

SPECIAL ARTICLE

George Ralph Mines, Ventricular Fibrillation and the Discovery of the Vulnerable Period*

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The discovery of the vulnerable period of the ventricle unmasked one of the major electrical properties of the heart. Since its description by George Ralph Mines in 1914, it has become a crucial concept in understanding the electrophysiologic basis for ventricular fibrillation. Mines also proposed the theoretical basis for the occurrence of reentrant arrhythmias. Although these concepts are widely known, Mines himself remains an obscure figure since his own sudden death at a young age. Mines was a

talented researcher who had a short but prolific career in electrophysiology. The historical importance of his work lies in the influence he had on our understanding and treatment of cardiac arrhythmias as well as in the experimental methods he developed, which inspired a new era of quantitative thinking in electrophysiology.

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Over the past century, the scientists of the Cambridge School of Physiology, spearheaded by Michael Foster, contributed greatly to the understanding of nerve, muscle and cardiac physiology (1). Among the most promising of the younger physiologists at Cambridge was George Ralph Mines whose career spanned only a decade, during which time he made two major contributions to electrophysiology. His scientific legacy includes elucidating the theoretical basis for the occurrence of reentrant arrhythmias and the discovery of the vulnerable period of the ventricle. Shortly after leaving Cambridge to assume the Professorship of Physiology at McGill University in Montreal in 1914, Mines was found dead in his laboratory at the age of 29 under unexplained circumstances. His life and work will be reviewed briefly in the context of the developments in cardiology that have occurred since his discoveries were made over 80 years ago.

Life of Mines and His Work at Cambridge

George Ralph Mines was born in Bath, England, on May 13, 1886, the son of H. R. Mines, and Alice G. Ward (2,3). His early education was at Bath College and later at the Grammar School in Kings Lynn. He entered Sidney Sussex College, Cambridge University, at the age of 19 as an exhibitioner in 1904. He gained a First Class degree in both parts of the Natural Science Tripos. In 1908, Mines received the Allen

University scholarship, and in 1909 he was awarded the Walsingham Medal and elected to a fellowship at Sidney Sussex. That same year, he married Marjorie Rolfe of Newnham College, the daughter of the Rev. and Mrs. G. W. Rolfe. Marjorie was a poet who was drawn to the group of young men around Rupert Brooke whose fates were emblematic of the romantic and tragic aspects of the *belle époque*. Many of them, including Brooke, were killed in the Great War of 1914-1918, and Marjorie Rolfe's work is included in a book of poetry by these young Cambridge poets. Mines himself had a strong artistic bent and, being extremely gifted at the piano, had seriously considered a career in music before turning to physiology. A photograph taken at the age of about 27 years shows him to be an elegantly dressed, darkly handsome man (Fig. 1). He was also apparently personally charming and greatly liked by his colleagues, both at Cambridge and at McGill. Mines' reading tastes extended to Anatole France—a writer who enjoyed a mixed reputation at the time—and he had expressed the wish that his next son be named for the author. When his daughter was born posthumously, she was given this masculine name in order to respect her deceased father's wishes. Anatole, who became a professional viola player, was Mines' last surviving child and died in 1993 at the age of 79.

Mines was elected to the Physiological Society in 1910, together with his friend A. V. Hill. In 1911, he won the Gedge Prize and was subsequently appointed Assistant Demonstrator in the Physiological Laboratory at Cambridge. It was while he was working here that he was offered a temporary position for a few months as assistant to Professor T. G. Brodie at the University of Toronto (4). Before leaving for Toronto in 1914, he had had 4 very productive years at Cambridge. Besides acting as demonstrator, he taught a physiology course at Newnham College, Cambridge, and there met Dorothy Dale (no relative to Sir Henry Dale) in 1910 while she was a

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Figure 1. George Ralph Mines, about 27 years old. (Photograph provided by the Physiological Laboratory, Cambridge University, England. Reprinted with permission.)

second-year student. She assisted him in his experimental work until 1914, and they published much of their work together, largely in the *Journal of Physiology* (3,5,6). It is remarkable to note the enormous productivity of the Physiological Laboratory during this period. Mines himself published over a dozen papers between 1910 and 1913 in this journal, accompanied in the same volumes by authors whose names have since passed into the annals of contemporary science: Langley, Adrian, Hill, Starling, Bayliss, Sherrington and (Thomas) Lewis.*

Some idea of Mines' high level of scientific activity and almost restless energy can be gathered by his movements during the 2 years before he left for Canada in 1914. In the summer of 1912, he and Dorothy Dale worked for 10 weeks in the Marine Biological Laboratory in Plymouth. Mines also worked at the Zoological Station in Naples, probably also in 1912, and at Roscoff in France in August 1913. It was at the Biological Station in Roscoff that Mines did the experiments leading to the key concept of the vulnerable period of the ventricle that would be published posthumously the following year. In September 1913, he took part in the Ninth International Congress of Physiology at Groningen, The Netherlands, presenting a paper on his work done at Roscoff entitled "Functional Analysis of Cardiac Muscle (With Demonstration, Projection and Cinematographic Projection)" (3). By early 1914 he was at Brodie's laboratory at the University of Toronto for a few months, traveled to Montreal to lecture at McGill and then left for England at the end of the summer via Boston. He arrived in Cambridge in time for the dedication ceremony and official opening of the new Physiological Laboratory in June of 1914. The Professor of Physiology was J. N. Langley, and the department was made up of W. Gaskell, E. D. Adrian, A. V.

Hill, K. Lucas, F. G. Hopkins, W. B. Hardy, H. K. Anderson and W. M. Fletcher. After the dedication, Mines returned to Canada for the commencement of the fall term at McGill with his wife and his two children, a girl of 4 and a boy of 2½ years. His wife, who was pregnant at the time, moved back to Cambridge after his death, where Anatole was subsequently born. Marjorie Mines subsequently remarried and moved to Sussex, living until the mid-1960s.

Appointment at McGill University

Due to the shortage of qualified physiologists in physiology in Canada, Mines came as assistant to Professor T. G. Brodie at the University of Toronto for a few months during the winter of 1913-1914. Brodie himself was one of the many British scientists who staffed Canadian medical schools in the early part of this century (4). At Toronto, Mines came to the attention of the faculty at McGill University in Montreal, where the post of Professor of Physiology had been vacant for a year. J. G. Adami, the Professor of Pathology at McGill, was put in charge of the search for a new Professor. Mines was invited to Montreal to lecture there, and the McGill faculty was suitably impressed by the young physiologist (3). It is clear from the letters exchanged between Cambridge, McGill and Toronto that, although he was barely 29 at the time, Mines had already made his mark on physiology and had established himself as an important figure at Cambridge and in Canada. The high regard his colleagues had for him is evident in the glowing letters written to Adami by Langley, Gaskell and Lucas of the Physiological Laboratory at Cambridge, with praise for Mines and his scientific work (3). Before he returned to Cambridge in the summer of 1914, Mines was contacted by Principal William Peterson of McGill University and offered the position of Professor and Chair of Physiology, to commence that fall. He demurred because the annual salary of \$4,000 offered was insufficient to support a wife and two young children. After negotiations, he accepted the position and hurried back to England for the opening of the Physiological Laboratory at Cambridge, after spending a couple of days in Boston. It is apparent that the Dean and the faculty at McGill thought so highly of their newest professor that Mines was also asked to give the Founder's Day oration in October 1914, only 2 months after he returned to Montreal.

Experimental Work in Physiology: The Discovery of the Vulnerable Period

Mines had a great facility for making his own equipment and devices for his experiments, and in several of his papers, he provided drawings and photographs of the equipment he invented or adapted. For some of his experiments, he constructed a teak box with a roller-and-drum mechanism that held rolls of bromide paper for photographing electrocardiograms while studying the actions of electrolytes and electrical stimuli on the heart (5). Mines reported the still-novel method

*A comprehensive list of Mines' publications was compiled by F. C. MacIntosh and deposited in the Mines Archives at the Osler Library, McGill University, Montreal.

of recording the contraction of the frog heart by photographing it at fifteen frames per second on bromide paper, using a method modified from Bull (5). A photographic sequence of 24 photographs of this experiment was published in the same paper. Having developed a great interest in the new cinematographic and photographic processes of the time, he became a passionate photographer and negotiated actively with a London studio to become a part-time scientific and educational filmmaker. After corresponding with Lucien Bull, he visited the Marey Institute, a physiological laboratory in Paris founded by Étienne-Jules Marey (2). The remarkable Marey, a physician and eminent cardiovascular physiologist, who had described the existence of the refractory period in heart muscle, was also the first to record the electrocardiogram by using a photographic technique using the capillary electrometer invented by Lippmann (7,8). While working with sequential photographs, (chronophotography), Marey had developed the first moving-image camera in 1888 and applied this technique successfully to the study of cardiac contraction and to human and animal locomotion (9). Mines was thus one of the early workers to adapt and utilize the innovative Marey-Bull method of cinematographic study to cardiac physiology. Additionally, Anatole Mines, had in her possession a machine that Mines had invented to record the progress of an experiment, which he called a "chronodictaphone" (Anatole Mines, personal communication, 1992) (10).

In the mathematical analysis of data from some of his early experiments, he was aided by A. V. Hill, his friend and colleague. Hill, then a Fellow of Trinity College, was already making his own brilliant career in muscle mechanics. Hill was an excellent mathematician before switching to physiology, and although he came to know Willem Einthoven well personally, he himself was not inclined toward studying the electrocardiogram (11). Einthoven, of course, earned the Nobel Prize in Medicine in 1924, for developing the electrocardiogram as a standard clinical tool. Despite his close friendship with Hill and his work in electrophysiology, it is unlikely that Mines was personally known to Einthoven. Mines' own electrophysiologic studies included the effects of the vagus and of various salts such as barium, calcium and potassium on the electrocardiogram and the effect of strophanthin and Munchi arrow poison on the heart (5,6,12,13). Mines' experiments required the meticulous measurement of both electrocardiographic intervals and elapsed time during an experiment, and although he developed several ingenious devices for doing so accurately (5,6,12-15), it is two other important contributions to cardiac electrophysiology that he published in related papers that have endured and which will be described briefly here.

The first concept that Mines advanced, in 1913, was a description of how reentrant or circus rhythms were generated in excitable tissue (14). He provided recognition of an arrhythmia that he named "reciprocating rhythm," which he first recognized in the hearts of the electric ray and the frog. This arrhythmia was subsequently described in humans by Drury in 1924 (16), and the explanation that Mines provided was nothing short of brilliant. The model Mines proposed was the

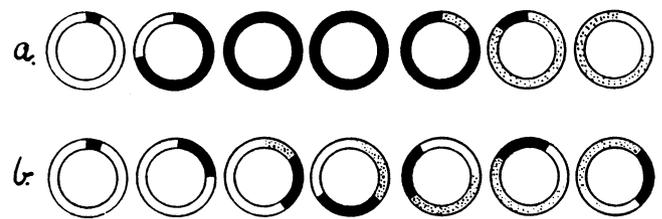


Figure 2. Diagrammatic representation by Mines to demonstrate circulating rhythm in closed circuits in myocardial tissue. **a**, Normal tissue with rapid conduction with no reentry. **b**, Abnormal tissue with delayed conduction permitting reentry to occur. **Dotted areas** = relative refractory phase in the cycle. (Reprinted, with permission, from Mines [14].)

presence of a dual pathway in the atrioventricular conduction system (including muscular connections between the atria and ventricles) with differing electrophysiologic properties, one allowing only anterograde conduction and the other only retrograde conduction of an impulse. This set of conditions permitted passage of an impulse from the atrium into the ventricle down one pathway and retrograde conduction up the second pathway and back into the atrial chambers. Mines also found that such an arrhythmia, once started, could be terminated by an extrasystole or provoked by another premature beat. He wrote that "the favorable conditions of slow conduction and short refractory periods . . . suggest that a circulating excitation of this type may be responsible for some cases of paroxysmal tachycardia as observed clinically" (14). Mines' concept of circular movement was built on previous contributions to the electrophysiology of reentrant impulses made by Romanes (17), Kent (18), Mayer (19) and Garrey (20). Although Garrey's classic paper on fibrillation and reentrant rhythms appeared in print only in 1914, his work was already well known after being presented at Saint Louis on November 12, 1912 (20).

Mines applied his concept of reentry to myocardial tissue and suggested that closed circuits may also exist within heart muscle. Under normal conditions, these circuits are uniformly excited, and an excitatory wave dies out. He suggested that the twin conditions of unidirectional block and slow conduction may occur in abnormal myocardial tissue. Thus, tissue in a reentrant circuit may allow a circulating wavefront to be sustained by virtue of conductive tissue being always available for excitation. In this paper, he also published a now classic figure by illustrating the concept of circus movement in such small myocardial circuits, and this diagram is still used unchanged today in teaching this mechanism to students of electrocardiography (14) (Fig. 2). Mines wrote, "The data provided in this paper suggest an explanation of the important and interesting condition of *delirium cordis* or fibrillar contractions." He went on to say that "The circulating rhythm here described is precisely comparable to the state of affairs produced in rings cut from the bells of Medusae in the experiments of A. G. Mayer" (14).

Thus, in just one series of experiments, Mines proposed the

mechanisms responsible for macroreentrant tachycardias seen in atrioventricular node reentry and in the Wolff-Parkinson-White syndrome, as well as for microreentrant circuits that are presumed to be the basis for ventricular fibrillation. He made an additional important discovery during the course of these experiments: That section of the ring instantly stopped the circulating waveform. Today, this experiment forms the basis for surgical sectioning or radiofrequency ablation of bundle branches in the conduction system of the heart, or of abnormal pathways responsible for recurrent reentrant arrhythmias in pre-excitation syndrome.

Mines' second major contribution was also his most important discovery. It was published posthumously in 1914, entitled "On Circulating Excitations in Heart Muscles and Their Possible Relation to Tachycardia and Fibrillation" (15). The material for this signal paper was obtained during a relatively short stay in 1913 at the Station Biologique, Roscoff, France, under the patronage of Professor Yves Delage. There was much interest at that time in the mechanisms of ventricular fibrillation, the essential arrhythmic mechanism for sudden death. This rhythm disturbance, which was produced by subjecting the heart to electrical shocks, had been considered largely an experimental curiosity after being discovered by Ludwig and Hoffa in 1850 and named *mouvement fibrillaire* by Vulpian in 1874 (21). It was the Scottish physiologist John Alexander MacWilliam who advanced the hypothesis in 1889 that ventricular fibrillation was the primary mechanism of sudden death in humans (22,23).

The most common method of inducing fibrillation was by the application of repeated electrical shocks to the heart through an induction coil. Mines' innovation in studying the onset of fibrillation was to modify the method by applying single shocks to the rabbit heart, and by timing them precisely at various periods during the cardiac cycle. For his experiments, he used rabbit hearts perfused by Langendorff's method using Brodie's perfusion apparatus (15). Unlike present-day devices for studying vulnerability of the heart to fibrillation, the beating of the heart was measured by connecting the ventricular apex to a kymograph using a thread, and the timing of the delivered shock was recorded mechanically, rather than by using electrical timing devices coupled to the electrocardiogram. However, Mines did record the electrocardiogram using an Einthoven galvanometer to document the onset of fibrillation. A pair of platinum electrodes with an interelectrode distance of 2 to 3 mm were placed on the ventricles and connected to an induction coil. Stimuli were delivered by single taps of a Morse key, and the moment of application of the stimulus was signaled by the use of a sparking coil connected to an insulated pointer that produced dots on the kymographic trace. Correlation of the position of the dots on the mechanical trace with the electrocardiogram provided an indication of its timing in electrical diastole.

By so doing, "it was found in a number of experiments that a single tap of the Morse key *if properly timed* [his italics] would start fibrillation which would persist for a time. . . . The point of interest is that the stimulus employed would never cause

fibrillation unless it was set in at a certain critical instant" (15). Mines also made three other important observations: that the zone which caused fibrillation immediately followed the refractory phase; that a stimulus delivered beyond this zone merely caused an extrasystole; and that fibrillation was never transmitted back to the atria from the ventricles.

The importance of this work lies in the fact that Mines identified for the first time a narrow zone fixed within electrical diastole during which the heart was extremely vulnerable to fibrillation. An external stimulus, or a stimulus generated from within the heart, if properly timed to fall within this zone, could trigger a fatal arrhythmia and cause death. This observation has spurred three generations of scientists to study the factors which cause death by disruption of what Mines called "the dynamic equilibrium of the heart" (14). Later researchers who were experimenting with the use of electrical shock across the thorax to terminate arrhythmias electively did not realize that such discharge might provoke ventricular fibrillation if it occurred during the vulnerable period as described by Mines in 1914. This realization came belatedly, and it was not until 1961 that Lown and his co-workers incorporated a timing device to synchronize capacitor discharge with the R wave of the electrocardiogram to avoid ventricular fibrillation during cardioversion (24).

Death of Mines and His Place in History

On the evening of Saturday November 7, 1914, the night janitor entered Mines' laboratory and found him lying unconscious with equipment attached, apparently for the recording of respiration (25). He was taken immediately to the Royal Victoria Hospital where he regained consciousness only briefly. Shortly before midnight, he developed seizures and died without regaining consciousness. A complete autopsy was performed, including examination of all the abdominal and thoracic viscera and the brain, but no final diagnosis was rendered (26). The presumption was that death resulted from self-experimentation. In his tribute after Mines' death, Principal Peterson of McGill University, said "he was one of the most distinguished of the younger groups of scientists at Cambridge." The Dean of Medicine, Dr. H. S. Birkett said the tragic death of Mines was a great loss to the world (3,25). On November 9 at 3 PM, a funeral service was held at the chapel of the Royal Victoria Hospital, and the Rev. Arthur French officiated. Professor T. G. Brodie, who was Mines' last superior, was present representing the Toronto Faculty.

What is perhaps most surprising about Mines' place in medical history today is that despite his early success and the widespread knowledge of his contributions to electrophysiology, very little is known about him, and he remains an enigmatic figure. The circumstances of his death are known to only a few outside the Physiology Department at McGill, and this department, in recognition of his seminal contributions, commemorated him in a conference on electrophysiology held about a dozen years ago. At Cambridge, he is still remembered by those who know of his history as a brilliant, but somewhat

tragic figure (Sir Andrew Huxley, personal communication, 1993). In their historical survey of electrocardiography, Burch and DePasquale (27) acknowledge Mines' work on circulating rhythms and reciprocal rhythm. Rytdand (28), obtaining biographical information from Dorothy (Dale) Thacker, published a brief biographical sketch in 1966. Winfree (29), making reference to Mines, acknowledges his major contributions to cardiac electrophysiology and refers to the unfortunate circumstances of his death. More recently, Rosen (30) commented on the contribution that Mines made to the understanding of reentrant arrhythmias, especially in regard to the Wolff-Parkinson-White syndrome. However, a comprehensive history of electrophysiology published in 1994 makes no note of his contributions (21). Until 1996, the scientists at the Biological Station in Roscoff were unaware of the discovery that Mines had made there, and a preliminary search has found no scientific record of his work (Professor André Toulmond; personal communication, 1996).

Mines is mentioned in Harvey Cushing's (31) magisterial Pulitzer Prize-winning biography of Sir William Osler, as one of the members of the Physiological Laboratory when it was opened in 1914. Osler had traveled up to Cambridge in early June of 1914, from Oxford, where he was Regius Professor of Medicine. The occasion was the culmination of Michael Foster's efforts since 1870 to create what has since become famously known as the Cambridge School of Physiology (1). The new laboratory was opened by Prince Arthur of Connaught, but it had already been in full operation for some time. Demonstrations were arranged for the opening by Langley, Mines, Miss Dale, R. A. Peters, A. V. Hill, W. H. R. Rivers, J. Barcroft, W. Fletcher, W. B. Hardy, Keith Lucas and many others. Mines had returned to Cambridge from Canada for the opening before formally accepting the position at McGill. It is likely that Osler and Mines met on this occasion because Osler had previously attended McGill as a medical student and had been Professor there as well.

Mines' last published piece was his address to the McGill faculty on Founder's Day, which he gave on October 6, 1914, almost exactly a month before he died (32). In this address, he makes an important allusion that was to strangely portend his death. It was a fairly long address, scholarly in its sweep and very thoughtful and philosophical for a man who was only 29 at the time. Mines, in describing the pursuit of experimental physiology, quotes two examples of self-experimentation by physiologists. He remarked on Head's experiments at the London Hospital, involving severing nerves in his arm to study skin sensation. Mines also cited studies on digestion by Cannon and Washburn at Harvard, where the latter swallowed a stomach tube. It would seem from these remarks that by the time of his arrival at McGill, Mines had apparently decided that the time had come for human experimentation in his own field.

Mines is buried in Mont Royal Cemetery in Montreal in a grave marked only by a very low headstone that indicates that he died during self-experimentation. Although Mines as a person has been almost forgotten by the world of cardiology,

he is recognized as being the first to propose the basic mechanisms for reentrant arrhythmias and for identifying the vulnerable period. These concepts have become entrenched as cornerstones in cardiac electrophysiology. The prodigious strides made in electrophysiology since his contributions have been in large measure because of his discoveries. The concepts he advanced have also had an impact on research on sudden death and on the development of therapeutic measures to terminate life-threatening arrhythmias using both electrical and surgical means. An analysis of Mines' work demonstrates the value of the scientific method and the power of deductive reasoning at a time when biomedical technology was still in its infancy. Furthermore, Mines' experimental innovations and precise methods added a new dimension of quantitative thinking to cardiac electrophysiology.

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