The origin of the heart beat: a tale of frogs, jellyfish, and turtles

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ONE OF THE MOST remarkable phenomena of nature is the incessant rhythmic action of the heart. Although physicians and philosophers have proposed theories to explain the heart beat for centuries, its mechanism remained elusive until a century ago, when a group of young physiologists working with Michael Foster in England unraveled the mystery through a series of elegant experiments. Critical insight into the origin of the heart beat came from studies performed on jellyfish by George Romanes, one of Foster’s pupils. Although this research was not initiated to elucidate the origin of the heart beat, Romanes soon recognized its relevance to the work of his mentor. Through their efforts, and those of Walter Gaskell, another of Foster’s pupils, the long debate over the origin of the heart beat was eventually settled.

Although it was not universally accepted until the present century, the myogenic theory of the heart beat has a long tradition. Galen, whose views influenced Western medical thought for more than a millennium, discovered in the second century that the excised heart of animals often continued to beat for some time. He asserted, “The power of pulsation has its origin in the heart itself. . . . The fact that the heart, removed from the thorax, can be seen to move for a considerable time is a definite indication that it does not need the nerves to perform its own function.”1 Although Galen did not discuss the mechanism of the heart’s automatic activity, he concluded, “The pulsative faculty of the heart has its source in its own substance.”2

William Harvey did not address the origin of the heart beat in his monumental work De motu cordis published in 1628, but he did discuss the subject two decades later. Harvey’s view reflected the teachings of Aristotle, which held that the blood within the heart triggered cardiac contraction.3 In his De generatione animalium, published in 1651, Harvey explained, “The pulse has its origin in the blood. . . . the cardiac auricle from which the pulsation starts, is excited by the blood.”4 Harvey’s theory of the heart beat was essentially myogenic—nerves played no role in its genesis.5

The neurogenic theory of the heart beat was elaborated by several 17th century anatomists and physicians who were investigating the role of nerves in controlling muscular activity throughout the body.6 Englishman Thomas Willis argued that nerves arising in the cerebellum carried a “nervous liquor” to nerves in the heart walls, which stimulated the heart to contract.7 8 This neurogenic theory of the heart beat was widely accepted as a result of the writings of Willis and his contemporaries.

Experimental evidence was presented, however, that questioned the validity of the neurogenic theory of the heart beat. On the basis of animal experiments, Albrecht von Haller concluded in the 18th century that the heart beat spontaneously, independent of nervous or other connections. When he removed the hearts from animals, Haller found that they continued to beat despite the severance of nervous connections. He argued that the heart muscle had intrinsic irritability that was normally stimulated by the flow of blood over the walls of the organ. Physiologist William Howell claimed in 1905, that Haller “formulated a clear-cut myogenic hypothesis which served to mark the beginning of a new discussion lasting until the present day.”5 9

For more than half a century, Haller views about the myogenic origin heartbeat were widely, although not universally, accepted. The French physiologist and physician Cesar Julien Jean Legallois undertook a long series of experiments on the functions of the spinal cord
during the first decade of the 19th century. From experiments in which he abruptly crushed the spinal cord in mammals and found that the heart stopped beating, he concluded that the heart beat was neurogenic in origin. Legallois’s experiments undermined Haller’s doctrine and stimulated renewed interest in the heart beat.

Further investigations led to apparently conflicting results. Benjamin Collins Brodie, a British surgeon, decapitated dogs and rabbits and observed that their hearts continued to beat. He concluded, therefore, that the heart beat was not dependent on the higher nervous centers. Other scientifically oriented physicians, most notably Wilson Philip and William Clift in Britain, John Reid in Scotland, and Marie Jean Pierre Flourens in France, also pursued this area of research in the early 19th century. Their animal experiments failed to support Legallois’s belief that the heart beat was dependent on the central nervous system, and, specifically, integrity of the spinal cord. Controversy persisted. By the 1830s, most British workers continued to accept Haller’s myogenic theory, whereas the French favored Legallois’s neurogenic theory.

Simple observation and experiments based on destruction of the connections of the heart and nervous system gradually gave way to more elegant experiments during the middle of the 19th century as experimental physiology became more sophisticated. Employing new electrical apparatus, continental workers studied the effects of electrical stimulation of the heart and nerves to elucidate the origin of the heart beat. The German physiologists Gabriel Valentin, Alfred Volkmann, and Johannes Müller were among those who sought to explain the mechanism of the heart beat. By the middle of the 19th century, most investigators had concluded that, like skeletal muscle, heart muscle would respond to a wide variety of stimuli such as heat, cold, trauma, and electricity. The property that appeared to be unique to cardiac muscle, however, was its rhythmicity.

As understanding of the anatomy and physiology of the sympathetic nervous system grew, a new theory of the origin of the heart beat evolved. A master of vivisection, French physiologist François Magendie carefully dissected away the sympathetic nerve supply to the heart and the first dorsal ganglion and found that the heart continued to beat rhythmically. In 1839, Robert Remak, a pupil of Johannes Müller, demonstrated ganglion cells in the substance of the heart. These cells were most prevalent in the atria, where is was widely acknowledged that the cardiac impulse had its origin. After Remak’s discovery of ganglion cells in the sinus venosus of the frog heart, Heinrich Bidder demonstrated them at the auriculoventricular junction, and Carl Ludwig identified them in the interatrial septum.

It was proposed that the ganglia in the sinus venosus were responsible for the heart beat by sending out stimuli at regular intervals. Analogy was drawn to the accepted mechanism of the automatic nature of respiration, which was attributed to periodic stimuli from nerve cells in the respiratory center. Müller claimed, “The primary cause of the rhythmic contractions of the organic muscles is connected with the mode of action of the sympathetic nerve on the muscles; it is not seated in the brain or spinal cord.” He attempted to explain the apparent inconsistencies of earlier observations:

The cause of the rhythm may be in the muscular fibres themselves, or it may be in the nerves. If it be in the muscular fibres, we must suppose that while the action of the nerves is constant, the muscular fibres of the heart lose for a time their capability of contracting, which is restored during a short repose. If the cause of the rhythm have its seat in the nervous fibres, the susceptibility of the muscle must be persistent; but the current of nervous principle must . . . be emitted from them so as to act on the muscles only periodically. The hypothesis that the heart each moment, or eighty times in a minute loses its susceptibility of the still constant influence of the nervous principle, and as often regains it, is improbable, from the circumstance that all other muscles are capable or persistent action if the stimulus be continued. . . . The second hypothesis, namely, that the excitability of the heart is persistent, but the action of the nerves on it periodic, is more probably correct.11

Müller went on to describe the discovery of ganglia in various organs and tissues and concluded, “Not merely the larger ganglions of the sympathetic, but even its ultimate ramifications in the tissues of organs, seem to possess the power of giving rise to periodic motions, [so] we can understand how the rhythmic movements of the heart and intestine . . . continue when these organs are removed from their connections in the body.” Thus Müller proposed that the sympathetic nervous system was the source of the constant stimulus that acted on the heart to trigger its beat. The dilemma was “How can the constant motion of the nervous fluid be changed to a periodic motion?” Drawing on recent developments in the physics of electricity, Müller drew an analogy between the situation with the heart and what happens when “a constant current of electricity meets with an imperfect conductor.” He proposed that a certain amount of nervous energy accumulated in the ganglia until it exceeded the critical level at which a nervous discharge triggered the heart beat.

One of the most important discoveries in cardiovascular physiology during the 19th century was the recognition of the effect of the vagus nerve on the heart. The German physiologists Eduard and Ernst Weber discovered the inhibitory influence of the vagus nerve
on the heart in 1845. They showed that electrical stimulation of the vagus nerve would slow or even stop the heart beat.\(^{12}\) On the basis of an extensive series of sophisticated animal experiments, the Webers concluded that the sympathetic nerves were the motor nerves of the heart and that they acted through the intracardiac ganglia they innervated. In their opinion, the isolated heart continued to beat because of intrinsic rhythmicity of the cardiac ganglia. The activity of the cardiac ganglia, and therefore the heart beat, was influenced by the vagus nerve, which inhibited the ganglia.

The Webers’ recognition of the cardioinhibitory influence of vagal stimulation encouraged several workers to intensify their investigations of the mechanism of the heart beat. Initially, it appeared that the discovery of vagal inhibition lent strong support to the belief that heart beat resulted from nervous impulses acting on the muscle. Further insight into the relationship of the nervous system and muscles in the cardiovascular system was provided by French physiologist Claude Bernard, who demonstrated the existence of vasomotor nerves around 1850. One historian has claimed that these discoveries meant “the entire cardiovascular system could now be seen as a sort of muscular puppet whose strings were controlled by agents in the sympathetic nervous system.”\(^{13}\)

New observations from European laboratories enabled physiologists to refine their theory of the heart beat. In 1850, Moritz Schiff demonstrated the phenomenon of the refractory period of heart muscle.\(^{14, 15}\) Hugo Kronecker and Jules Marey independently confirmed Schiff’s results, and the concept of the refractory period gained widespread acceptance. This discovery strengthened support for the neurogenic origin of the heart beat, since it provided an explanation for its intermittent nature despite constant nervous impulses that originated in the so-called motor ganglia in the heart.

Experiments in which the entire heart or sections of it were excised to study the results of such interventions on the heart beat became more sophisticated during the 19th century as histologic and physiologic techniques were refined. In 1852, H. F. Stannius showed that it was possible to interrupt the heart beat by placing a ligature between the sinus venosus and the body of the right atrium. By electrically stimulating the tissue near the auriculoventricular junction, he also demonstrated that it was possible to restore the rhythmic beat of the heart. These experiments, combined with the discovery of cardiac ganglia, reinforced the belief that it was these ganglia that controlled the heart beat.\(^{16}\) Although a clearer picture of the nature of the heart beat was emerging, there were still many inconsistencies and observations that defied explanation. An anonymous reviewer of cardiac physiology asserted in 1860 that the origin of the heart beat remained “a subject of a very debatable character, and one on which much remains open for investigation.”\(^{17}\) It was in this context that the career of Michael Foster began.

Foster studied under William Sharpey, “the father of modern physiology in Britain,” at University College, London. His interest in the heart beat began early in his career. In 1859, he published a brief note on a study of the snail in which he discovered that very small pieces of excised heart continued to beat rhythmically for some time. He concluded that the heart beat was not “the result of any localized mechanism, but is probably the peculiar property of the general cardiac tissue.”\(^{18}\)

While teaching experimental physiology at his alma mater, Foster published a summary of his experiments on the effect of interrupted current on the frog ventricle. It had been shown that if the ventricle of the frog’s heart was divided transversely, the apical segment would not beat spontaneously whereas the basal segment would. The accepted explanation was that ganglia were necessary to trigger the heart beat, and these had been demonstrated in the basal portion of the ventricle but not in the apex. Foster found that a weak interrupted current applied to the isolated apex produced a series of beats “separated from each other by distinct intervals of complete rest.” This was in contrast to the effect such interrupted current had on skeletal muscle, which would be “thrown into tetanus.” Based on these experiments, Foster drew the important conclusion that “cardiac muscular tissue itself differs for some reason or other from ordinary muscular tissue in a disposition towards rhythmic rather than continuous contraction; and that the influence of the ganglia is probably not rhythmic but continuous, whatever the exact nature of that influence be.”\(^{19}\)

In 1869, Foster delivered a series of lectures at the Royal Institution of Great Britain, excerpts of which have been published by historian Gerald Geison.\(^{20}\) Foster’s second lecture dealt primarily with the heart beat. He declared, “The cause of the heart’s beat is somewhere in the substance of the heart itself.” Foster was dissatisfied with the contemporary interpretation of the role of the ganglia in stimulating the heart beat:

Now when a physiologist in his searching after the hidden cause of some secret motion finds a ganglion, he cries ‘Eureka!’ and generally folds his hands as if his work were done. In the case of the heart, however, we may venture to go a little further and ask the question: in what way or by what means are these ganglia the cause of the heart’s spontaneous beat? Is it that a stimulus or disturbance periodically arises in the substance of the
potent active nerve cells and then hurries down to the muscular fibre as a nervous impulse causing it to contract? Or is it that the stimulus arises in the substance of the muscular fibre, or if you will, that like the cilia, the heart fibres periodically overflow with energy and from time to time burst out in action of their own accord, but that a conjunction with nerve cells is in some way or other necessary for the well being and perfect work of the muscle such as would insure the periodical rise of a stimulus or overflow of energy.

Only through further research could Foster hope to answer these questions. When he went to Trinity College, Cambridge, in 1870, Foster established a sophisticated program of advanced training and research in physiology. There, in a long series of elegant experiments, Foster and his pupils confirmed the myogenic theory of the heart beat and set the stage for our understanding of disorders of cardiac impulse formation and conduction. Foster was not alone in his search for the origin of the heart beat, however. Other investigators continued their work in the innervation of the heart and the physiology of the heart beat as well.

The world's leading center of cardiac physiology in this era was Carl Ludwig's laboratory at the University of Leipzig.21 There, recent Harvard medical graduate Henry P. Bowditch was performing a series of experiments under Ludwig's direction. Using the isolated frog heart preparation developed in Ludwig's laboratory, Bowditch demonstrated that, under proper experimental conditions, the isolated apex of the frog heart could be made to beat spontaneously despite the absence of ganglion cells. According to physiologist Chandler Brooks, these experiments represented "the first important study of cardiac excitability."22 23 Studies from Ludwig's laboratory by Bowditch and J. Merunowicz were useful to Foster and his pupils as they continued their investigation of the origin of the heart beat.

With A. G. Dew-Smith, Foster studied the effect of interrupted and continuous current on the excised but still beating snail heart and found that it was possible to induce rhythmic pulsations that would proceed from the atrium to the ventricle. From these experiments, they concluded that the "fibres" of the snail's heart were not isolated, as was the case in typical skeletal muscle; rather, they were "physiologically continuous; so that any change set up in any part of the ventricle can be propagated over the whole of it in the same way that a contraction-wave set going at any point in a striated fibre is propagated along the whole length of the fibre."24

At about this time, one of Foster's pupils, George Romanes, began his experiments on the jellyfish—experiments that contributed greatly to the elaboration and ultimate acceptance of the myogenic theory of the heart beat.25 26 Romanes worked in Michael Foster's physiologic laboratory with Walter Gaskell and A. G. Dew-Smith in the early 1870s. In 1874, he began a study of the medusa, or jellyfish, in which he sought to elucidate the mechanism of the rhythmic contractions of this invertebrate. Independently wealthy, Romanes set up a private biological laboratory at his summer home at Dunskaith on the Scottish coast.

Romanes informed his friend Edward Schäfer, another of Foster's pupils, "I am working very hard just now. . . . The medusae have now come on in their legion, and occupy my undivided attention. The results so far have proved as definite as they are interesting and important." The jellyfish, a coelenterate, moves through the water in response to rhythmic contractions of its "swimming bell," which includes a thin layer of muscular tissue with a rim containing "marginal bodies." Romanes found he could render the swimming bell immobile by excising either the strip of differentiated marginal tissue that surrounded the bell or all of the marginal bodies. This special nature of this marginal tissue was further shown by the discovery that the "severed margin continues its rhythmic contractions for two or three days."27 Romanes studied the tissue under the microscope and concluded the marginal tissue was nonstriated and did not seem to contain nerves. These observations led Romanes to conclude that the marginal bodies were responsible for the periodic spontaneous motion of the swimming bell of the jellyfish. He also showed that although the excised bell of the jellyfish did not contract spontaneously once the marginal tissue was removed, it would contract in response to mechanical or electrical stimuli. In the course of his experiments, Romanes demonstrated that progressive sectioning of the bell would ultimately lead to the development of "block" of the contractile wave. This concept of "block" would soon recur in Walter Gaskell's studies on the heart.

In another letter to Schäfer, Romanes mentioned:

...you no doubt remember that in the paper we heard Dr. Foster read, he said that, the snail's heart had no nerves or ganglia, but nevertheless behaved like nervous tissue in responding to electrical stimulation. He hence concluded that in undifferentiated tissue of this kind, nerve & muscle were, so to speak, amalgamated. Now it was principally with the view of testing this idea about 'physiological continuity' that I tried the mode of spiral & other sections mentioned in my last letter. The result of these sections, it seems to me, is to preclude on the one hand the supposition that the muscular tissue of medusae is merely muscular (for no muscle would respond to local stimulus throughout its substance when so severely cut), & on the other hand, the supposition of a nervous plexus (for this would require to be so very intricate, & the hypothesis of scattered cells is
without microscopical evidence here or elsewhere). I think, therefore, that we are driven to conclude that the muscular tissue of medusae, though more differentiated into fibres than is the contractile tissue of the snail’s heart, is as much as the latter, an instance of ‘physiological continuity.’

A critical link between Romanes’s experiments on jellyfish and Foster’s on the origin of the heart beat had therefore emerged. Romanes concluded that the behavior of the muscular tissue of the medusa was strikingly similar to that of the snail’s heart. He discussed this with Foster and informed Schäfer that “Dr. Foster fully agrees with me in this deduction from my experiments, & is very pleased about the latter, thus affording additional support for his views.” Romanes believed that “the properties of nerve and muscle are united in the contractile fibres of medusae.” He continued, “There can be no doubt whatever that the seat of spontaneity is as much localized in the margin, as the sensibility to stimulus is diffused throughout the bell. There must, therefore, be some structural difference in the tissue here to correspond to this great functional difference."

Romanes submitted a paper based on his medusa experiments to the Royal Society because he was convinced of their significance and Foster had written him “preaching high morality about it being the duty of all scientific workers to give their results to others as soon as possible.” After his presentation, Romanes received encouragement from a variety of sources. Charles Darwin wrote: “I have just heard that your lecture was a splendid success in all ways.” Writing 60 years later, Nobel laureate and pioneering neurophysiologist Charles Sherrington emphasized the relevance of Romanes’s experiments on jellyfish to subsequent developments in our understanding of the origin of the heart beat: “Romanes’s observations carried out with simple means were novel and fundamental. The questions which he put to the swimming-bell and answered from it, led, it is not too much to say, to the development of modern cardiology. Medusa swims by beat of its bell, and Romanes examining it discovered there and analysed the two phenomena now recognized world-over in the physiology of the heart, and there spoken of as the ‘pace-maker’ and ‘conduction-block’.

While Romanes was studying medusae, Foster extended his earlier studies of the effects of electric current on the heart. On the basis of frog experiments, Foster concluded, “The well known, easily recognized, ganglia of the heart play a subordinate part in the production of the heart’s spontaneous rhythmic pulsations. The real origin of these is to be sought for in the phenomena of muscular tissue.” He also showed that the isolated apex of the ventricle, although devoid of ganglia, could beat spontaneously. This observation supported German physiologist Theodor Engelmann’s concept of the “physiological continuity” of the entire ventricle. Foster summarized contemporary understanding of the origin of the heart beat in his classic physiology text, first published in 1877. He explained, “The beat of the heart is an automatic action; the muscular contractions which constitute the beat are caused by impulses which arise spontaneously in the heart itself.”

More than anyone else, Foster’s pupil Walter H. Gaskell was responsible for the ultimate acceptance of the myogenic theory of the heart beat. Foster served as the link between his pupils Romanes and Gaskell—information and interpretations were freely shared between the professor and his pupils. Historian John Lesch has claimed, “Romanes’ clear and decisive conclusions and the analogy he drew between the cases of the medusa and the heart were important elements in the background of Gaskell’s later demonstration of the myogenic origin of the heart beat.”

After preliminary education in London, Gaskell entered Trinity College, Cambridge, in 1865. When Michael Foster came to Cambridge five years later, Gaskell was attracted to the physiologist’s laboratory. As was the case with several other ambitious medical graduates interested in physiology, Gaskell also studied with Carl Ludwig in Leipzig. Describing Gaskell’s return to Cambridge from Leipzig in 1875, Foster’s biographer claimed, “Gaskell must have found himself virtually surrounded by men at work on beating hearts.”

In an 1882 paper, Gaskell acknowledged that most physiologists still attributed the heart beat of “the action of certain ganglion cells situated in the heart itself, while the cardiac muscular tissue is credited with the purely subordinate role of responding to the impulses generated in these nerve cells.” After summarizing the data that refuted this view, Gaskell declared, “Seeing how insecure is the hypothesis of the existence of automatically acting nerve cells. . . in the apex of the frog’s heart. . . it is well worth while to consider whether the phenomena in question may not be explained by the properties of the muscular tissues per se.”

Gaskell sought to go beyond traditional explanations of the cause of the heart beat and drew an analogy between it and glandular secretion, a subject then being studied by his colleague John Langley in Foster’s laboratory. In a lecture before the Royal Society, Gaskell proposed that the heart’s muscular protoplasm pro-
duced an "explosive substance" analogous to the products formed in gland cells that led to secretion. Incorporating Foster's earlier investigations and his own recent studies on the function of the vagus nerve into this scheme, Gaskell suggested that its role was to control the rate of formation of this substance.37 Gaskell (and Foster) recognized that the heart beat was affected by the vagus nerve, the cardiac ganglia, and the heart muscle itself, but the fundamental cause of the rhythmic beat remained obscure.

Significant advances in Gaskell's methods and his decision to turn from the frog to the tortoise facilitated his research at this point. He had developed a new method that enabled him to record separately any minor variations in the force of contraction of the atrium and ventricle of the isolated heart. Gaskell also made use of former Foster pupil H. Newell Martin's recently developed isolated heart preparation in which the coronary arteries were perfused.38, 39

Employing these new techniques, Gaskell sought to prove whether separate mechanisms were necessary to explain the rhythmic properties of the sinus, atria, and various segments of the ventricle. He found that the isolated tortoise ventricle "beats automatically with as great a certainty as the isolated auricle." And, unlike the frog, no chemical, mechanical, or electrical stimulus was necessary for the tortoise ventricle to continue to beat rhythmically. This critical observation led Gaskell to conclude, "The automatic rhythm of the ventricle is of the same kind as that of the auricle, and therefore as that of the sinus, so that if the latter is due to the presence of motor ganglia so too is the former, and on the other hand, if the former be due to some inherent rhythmical property of the ventricular muscle, then the latter is due to a somewhat better development of the same kind of property in the muscular tissue of the sinus."40

Since it was acknowledged that the apex was devoid of ganglion cells, it seemed likely that the muscular tissue itself possessed the ability to beat rhythmically. Based on sophisticated experiments in which he studied strips of isolated ventricular muscle, Gaskell argued that the heart rhythm was "automatic" and "due to some quality inherent in the muscle itself." On the basis of these experiments he concluded, "Between the rhythm of the sinus and the rhythm of the muscular strip from the apex no hard and fast line can be drawn; between two extremes a distinct gradation of rhythmical power is manifested, and wherever such automatic rhythm is developed the laws of its development are the same. What differences there are, are differences of degree not of kind."

Gaskell also sought to explain the orderly sequence of contraction of the atrium and ventricle. A few years earlier, Foster had encouraged Charles Darwin's son Francis to investigate the histology of the snail heart. In the course of that study, Darwin made the important observation "that there is muscular continuity between the auricle and ventricle."41 This discovery had significant implications for Gaskell's study of the conduction of the cardiac impulse.

Gaskell functionally distinguished two sections of the atrium, the "sinus-auricle," the part near the sinus itself, and the "ventricle-auricle," the part of the atrium near the auriculoventricular groove. He demonstrated that the direction of contraction was from the "sinus-auricle" to the "ventricle-auricle" and from there to the ventricle. Gaskell explained, "The ventricle contracts in due sequence with the auricle because a wave of contraction passes along the auricular muscle and induces a ventricular contraction when it reaches the auriculo-ventricular groove." As Gaskell progressively sectioned the atrium and narrowed the bridge of tissue that connected the atrium with the ventricle, he discovered that instead of a ventricular contraction following every atrial beat, the ventricle contracted in response to only every second atrial contraction. By cutting further this narrow bridge of atrial tissue, "then the contraction wave is absolutely unable to pass, then the 'block' is complete and any contraction of the ventricle which may occur are absolutely independent of those of the sinus and sinus-auricle."40

Although Gaskell did not mention Francis Darwin's observations, he was certainly aware of them. In an earlier paper, Gaskell had demonstrated that heart block would occur if this muscular bridge were divided: "If the auricular muscle be carefully separated from the ventricle and along each side of the inter-auricular basal wall, so that the ventricle is connected with the sinus and auricle only by the band of tissue which contains the large nerves and coronary veins, then the sequence [of contraction] between auricle and ventricle is entirely lost; i.e. the sequence does not depend upon the nerve trunks between sinus and ventricle."38

In his 1883 paper, Gaskell credited this terminology of "block" to his friend George Romanes: "In his experiments upon the passage of contraction waves along the muscular tissue of the swimming bell of the Medusae, Romanes has throughout made usage of the term 'block' to express any artificial hindrance to the passage of the contraction. I therefore make use of the same term in speaking of the results of experiments on the cardiac muscle which are very similar to those which he performed on the muscle of the medusae."
Gaskell claimed that his experiments showed conclusively that ventricular contraction occurred only after the passage of a contraction wave to the auriculoventricular groove.\textsuperscript{40}

Gaskell now sought to elucidate the mechanism of the delay between contraction of the auricle and the ventricle "by examining whether any particular portion of the auricles and ventricle is especially concerned with the maintenance of the sequence of ventricular upon auricular beats, and at the same time investigating the structure of the auriculo-ventricular groove." \textsuperscript{41} In a series of elegant experiments, Gaskell proved that the basal part of the auriculoventricular groove where the sympathetic nerve fibers enter and where ganglion cells are most prevalent, "has the least share in the maintenance of the sequence of the ventricular and auricular beat." Gaskell claimed, "The muscular tissue of the sinus however is not the only rhythmical tissue of the heart. When the sinus is removed regular contraction waves still pass over the heart which originate from that part of the remaining muscular tissue which possesses the greatest rhythmical power."

Although Geison has recently asserted that this 1883 paper by Gaskell marked a "watershed" in the history of cardiovascular physiology, the long-standing myogenic-neurogenic debate was not suddenly resolved. Gaskell's comprehensive summary of his experiments on the tortoise heart lent strong support to the myogenic theory of the heart beat, yet some continental physiologists continued to favor the neurogenic theory. Resistance to the myogenic theory was gradually overcome as additional investigations were undertaken, and, especially, as morphological studies provided a structural framework for the theory.

Initially, there was reluctance to accept Gaskell's theory of the heart beat in the frog and tortoise as the mechanism in higher warm-blooded animals. Eventually, however, several workers such as Stanley Kent and Rudolf Krehl demonstrated muscular continuity in the mammalian heart "quite sufficient to account for the passage of a contraction wave" between the atria and ventricles.\textsuperscript{42, 43} In 1891, British physiologists William Bayliss and Ernest Starling showed that the contraction wave in the mammalian ventricle passed from base to apex just as in the case of the frog and other cold blooded animals. American physiologist William Porter of Harvard, best known for his classic experiments on ligation of the coronary arteries, studied the cause of the heart beat in mammals at the close of the 19th century and confirmed that Gaskell's observations on the tortoise heart also applied to mammals.\textsuperscript{44}

In a comprehensive review of research on the origin of the heart beat published in 1900, Gaskell, in the opinion of physiologist and historian Chauncey Leake, unequivocally "established the validity of the myogenic theory of cardiac contractility."\textsuperscript{45} Gaskell summarized his contributions to the subject as well as those of other scientists and concluded that his explanation of 1883 "of the reason why different parts of the heart differ in rhythmical power—and explanation dependent upon the morphological differences of the muscular tissue and not upon the presence or absence of ganglion cells—is right. Nothing that has since been written has tended to make me alter that opinion." He also reiterated his belief that the sequence of contractions of the various parts of the heart was "not dependent upon the presence of ganglion cells any more than the heart-beat itself."\textsuperscript{42}

In Gaskell's words, "The fundamental experiment, and it is one of very great importance for all questions connected with the heart, is an experiment of the same character as that originally performed by Romanes on the muscular tissue of the Medusae; an experiment, namely, of cutting the muscular tissue of the heart, so as to leave only a small bridge of tissue over which the contraction must pass, and then studying the block to the passage of that contraction caused by reducing this bridge more and more." Gaskell concluded, "Clearly, then, the natural pause between the contractions of auricle and ventricle, can be explained without the intervention of any special nervous mechanism, if the contraction of the heart signifies the passage of a contraction wave from one end of the heart to the other, over muscular tissue of varying power of conductivity."\textsuperscript{42}

A major advance in our understanding of the origin of the heart beat occurred in 1907 when Arthur Keith and Martin Flack published their classic observations on the sinus node. They wrote "Our search for a well-differentiated system of fibres within the sinus, which might serve as a basis for the inception of the cardiac rhythm, has led us to attach importance to this peculiar musculature surrounding the artery at the sino-auricular junction. In the human heart the fibres are striated, fusiform with well-marked elongated nuclei, plexiform in arrangement, and embedded in densely packed connective tissue." They concluded that it was within this specialized cardiac muscle "that the dominating rhythm of the heart normally begins."\textsuperscript{46}

These studies finally provided a morphologic framework that made it possible to explain the physiologic phenomena that had been elucidated over the past century. The weight of this additional evidence, together with Gaskell's comprehensive and persuasive sum-
mary of the myogenic theory published in 1900, essentially settled the long debate about the origin of the heart beat. As Geison observed in 1978, Gaskell’s “myogenic theory and his concept of heart block were incorporated into the pathology, pharmacology, and therapeutics of the heart, and his conclusions have remained at the base of cardiology ever since.”

The classic observations of Foster, Romanes, and Gaskell were the “stepping-stones,” in Sherrington’s opinion, to the clinical work of James Mackenzie and Thomas Lewis that established the scientific study of cardiac arrhythmias in man. The electrocardiograph, of course, was invaluable in identifying and classifying abnormalities of impulse formation and conduction in man. The work of these men and their contemporaries who established the “new cardiology” is beyond the scope of this review. A recent article by Lawrence outlines the early clinical applications of the scientific studies that have been described here.

References
2. Siegel RA: Galen system of physiology and medicine: an analysis of his doctrines and observations of bloodflow, respiration, humors and internal diseases. New York, 1968, S. Karger, p 45
5. Howell W: The cause of the heart beat. Harvey Lect Series 1905-06, p 305
27. Romanes to Schäfer, 4 June 1875, Sharpey-Schafer Collection, Contemporary Medical Archives, the Wellcome Institute for the History of Medicine, London, England. (Hereafter Sharpey-Schafer Collection; excerpts from these letters appear in The Life and Letters of Romanes, fn 26)
28. Romanes to Schäfer, 24 June 1875, Sharpey-Schafer Collection
29. Romanes to Schäfer, September 1875, Sharpey-Schafer Collection
30. Darwin to Romanes, 29 April 1876. In The Life and Letters of Romanes, fn 26
32. Foster M, Dew-Smith AG: The effects of the constant current on the heart. J Anat Physiol 10: 735, 1876
43. Martin EG: The rise of the present conceptions as to the cause of the heart-beat. II. The myogenic theory, and modern studies of rhythmicity. Johns Hopkins Hosp Bull 16: 377, 1905
46. Keith A, Flack M: The form and nature of the muscular connections between the primary divisions of the vertebrate heart. J Anat Physiol 41: 172, 1907
47. Erlanger J: The localization of impulse initiation and conduction in the heart. Harvey Lect Series 1912-13, p 44
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