial infarction from a pathologic point of view was gradually making its appearance in the clinical literature of Europe, Great Britain, and America. William Osler discussed the pathophysiology of ischemic heart disease and suggested the possibility of short-term survival after coronary occlusion in 1889. He claimed

The local disturbances of nutrition caused by the blocking of a terminal branch of a coronary artery produce the condition known as infarct of the heart. . . . The danger is not alone at the period of preliminary softening, but time gradually effects a transformation of the softened areas into fibrous tissue, which yield and in many cases to aneurism of the cardiac wall and rupture. . . . In a number of cases death occurs suddenly, without any premonition; in other cases, precordial distress, pain in the left side, and signs of cardiac trouble have preceded the fatal illness for days or even weeks.33, 34

In 1892 Osler declared, "A knowledge of the changes produced in the myocardium by diseases of the coronary vessels gives a key to the understanding of many problems in cardiac pathology."35 Still, confusion about the causal relationship of pathologic findings to symptoms is apparent in contemporary publications. The American pathologist William Welch, who had studied with Cohnheim and Weigert in the mid-1880s, presented a specimen "in which a thrombus had formed in the apex of the left ventricle, a portion breaking off obstructed the anterior coronary artery completely, thus causing anaemia of the wall, coagulation necrosis, and a white infarction."36 The pathologic observations were undoubtedly accurate, but the sequence of events described reveals a lack of understand of the pathophysiology of myocardial infarction and its sequelae.

Pathologists continued to bemoan the lack of interest among clinicians in coronary artery disease. In 1893 Steven complained before the members of the British Medical Association, "Of late years the etiology and morbid anatomy of the lesions of the myocardium have been much studied, but it may well be doubted whether these important, and in many cases suddenly fatal, affections have received the attention they deserve from the clinical side." He emphasized the value of the recent discoveries reported at the International Medical Congress held the previous year in Berlin and claimed, "The wealth of pathological observation and experiment then recorded [on the disturbances of the myocardium] gave promise of abundant and early fruit in the fields of clinical research and practical medicine."37 This congress was attended by 5000 representatives including 500 from the United States. Although von Recklinghausen delivered an important talk on myocardial diseases and there were other sessions devoted to heart disease, the topic that attracted the most attention was bacteriology, with its implications for public health and the practice of medicine and surgery.38 The preoccupation of physicians with bacteriology in the closing years of the 19th century almost certainly contributed to the long delay between the important observations of Weigert, Cohnheim, Leyden, and others in the 1880s and the appreciation of the clinical relevance of their findings a generation later. Some individuals continued to focus on the heart, however, and studies on sudden death and experimental coronary occlusion by John MacWilliam, William Porter, and others ultimately led to the recognition of the spectrum of syndromes associated with coronary artery disease and myocardial ischemia.39, 40

One of the first antemortem diagnoses of myocardial infarction was reported in 1896 by George Dock, who had studied in Germany with Weigert, Huber, and Leyden after his graduation from the University of Pennsylvania School of Medicine in 1884. Dock claimed, "The epoch-making discovery of mediate auscultation engrossed the attention and diverted the minds of physicians especially toward the examination of the valves of the heart, and away from the muscle itself."41 He attributed the renewed interest in the coronary arteries to the growing awareness of their significance in cases of sudden death and claimed, "From an early period physiologists and pathologists investigated the subject experimentally, with great advantage." Dock ascribed the tardy recognition of the importance
of coronary artery disease among clinicians “to a pecu-
liarity of the disease or diseases in question. From the
nature of the cases hospital physicians see but a part of
their course, and that not always the most important for
a successful diagnosis.” Dock anticipated the role Herr-
rick would ultimately play when he declared, “It must,
therefore, remain for those physicians in general prac-
tice who have an oversight of patients for long periods,
and who at the same time have the sort of scientific zeal
that influenced a Jenner to give the final touches to the
pictures of coronary disease.”

In 1896 William Osler delivered a series of lectures
on angina pectoris in which he recounted recent experi-
ments that were shedding light on the pathophysiology
of ischemic heart disease. Although the theme of his
lecture series was angina, Osler’s comment that “the
effect of plugging of the [coronary] artery is the pro-
duction of what is known as an anaemic infarct, a well-
recognized pathological condition, the consideration of
which need not detain us” is revealing. He made no
mention of the clinical counterpart of the “pathological
condition” of myocardial infarction. The clinical fea-
tures of what we recognize as acute myocardial infar-
cion were described as part of a broad spectrum of
angina pectoris. Osler was aware of the occurrence of
coronary thrombosis, but believed this was fatal in
virtually all instances; he characterized the left anterior
descending artery as “artery of sudden death.” There
was, however, a growing awareness that coronary occlu-
sion was not invariably fatal. William Welch,
Osler’s colleague at Johns Hopkins and America’s
leading pathologist, declared in 1889, “Thrombosis of
the coronary arteries is . . . an affection of great clinical
importance.” After summarizing recent publica-
tions Welch claimed, “The main trunk of one of the
two coronary arteries may be plugged by a thrombus
without causing sudden death. . . . If the patient lives
long enough, the usual, but not absolutely imperative,
anatomical result . . . is infarction in the area supplied
by the occluded artery.” Although Welch believed “the
symptoms associated with coronary thrombosis are
those of the angiosclerotic heart, so that it is hardly
possible to make a positive diagnosis of thrombotic
occlusion of the coronary arteries,” he proclaimed,
“cardiac infarction . . . is more common than would
appear from the meager attention usually given to the
subject in text-books, and is of much anatomical and
clinical interest.” Although at first reading the 1900
statement of a pragmatic Minnesota physician seems
overly pessimistic, his conclusion was quite true. He
claimed, “As regards diagnosis, there appears to be
nothing characteristic in the symptoms nor physical
signs in a case of thrombosis of the coronary arteries
which would enable us to distinguish it from the heart
in a case of general arteriosclerosis. We can here how-
ever console ourselves with the fact that could we
diagnosticate the condition nothing could be done to
avert the inevitable fatal termination of these cases.”

It would be several decades before research would lead
to the development of means to identify and treat the
arrhythmias that are often the fatal event in ischemic
heart disease. Ludwig Hektoen, a Chicago pathologist and
Herrick’s colleague, was almost certainly the author of an
1899 editorial, “Infarction of the Heart.” Referring to
the recent work of Porter and Baumgarten at Harvard,
the writer claimed, “These experimental studies are
very interesting, because they show more in detail
what must happen in occlusion of the coronary arteries
in the human heart. From the experience of patholo-
gists cardiac infarction seems to be much more fre-
quent than is indicated by the small amount of attention
given to the subject in text-books of clinical medi-
cine.” Hektoen’s concluding sentence reveals his un-
derstanding of the pathophysiology of coronary occlu-
sion: “While cardiac infarction may be caused by
embolism, it is caused much more frequently by
thrombosis, and thrombosis again is usually secondary
to sclerotic changes in the coronaries. . . .” The
growing recognition that coronary occlusion was not
invariably fatal led to a renewed interest in the debate
over the functional significance of coronary anastom-
oses. Porter and several European investigators be-
gan studying this subject. Two decades of research
were finally resulting in a shift from the concept of
inflammation to ischemia as the underlying mecha-
nism of many of the symptoms and pathologic findings
in cases of myocardial disease. A Philadelphia physi-
cian observed in 1906, “The comparative importance
of myocarditis to other pathological changes in the
heart muscle steadily diminish as knowledge in-
creases. . . .” The New York physician and pioneer
electrocardiographer Alfred Cohn claimed in 1912,
“While up to five or six years ago we concerned our-
selves with valvular lesions . . . now we have come to
regard the heart as a whole, and to lay more stress on
its working muscular portions and less on its automati-
cally acting valves.”

The European and American studies of the patho-
physiology of ischemic heart disease were known to
two Russian physicians, Obrastzow and Straschesko,
when they published an article on coronary thrombosis
in 1910. Obrastzow was a pathologist who had visited
several European laboratories, including Virchow’s.
After presenting cases with autopsy correlation, these authors concluded, “The differential diagnosis of coronary thrombosis from angina pectoris is made by the presence of status anginosus with coronary thrombosis and its absence with isolated attacks of angina pectoris. Although cardiac dysfunction occurs with angina pectoris, in the presence of coronary thrombosis, it does not remit with the termination of an angina attack but persists quosque ad finem vitae.”59, 50 The views of the Russians were known to, and shared by, James Herrick. Herrick matriculated at Rush Medical College in Chicago in 1885 and, after an internship at Cook County Hospital, entered private practice. He was appointed attending physician at Cook County, where he was actively involved in medical teaching. Herrick spent the summer of 1894 in Europe “to do some practical work in pathology and clinical diagnosis,” and worked primarily with the pathologist Hans Chiari in Prague.51 Writing from Europe, Herrick claimed, “It is somewhat comforting to find that we, in America, are not the only ones who sometimes err in matters of diagnosis. I have seen here the best of the teachers make mistakes. Perhaps the most instructive feature of it all is to see the interest the diagnostician takes in the autopsy, and his eagerness and readiness to profit by his errors. The European teachers certainly have a great advantage in having their mistakes corrected by autopsy.”52

In 1910 Herrick complained to members of the American Medical Association that the image of an attack of angina pectoris and its subsequent course was so “fixed in the minds of many physicians that they are unable to admit any deviation from its details as consistent with this disease.” He proposed that the attitude toward angina was “two narrow” and that, although it generally carried a grave prognosis, “the fatal termination may be deferred for years and, exceptionally, complete recovery seems to ensue.” Herrick closed his presentation with the suggestion, “closer observation of the atypical cases, with collation of the results with those of anatomic and experimental studies will lead to unifying knowledge concerning the pathogenesis of this disease, to greater precision in its recognition, and to more appropriate treatment.”53 Elsewhere, I have discussed the fact that Herrick was familiar with the experimental studies of coronary occlusion performed by Porter and extended by Joseph Miller of Chicago.54 Miller, who was present during the reading of Herrick’s 1910 report, commented that his recent experimental studies had demonstrated that pharmacologic interventions might alter the outcome of acute coronary occlusion. Like Herrick, Miller was an attending physician at Cook County Hospital so it is probable that the two discussed their mutual interest in ischemic heart disease. Through Miller, Herrick had a personal link to basic research on coronary occlusion. Moreover, the pathologist who performed autopsies on several of Herrick’s patients, including the case in which Herrick first made the diagnosis of coronary thrombosis during life, was Ludwig Hektoen who had been interested in coronary artery disease for two decades. Herrick undoubtedly benefitted from his colleagues’ experiences and counsel.

Herrick later claimed there were two lessons to be learned from his experiences leading to the widespread clinical recognition of coronary thrombosis: “the first was that all medicine needs periodic overhauling. We should avoid the paralyzing influence of the dead hand of tradition . . . . The second lesson was . . . . that there was still room for sane, careful, bedside observation. Neither the all-time hospital clinician nor the laboratory worker had a just claim to proprietary ownership of productive, healthy doubt and skepticism. There was a place for all types of investigation. The laboratory, the ward, the library should all be regarded as workshops for observation, experiment, and logical thinking. The watchword should be cooperation.”54 Herrick admitted that when he initially presented his first case of coronary thrombosis in 1910 he “did not at once grasp the full significance” of it. By 1912, however, he had synthesized his views and presented them before the Association of American Physicians. His address was widely circulated when it was republished in the Journal of the American Medical Association. The purpose of Herrick’s report was to “prove that sudden obstruction [of a coronary artery] is not necessarily fatal. Such proof is afforded by a study of the anatomy of the normal as well as the diseased heart, by animal experiment and by bedside experience.” After a concise synopsis of the relevant European and American literature Herrick claimed, “experimentally, then, sudden death, even late death, is not a necessary consequence of obstruction of even large branches, such as the descending branch of a coronary artery.” Herrick deduced from the work of others and from his own experience that survival after coronary thrombosis was a distinct possibility. It is this declaration that makes Herrick’s achievement notable. Others had provided the experimental, clinical, and pathologic data that enabled Herrick to conclude “from a consideration of the clinical histories of numerous cases in which there have been careful autopsy control, from animal experiments and from anatomic study, that there is no inherent reason why the stoppage of a large branch of a
coronary artery, or even of a main trunk, must of necessity cause sudden death. Rather may it be concluded that while sudden death often does occur, yet at times it is postponed for several hours or even days, and in some instances a complete, i.e., functionally complete, recovery ensues."

Clinicians had long complained of the difficulty of diagnosing coronary sclerosis during life. Herrick provided a pathophysiologic explanation of the broad spectrum of symptoms that might accompany coronary thrombosis: "The clinical manifestations of coronary obstruction will evidently vary greatly, depending on the size, location and number of vessels occluded. The symptoms and end-results must also be influenced by blood-pressure, by the condition of the myocardium not immediately affected by the obstruction, and by the ability of the remaining vessels properly to carry on their work, as determined by their health or disease. No simple picture of the condition can, therefore, be drawn." Herrick included two cases of his own and a description of the various symptoms he believed might accompany coronary thrombosis. He advocated absolute bed rest for patients thought to have suffered acute coronary thrombosis and claimed, "The hope for the damaged myocardium lies in the direction of securing a supply of blood through friendly neighboring vessels so as to restore so far as possible its functional integrity."55 Earlier observers had come close to recognizing the syndrome of coronary thrombosis, but it remained for Herrick to synthesize the clinical observations and experimental results of more than half a century and thereby delineate the clinical manifestations of myocardial infarction.

Herrick recalled that his presentation on coronary thrombosis before the leading internists of the day "fell like a dud" and the publication of his manuscript "aroused no more comment than it did when it had been read six months before."54 He claimed, "The fate of that early paper was a surprise to me and a keen disappointment. I did not realize, as I do now [1936], that in medical history, as in the history of the growth of ideas in general, while some new facts are accepted as soon as announced, or at least attract enough attention to be subjects for discussion, very often others are passed unnoticed or unapproved until again brought forward in more striking form or with more convincing proof and at a time when the medical world is more ready to listen."56

The application of the relatively new technique of electrocardiography to coronary artery disease provided Herrick with "more convincing proof" of the clinical event we call acute myocardial infarction. The electrocardiograph, developed by William Einthoven and Thomas Lewis, was introduced into America in 1909 at Mt. Sinai Hospital in New York by Alfred Cohn.57 Cohn had studied with Thomas Lewis, as had another New Yorker, Bernard Oppenheimer, who with Lewis used the electrocardiograph to determine the origin of the heartbeat in the dog in 1910.58 For the first decade after the electrocardiograph was introduced into clinical practice it was used almost exclusively to investigate cardiac arrhythmias.59 Working at Mt. Sinai, Oppenheimer extended the scope of electrocardiographic studies to include abnormalities of the wave forms independent of cardiac arrhythmias.60 When Oppenheimer reported his results in 1917, Emanuel Libman, who had made the only comment after Herrick's 1912 presentation on coronary thrombosis, mentioned the difficulty of recognizing coronary thrombosis clinically. Libman remarked, "An electrocardiograph examination might be of value in confirming the diagnosis." Herrick, also present for Oppenheimer's report, revealed to the audience that he and his colleagues in Chicago had been investigating the electrocardiographic manifestations of experimental coronary occlusion in dogs. Moreover, Herrick recognized a similarity between the electrocardiogram recorded from one of Oppenheimer's patients found at autopsy to have coronary thrombosis and "that which we got in dogs by ligating the left branch of the coronary artery."

Fred Smith, a recent graduate of Rush Medical College and Herrick's assistant, published the results of an electrocardiographic study of experimental coronary ligation in 1918.61 This investigation was suggested by Herrick who observed,

There is some hope that the work may assist in interpreting abnormal human electrocardiograms. The thought has been that if it can be proved that with a certain artery obstructed there is a definite lesion in the heart muscle or in the conducting system, and if with that lesion there is a definite electrocardiogram, may we not, when we encounter that abnormal electrocardiogram in the human being, particularly if he has had symptoms suggestive of coronary thrombosis, be able to state with a reasonable degree of certainty that the patient has had obstruction in a particular portion of the coronary system?62

After the publication, in 1918, of Smith's and Herrick's articles on coronary thrombosis and its recognition with the aid of the electrocardiogram, Herrick claimed, "There was a veritable flood of articles on this topic."56 During the 1920s physicians made the diagnosis of coronary thrombosis with increasing frequency.63 Through Herrick's efforts, they were more aware of the clinical features of this event, and the growing availability of the electrocardiograph allowed
them to confirm the diagnosis. Herrick’s perseverance had paid off; the impediments to the recognition of acute myocardial infarction outlined in the introduction to this article had been overcome.

It may seem hard to understand why it took clinicians more than half a century to incorporate the important scientific observations of European pathologists into clinical practice. The recent “discovery” of mitral valve prolapse is quite analogous to the delayed recognition of acute myocardial infarction. The new techniques of angiography and echocardiography were critical in identifying the source of the auscultatory abnormalities that had been recorded for decades but were poorly understood. Once there was a means to diagnose this condition it was possible to study the various manifestations of the syndrome and delineate its natural history. In each instance new technology provided the critical link between the observations of clinicians and pathologists. Only when there was a means to identify a pathologic condition during life could clinicians and pathologists begin a meaningful dialogue and systematically study the “new disease.”

The diagnostic instruments employed by clinicians are the result of countless basic scientific discoveries, which further reveals the reliance of clinical medicine on basic research. The electrocardiogram was not developed as an aid to the diagnosis of myocardial infarction, but evolved from instruments designed to quantitate electric currents. Its potential value in the diagnosis of myocardial infarction was first appreciated by clinicians with thorough training in, and great respect for, pathology. Herrick provided clinicians with a new approach to the diagnosis of coronary thrombosis and an intellectual framework for conceptualizing survival after this event. When his colleagues failed to respond to his masterful description of the clinical manifestations of acute myocardial infarction, he was not deterred. He applied new techniques to the study of ischemic heart disease and helped establish the critical role of electrocardiography in identifying acute coronary occlusion. His intellectual curiosity and pragmatism led him to accept new experimental evidence to “avoid the paralyzing influence of the dead hand of tradition.”54, 56

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