H. Newell Martin and the isolated heart preparation: the link between the frog and open heart surgery

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Sarnoff claimed in 1958, “The present understanding of myocardial function has been made possible to a substantial extent by study of the classical isolated heart or heart-lung preparations. The main virtue of these preparations is the possibility of imposing a degree of control on the experimental study which in the past has not been readily achieved in the intact animal.” In addition to its vital role in numerous important discoveries in cardiovascular physiology and pharmacology, the isolated heart preparation was a fundamental precursor to the invention of the heart-lung machine, without which open heart surgery could not have developed.2 The pioneer of the heart-lung machine, John H. Gibbon, Jr., claimed in one of his earliest publications, “It is obvious that any operative procedure upon the heart could be performed better if that organ were temporarily relieved of its function of pumping blood. For example, if the flow of blood through the heart and lungs could be safely stopped for 30 minutes, it is conceivable that a new field of cardiac surgery might be developed. The problem which presented itself to us was largely one of adapting one or more of the various perfusion methods which have been used in the past in the study of isolated organs.”

The isolated mammalian heart preparation was developed just over a century ago by H. Newell Martin, the first professor of physiology at the Johns Hopkins University. Half a century later the American physiologist Walter Meek claimed Martin’s “work in devising a form of perfusion for the isolated heart ranks possibly as the greatest single contribution ever made from an American physiological laboratory.”

Martin was born in Ireland in 1848 and attended University College, London, where he was exposed to faculty members who placed unusual emphasis on science in their medical teaching.5-7 Martin was particularly influenced by Michael Foster, who began teaching practical physiology and histology at the institution in 1867. Martin’s talents were appreciated by his teachers and he was invited to serve as demonstrator for Foster and assistant to Thomas Huxley, Britain’s leading biologist. Huxley, a leading spokesman for scientific education, was requested by Daniel Gilman, president of the Johns Hopkins University, to suggest candidates for the chair of biology at the Baltimore institution where instruction was to begin in the fall of 1876. Huxley responded, “I do not think you could possibly have a better man than Dr. Martin. He is thoroughly well trained in Physiology & general Biology; a Fellow of his College in Cambridge; young, energetic, very pleasant in manner and a thorough gentleman.” After negotiations in which Martin demanded a higher salary than originally offered, the promise of the construction of a biological laboratory, the title of professor, and “with the rest of the teaching staff, a direct voice in the arrangement of the curriculum and studies of the University,” Martin took the Baltimore position.

Only 28 years of age when he initiated his Hopkins career, Martin’s youth was consistent with Gilman’s philosophy of building a faculty committed to research who “had twenty years before them rather than twenty years behind them.” In his inaugural address, Martin proclaimed the importance of pure science: “This is a university: and the object of a university, I take it, is directly to promote liberality of thought and culture and only indirectly to concern itself with the practical advancement of material welfare.” On the qualities necessary for researchers, Martin declared, “The only absolutely necessary faculties for the scientific investigator are love of his work, perserverance, and truthfulness.” He continued, “One difficulty which I have met with is that many seem to consider that a physiological investigation can be carried on by devoting to it an hour or two at irregular intervals; I feel quite sure that no good work is likely to be done in that way, and am not inclined to encourage such workers.”

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By the early 1880s, Martin’s physiology department at Johns Hopkins was thriving. His research program was taking shape and an outstanding group of productive young scientists had been assembled at the new Baltimore institution. Morale among the faculty and students was high; it was widely acknowledged that Johns Hopkins provided the most satisfactory opportunity for advanced instruction and research in the biological sciences in the United States. A medical editor claimed in 1881, “The opportunities for physiological and morphological study and research at the university in question are probably the best to be found in this country. And it is a centre which has already shown evidences of good scientific work. The medical profession should feel gratified that opportunities for such original work now exist in this country.”12 Martin had set his sights high and in his five year report explained that among his aims were “to train men as specialists in Physiology, so that they might not only be qualified to teach it, but to add to our knowledge of the working of the living body . . . . Physiology has only recently begun to advance into that fortunate position . . . to be pursued for its own sake.”13

In the early 1880s, Martin’s research began to center around the circulatory system, which was also the primary research focus of his mentor, Michael Foster. Foster, and his pupils, most notably Walter Gaskell and Albert Dew-Smith, published several papers on cardiac physiology while Martin was Foster’s assistant at Cambridge. By 1874, Foster “directed all of his energies as well as those of his studies toward a solution to the problem of the heart beat and its origin.”14 Their initial experiments involved electrical stimulation of the isolated apex of the frog’s ventricle. Eventually, Foster’s group extended their studies to include the whole ventricle, and ultimately the entire heart. Martin would pursue a similar line of research in Baltimore six years later. As Foster’s main assistant in the practical physiology course at Cambridge, Martin mastered many experimental techniques that helped him inaugurate his Hopkins program.

During the summer of 1870, Foster toured continental laboratories, including Carl Ludwig’s Physiological Institute at Leipzig, where circulatory physiology was a major research theme. Ludwig had recently developed an approach to perfusing isolated organs, including the heart, to study their physiology in the denervated state.15 Ludwig’s method for perfusion of the isolated frog heart, developed with his pupil Cyon, consisted of cannulas placed in the aorta and inferior vena cava, through which dog serum was perfused. With this method, the isolated frog heart retained its activity for more than 24 hours if the serum was exchanged periodically. Ludwig next attempted to develop a method for perfusing striated muscle from warm-blooded animals. His earlier studies on arterial blood gasses had given him insight into the high oxygen requirement of functioning muscle. For his experiments in warm-blooded animals, Ludwig perfused the biceps muscle of dogs with defibrinated blood and was able to keep skeletal muscle preparations functionally intact for up to eight hours.16

Ludwig’s technique of perfusing the isolated frog heart was refined in collaboration with a Scottish pupil, Joseph Coats, a recent medical graduate of Glasgow University.17, 18 As was typical of Ludwig, his name did not appear on Coats’ paper, although Coats did not speak German and spent only five months in Ludwig’s laboratory. A fellow Scotsman, Thomas Lauder Brunton, was working in Ludwig’s laboratory when Coats arrived, and served as translator between teacher and pupil. Brunton later recalled, “More than to anyone else since the time of Harvey, do we owe our present knowledge of the circulation to Carl Ludwig.”19 The isolated heart preparation developed by Coats and Ludwig was illustrated and described in a laboratory handbook prepared by Foster and his British colleagues in 1873.20 The method was described as follows:

The heart is freed of its pericardium . . . . The next step is to tie one branch of the aorta, and then to pass a cannula through the other and the bulb into the ventricle . . . . A ligature is passed round [the inferior vena cava] which is then slit open so as to allow a large cannula to pass into the right auricle . . . . The tube which is inserted in the right auricle be fitted with a flexible tube and connected with a glass reservoir . . . . filled with red-dish rabbit serum. The aorta is in like manner connected with a manometer . . . . [then] The heart is charged with serum and brought into action by filling the reservoir. From thence the fluid fills the right auricle, passes therefrom to the ventricle, and is discharged by it into the manometer.20

John Burdon-Sanderson, who published this description, noted that experiments based on the technique provided “a reliable estimate” of cardiac work in the frog and declared, “If exact information were attainable as to the quantity which the heart actually discharges at a stroke, it would be possible to measure the quantity of work done by the heart in the maintenance of the circulation in a mammalian animal, and inferentially in man; but inasmuch as no such method at present exists, no estimate can be given which possesses even approximate value.”20

Foster observed Coats’ and Ludwig’s isolated heart preparation during his visit to German laboratories, and his pupil Gaskell had become familiar with its use.
during the year (1874-1875) he spent in the Leipzig laboratory. While working with Ludwig, Gaskell studied blood flow through isolated skeletal muscle. Martin worked in Ludwig’s laboratory during the summer of 1875 as well, so he would have seen firsthand the technique of preparing isolated hearts. Describing Gaskell’s return to Cambridge from Leipzig, Foster’s biographer has claimed, “Gaskell must have found himself virtually surrounded by men at work on beating hearts.” Even after his departure from Cambridge to join the Hopkins faculty, Martin was kept informed by his friend Edward Schäfer of Foster’s efforts to elucidate the mechanism of the heart beat. Martin would learn of recent approaches to perfusion of animal organs through his first graduate student, Henry Sewall, who traveled to Europe in 1879 to work with Foster and Ludwig. Sewall returned to Baltimore full of enthusiasm for circulatory physiology and soon published a paper on the relationship of intracardiac pressure and vagal stimulation.

The direct stimulus for Martin’s development of an isolated mammalian heart preparation was a series of experiments on coronary blood flow he initiated in 1880 with William Sedgwick, one of his fellows. Martin explained that the pressure and character of the coronary pulse wave had not been described previously, “in spite of the recognized fact that great interest and importance belong to their study.” Martin’s experiments were undertaken to test the theories of Thesius and Brücke that the aortic valve leaflets covered the coronary ostia during systole, thereby preventing coronary blood flow during this phase of the cardiac cycle. Beyond addressing this question, Martin declared, “We venture to believe that the work possesses interest of its own; and that the discovery that it is quite possible to get tracings of the blood-pressure in the arteries of the dog’s heart, lays open a considerable field for investigations upon the mammalian heart in general — an organ which has hitherto been somewhat baffling to the physiologist.” Using dogs, Martin inserted a cannula in the left anterior descending artery beyond the origin of the septal artery. This procedure was facilitated by intermittently interrupting the artificial respiration and suspending the heartbeat by electrical stimulation of the vagus nerve, which enabled Martin to isolate a segment of the artery, incise it, and insert a cannula. This cannula and one placed in the carotid artery were connected to a kymograph that permitted the graphic recording of simultaneous coronary and carotid pressures. Martin found, in repeated experiments in which the heart rate and blood pressure were varied, that the carotid and coronary pressure tracings were synchronous and similar in character. This led him to conclude “that the pressure in each artery is directly determined by the same cause, viz. aortic pressure.” Martin had proved that the coronary arteries were not occluded by the aortic leaflets during systole and that there is coronary perfusion throughout the cardiac cycle.

Henry Sewall described the origin of Martin’s idea for his isolated heart preparation:

I very well remember one morning, I think it was in the Fall of 1880, Martin said to me, in effect, ‘I could not sleep last night and the thought came to me that the problem of isolating the mammalian heart might be solved by getting a return circulation through the coronary vessels.’ The idea seemed reasonable and at the close of the day’s work we anaesthetized a dog, prepared him for artificial respiration and then Professor Martin opened the chest and ligatured one by one the veins caveae and the aorta in such a way as to leave sufficient amount of blood in the heart itself. The heart continued to beat in a normal manner, the circuit made by the blood being from the right side, through the lungs to the left side and back through the coronary vessels and the heart wall to the right auricle again. Thus heart and lungs were completely isolated from the rest of the body and could be studied unaffected by the interference of factors foreign to itself. Martin grasped the full significance of his discovery and elaborated with infinite patience the practical details involved in submitting the isolated organ to experimental conditions.

It is not surprising that Martin attempted to extend to mammals the experiments performed earlier in frogs. He declared, “To obtain a mammalian heart isolated from the rest of the body and keep it alive for a time sufficient to allow the examination of the effects of various conditions upon its activity has long been a physiological disideratum.” He explained,

In the course of some experiments made by me in conjunction with Dr. T. Sedgwick, on blood pressure in the coronary arteries of the heart, the fact was impressed upon me that the mammalian heart is no such fragile organ as one is usually inclined to assume, but possesses a very considerable power of bearing manipulation. On the other hand, I knew of various unsuccessful attempts to isolate the mammalian heart and study the physiology apart from the influence of extrinsic nerve centres, in a manner more or less similar to the methods so frequently used for physiological investigations on the heart of a cold-blooded animal; the mammalian heart, however, always dies before any observations could be made on it. Thinking over the apparent contradiction, it occurred to me that the essential difference probably lay in the coronary circulation; in the frog, as is well known, there are no coronary arteries or veins, the thin auricles and spongy ventricle being nourished by the blood flowing through the cardiac chambers, but in the mammal the thick-walled heart has a special circulation system of its own and needs a steady flow through its vessels, and cannot be nourished, as appears to have been forgotten, by merely keeping up a stream through auricles and ventricles. The greater respiratory needs of the heart of the warm-blooded animal also needed consideration; the lungs ought either to be left connected with it, or replaced by some other efficient aërating apparatus; if entirely separated from the central nervous system there seemed no need to replace the natural lung by an artificial one.
Martin published the details of his method in 1881 and summarized the course of the circulation: "Left auricle, left ventricle, commencement of aorta, (and along the left subclavian to the cannula which is connected with a manometer), coronary system, right auricle, right ventricle, pulmonary vessels of one lung, and then back to the left auricle; in other words, the only section of the systemic circulation left is that through the vessels of the heart itself." 25 (See figure 1.) Using this method he was able to keep cat hearts alive for more than an hour, "beating with perfect rhythm and normal force."

Martin was not satisfied; he "wanted the heart alive much longer; a means of keeping it at a uniform temperature; a method of renewing the blood . . . and opportunity to run blood, to which various substances had been added, through the heart from time to time in order to study their action upon it." 26 By refining his preparation, Martin was able to keep an isolated mammalian heart beating regularly for more than five hours. As had been the case in Ludwig's skeletal muscle preparations, Martin perfused the isolated mammalian hearts with defibrinated blood. He could alter the rate of flow and pressure of his perfusate and record pressure tracings from the left subclavian artery. Martin proclaimed that his preparation permitted "the study of the physiology of the mammalian heart . . . to an extent never before attainable." 26 With respect to cardiovascular pharmacology, Martin claimed, "To investigate the direct action of any drug on the heart one would have only to inject it by a hypodermic syringe into the cardiac end of the tube i (inserted into the superior vena cava) as in the usual manner of injecting curari into a vein." 26

Martin presented his results before the Medical and Chirurgical Faculty of Maryland in 1882. He informed his audience of practicing physicians that he had been "mainly occupied with the study of the influence of various conditions upon the pulse rate of the . . . isolated heart . . . [and] thought that possibly some account of these experiments might interest you, as the pulse-rate is so valuable an indication in many forms of disease. A practitioner may, nowadays, when making a professional visit, omit to say 'Put out your tongue' without being thought to have neglected his duty, but the family doctor who fails to feel his patient's pulse seriously risks losing the confidence of mater-families." 27 Martin emphasized the potential clinical relevance of his basic research, explaining, "In many cases the pulse-rate is a most valuable factor in forming a diagnosis, making a prognosis, or deciding upon a treatment. I therefore venture to hope that what little I may be able to add to your knowledge of the causes which influence the rate of the beat of the heart may be not unwelcome." Martin's highly technical presentation was warmly received. A reporter observed, "The originality, ingenuity, and great value of Professor Martin's researches excited profound interest, and his communication was received with the greatest applause." 28 A Philadelphian reviewer declared, "This line of research will, doubtless, lead to very important results." 29 Johns Hopkins' president, Daniel Gilman, was also impressed with Martin's development of the isolated heart preparation and concluded that its use "in the thorough study of cardiac physiology will supply abundant work for many hands for several years, numerous problems which have hitherto been unattacked being now rendered available for investigation." 30

Martin returned to England in 1882 and presented his work on the isolated heart preparation to members of the Physiological Society. The significance of Martin's accomplishment was further acknowledged by the selection of his paper for the prestigious Croonian lecture of the Royal Society of London in 1883. 31 Martin made several empiric observations while using the isolated heart preparation to investigate cardiac function. He concluded that calf's blood was less satisfactory than dog's blood for use in the isolated dog heart preparation. Recognizing that clotting did not occur when defibrinated blood was circulated through the isolated heart for several hours, he concluded that fibrinogen was not produced by the heart. Martin's studies provided new insight into the complex interrelationships of hemodynamic variables. In the past, arterial pressure had been increased by clamping the aorta, but Martin recognized that this would result in a decrease in venous return to the right heart, which would lower the rate of diastolic filling and the end-diastolic pressure. 32

It had not previously been possible to measure the stroke volume accurately in mammals, but Martin’s new isolated heart preparation could be used to address this problem. He encouraged his pupils William Howell and Frank Donaldson, Jr., to study this subject in 1881. In the introduction to their report, Howell and Donaldson reviewed the literature but discounted “earlier observations made upon dead hearts, since these are universally allowed to be of but little value.”33 Using the isolated heart, they sought to answer four separate questions: “I. The maximum quantity of blood which can be thrown out from the left ventricle at a single systole. II. The influence of variations of arterial pressure on the work done by the heart. III. The influence of variations of venous pressure on the work done by the heart. IV. The influence of variations of pulse-rate on the work done by the heart.”33 Citing the observations of Weber, Heidenhain, and Fick, the authors stated,

It has been proved for ordinary skeletal muscles that the work done in contracting, measured by the product of the load into the lift, increases up to a certain limit with the load to be raised . . . If, now, aortic pressure is taken as the equivalent of the load which an ordinary muscle raises when it contracts, the law given above for the work of the left ventricle may be expressed in the terms of muscle physiology in this way. The work done by the heart muscle when it contracts, measured by the product of the weight of blood ejected at each contraction into the height of aortic pressure, not only increases with the load against which it contracts, but increases in direct proportion to the load, within the limits given.33, 34

It should be noted that Martin’s heart preparation was de facto denervated because of asphyxia of the nervous system. In view of the denervated state of their preparation, Howell and Donaldson rejected the claim “that this proportional increase of work by the heart muscle is owing to any nervous mechanism co-ordinating the discharge of energy with the resistance to be overcome.”33 They declared, “An explanation more in accordance with what is known of the physiology of ordinary muscle is found in the supposition that as the load increases a greater amount of energy is liberated, in consequence of some change in the molecular state of the ventricular muscle associated with increased tension at the commencement and during the early stages of its contraction.” The authors suggested, “A curve of work constructed upon the arterial pressures as abscissas, and the work done at each beat of the ventricle under these pressures as ordinates, would, within the limits for which we have investigated it, be a straight line.” Addressing the issue of the result of changing the venous pressure on the work done by the heart, the authors found “It was not possible to keep the arterial pressure constant, since at the higher venous pressures the left ventricle pumped out much more blood at each systole.”33 They concluded, “The work done by the left ventricle at each systole increases with the venous pressure, but not proportionally, up to the point of maximum work.” Howell and Donaldson reached the important conclusion, “It is certain that the most direct factor influencing the quantity of blood sent out from the ventricle, and hence the work done by the ventricle, is the intra-ventricular pressure by which the ventricle is distended during diastole.”33

Martin’s role in these experiments should not be underestimated. The authors concluded their paper with an expression of thanks to him “for the aid and encouragement which he has given us during the progress of this work. We are indebted to him not only for many valuable suggestions in the earlier part of the investigation, when success seemed doubtful, but also for personal assistance which he has sometimes kindly given.”33 Martin was equally generous in his acknowledgment of his pupils’ role in the development of the isolated heart preparation: “I have received so much valuable assistance and so many hints as to modifying the apparatus and the method,” he claimed, “that I now hardly know what part of the perfected method is mine, what that of one or another of my pupils and assistants. The method as it now stands is the Baltimore method, and not that of any one individual, and as such, in so far as it has any value, should go forth to the world.”37

One of the subjects Martin studied using his isolated heart preparation was the effect of extremes of temperature on the heart beat. Martin explained in 1889, “Attempts made three or four years ago to solve these problems were futile, because near the liminal temperatures, high or low, the heart beat with so little force that its death seemed rather due to deficient circulation through the coronary capillaries than to direct influence of heat or cold on the cardiac muscular or nervous tissues. Our problem was, therefore, to keep the cardiac vessels well supplied with blood whether the heart beat feebly or strongly, and at the same time vary its temperature at will.”35 To supply the coronary vessels with adequate blood flow, Martin placed a Mariotte flask filled with blood at a constant height above the heart and allowed the blood to flow into the aorta through a cannula, thereby filling the coronary arteries. The blood was oxygenated as it circulated through the lungs in addition to being exposed to oxygen in the Mariotte flask. Martin proved by these studies that the cat heart could be cooled to 18°C without
affecting its function if it was rewarmed in a relatively short time. This study, with its associated modification of Martin’s preparation, revealed the importance of adequate coronary perfusion for optimal myocardial performance. This information would ultimately have clinical relevance when hypothermia techniques were applied to open heart surgery.

The momentum of Martin’s program in physiology was disturbed during the mid-1880s as his fellows and junior faculty members took positions in other institutions. As he explained to Daniel Gilman in 1886, these departures left him “with nearly all the under-graduate lecturing and teaching to do myself . . . . This leaves me but little time or energy for research or post graduate instruction.”36 Howell later recalled, “From the time [Martin] entered the new laboratory [in 1884] a kind of apathy became apparent in his work. Not very noticeable at first except perhaps in his own research activity it grew rather steadily in succeeding years, until at last it was only too apparent even to under-graduate students . . . . Martin’s verve and inspiration were dying out. For a time his work on the isolated heart was carried forward chiefly by advanced students but he had no new problems — no new methods were developed.”37 Alcoholism complicated by an intermittent painful and disabling neuropathy led the Hopkins officials to ask for Martin’s resignation in 1893.3 He was succeeded by his former pupil and associate William Howell, who would publish several papers over the next two decades based on research using the isolated heart preparation. This was no longer the focus of the laboratory as it had been in the early 1880s, however.

European workers were attempting to refine the isolated heart preparation during the closing years of the 19th century. In 1885 Max von Frey, a colleague of Ludwig’s, described an elaborate method for oxygenating blood without interrupting its circulation through isolated organs.38 Other Europeans, including Arnaud and Gilis, used Martin’s preparation to study various aspects of cardiac function.39 The German physiologist Oscar Langendorff, who had studied cardiac function for nearly 20 years, published his own method of isolating the mammalian heart in 1895.40, 41 Langendorff was apparently unaware of Martin’s refined 1889 method, but he was familiar with the earlier work of the Baltimore group. The refined Martin (1889) and Langendorff (1895) preparations were alike in most respects; the major difference was that Langendorff excluded the lungs and collected the blood that flowed through the right heart in a beaker.

The Harvard physiologist William Townsend Porter had become interested in hemodynamics and coronary blood flow while studying with Karl Hürthle and Johannes Gad in Germany in the early 1890s.42 In 1898, using a modified Martin preparation, Porter published the first account of the measurement of intracardiac pressure in the isolated heart and described the effect of changes in coronary blood flow on the force of left ventricular contraction and heart rate.43 Several workers addressed the instability of the blood used to perfuse the isolated heart preparation. Martin initially used calf blood in his dog and cat experiments because it was available in large quantities from local butchers. He recognized, however, that blood from different species was not optimal and felt that this was a major limiting factor in the viability of his preparation. Langendorff and others attempted to overcome this problem by diluting the animal’s own blood with Ringer’s solution. F. S. Locke, a British physiologist who worked with Porter and Bowditch in 1896, discovered that it was possible to use oxygenated Ringer’s solution in place of blood in the rabbit heart. He also demonstrated the benefits of supplying the isolated heart with Ringer’s solution to which dextrose had been added.44

By the early 20th century, several individuals in America and Europe were using the isolated mammalian heart preparation to study various problems in cardiac physiology. Beginning in 1910, Ernest H. Starling, working at University College, London, where Martin’s scientific career had begun half a century earlier, initiated a series of hemodynamic investigations using the preparation.45-47 His main modification of Martin’s method consisted of the addition of a means of varying arterial resistance. Using this technique, Starling and his colleagues extended the hemodynamic observations made in Martin’s laboratory by Howell and Donaldson 30 years earlier. Starling acknowledged the contributions of these workers and those of the German physiologist, Otto Frank, as the foundation upon which his own studies were built. In one of his final articles on the subject, Starling wrote in 1926, “Experiments . . . . have shown that in an isolated heart, beating at a constant rhythm and well supplied with blood, the larger the diastolic volume of the heart (within physiological limits) the greater is the energy of its contraction. It is this property which accounts for . . . . the processes of adaptation and compensation in the healthy and diseased organ that it was called by one of us ‘the law of the heart’ and regarded as a special instance of the law connecting energy of the contractile process with the initial length of muscular fibre.”48
CARL WIGGERS has claimed, "Starling's name has become attached to the heart-lung preparation, not because of the technical improvements that he and various associates made in 1912, but because he developed a continuing program for its use. Starling not only deduced plausible concepts regarding the regulation of the heart-beat and the coronary circulation from his experimental data but used them as clues for the projection of more significant experiments. This program has become so expansive that no single person—or even a single generation—could exhaust the information obtainable by its use." It is tempting, but fruitless, to speculate how Martin might have extended his work on the isolated heart had his career not been prematurely terminated by alcoholism at the age of 45.

Many advances in clinical medicine have resulted from the physiologic and pharmacologic research undertaken with the isolated mammalian heart preparation. One of the most dramatic developments that can be traced directly to this research model is the heart-lung machine, which is a fundamental requirement for open heart surgery. This sophisticated apparatus, devised by John H. Gibbon, Jr., shortly before World War II and refined by him and others during the next quarter century, is a direct extension of the isolated mammalian heart preparation and associated methods for oxygenating the blood. As noted earlier in this article, Gibbon recognized the direct relationship between his heart-lung machine designed for clinical use and the isolated organ preparations developed by physiologists generations earlier for the study of the heart and other organs. Clarence Crafoord, a Swedish pioneer of cardiac surgery, predicted in 1949 that a machine providing extracorporeal circulation "will be as important in securing good results in intracardiac surgery as has been the replacement of the patient's own breathing by mechanically controlled respiration in the development of ordinary intrathoracic surgery." It is interesting to note the involvement of a physiologist in the first attempt to perform intracardiac surgery in a human using total heart-lung bypass undertaken at the University of Minnesota in 1951. Although the patient did not survive, the surgeons declared that the apparatus "behaved admirably" and credited their interest in the development of the heart-lung machine to Owen Wangensteen and "Maurice B. Visscher, Chief of the Department of Physiology, for the suggestion of the problem initially and for invaluable counsel and encouragement during prosecution of it." Visscher provides a direct link to the Martin-based Starling isolated heart preparation; he spent a year working with Starling in 1925–1926 and participated in the British physiologist's final studies on ventricular function using this method. Physiologists quickly appreciated the significance of the isolated heart preparation as a powerful tool with which to study the function of the mammalian heart. In a review of Martin's contributions to physiology, F. S. Locke claimed in 1897, "The isolation of the mammalian heart will always remain one of the triumphs of experimental physiology." Martin's pupil, associate, and successor William Howell observed in 1908, in recent years the principle of Martin's method for investigating the functions of the heart has been widely used in experimental medicine, and it forms at present an accepted and almost indispensable means of research in cardiac physiology, pharmacology, and pathology. Martin himself saw clearly the value of his discovery and hoped that it would be designated in the physiological literature as "the Baltimore method" but it has been used so frequently and modified so often in details that it is to be feared that the originator of the idea will not be remembered in connection with it. It happens not infrequently in science that those who furnish the real thoughts are lost to view under the great amount of work which they call into existence, while, on the contrary, a name may long be kept alive by being linked with some comparatively unimportant fact or observation. Dame Fortune is capricious in this as in other respects.

More recent refinements in the isolated heart preparation have been employed by Sarnoff and colleagues, whose sophisticated studies have revealed many previously unrecognized interrelationships in cardiovascular physiology. After a century, advances are still being made and Martin's "Baltimore method" has come full geographic circle as Suga and Sagawa at Johns Hopkins have brought the preparation into the computer age with innovative new approaches significantly expanding the possible research applications of the isolated heart preparation. The ultimate benefits to be derived from the isolated heart preparation are as difficult to predict as open heart surgery would have been for Martin a century ago, when pericardiocentesis was the only cardiac operation.

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