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John MacWilliam, Evolutionary Biology and Sudden Cardiac Death

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Sudden death is frequently of cardiac origin, and its most common electrophysiologic mechanism is ventricular fibrillation. The concept that sudden death in human beings is due to ventricular fibrillation was first proposed by MacWilliam exactly 100 years ago, well before the electrocardiogram was invented. To conduct his experimental work, MacWilliam devised methods that laid the foundations for modern cardiac research and that provided the first comprehensive approach to successful cardiopulmonary resuscitation. He recognized the role of the autonomic nervous system in modulating both the mechanical and the electrical properties of the heart, and was the first to suggest that this effect had a role in the genesis of sudden death.

On the centennial of his theory of sudden death, MacWilliam's concepts are reviewed in the context of the effect of Darwinian influence on British physiology. It is suggested that his theorem was based on both sound experimental data and comparative physiology, drawing on the new evolutionary principle of similar structure and function in the hearts of various species. MacWilliam's basic physiologic concepts have survived intact for a century, greatly influencing more than three generations of research and practice in clinical cardiology.

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In 1874 when T. H. Huxley delivered his inaugural address, "Universities: Actual and Ideal," as Rector of Aberdeen University, physiologic research and training in Britain were in a state of disrepair (1). In this address and in later comments on medical education, Huxley urged greater support for teaching of the sciences and for experimental research if British science were to flourish. At the time, there was no physiologist in Britain comparable with the two giants in European medical science—Claude Bernard in France and Carl Ludwig in Germany. It was not surprising that, with Huxley's urging, Aberdeen University emerged shortly thereafter as a preeminent center for physiologic research in medicine in the person of John Alexander MacWilliam.

MacWilliam and His Hypothesis of Sudden Death

In 1889, MacWilliam proposed a fundamental concept that greatly influenced clinical cardiology and research for the next 100 years, namely, that sudden death was due to ventricular fibrillation in humans (2). Although this hypothesis arose from experiments in animals, it was based on purely theoretical considerations in humans. When MacWilliam made this daring proposal, the electrocardiogram had not been invented. Indeed, ventricular fibrillation had been recorded only from its mechanical trace and had not been described as occurring in humans. His speculation has been amply verified to the extent that sudden cardiac death from ventricular fibrillation is today considered to be the single most important cause of death in the western hemisphere (3).

MacWilliam deserves great credit not only for placing ventricular fibrillation in a proper clinical context, but also for establishing many of the basic methods for conducting experimental research in cardiac physiology. Unlike many experimental physiologists of his day, he extended observations from the animal laboratory to the bedside, suggesting clinical methods for the treatment of what was then called *fatal syncope*, describing the elements of cardiac resuscitation. Further, he recognized an integrated relation between the cardiovascular and central nervous systems on the basis of simple clinical observations during sleep and exercise. At a time of great Darwinian ferment in Victorian England, he perceived the phylogenetic continuity in electrical functioning of the heart, progressing from fish to frog to humans.

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Ludwig's Influence on MacWilliam

MacWilliam was a native of Kiltarlity, Inverness-shire, Scotland. Born in 1857, he graduated from the University of Aberdeen in 1880 with the medical degrees of MB and CM with first class honors (4). MacWilliam went to Edinburgh and then did research at the famous School of Physiology in Leipzig under the redoubtable Carl Ludwig. He was probably influenced in this decision by his professor of physiology, William Stirling, who, along with Walter Gaskell, Thomas Lauder Brunton and others, had studied with Ludwig in Leipzig.

Ludwig had invented the kymograph in 1847, an instrument that would revolutionize the study of physiology. Cranefield has compared the impact of this instrument on physiologic research to that of introducing the telescope to astronomy (5). The kymograph opened new vistas in the laboratory, and a golden age for physiologic research began to unfold in the latter half of the 19th century. The renowned physiologic institute Ludwig built in Leipzig in 1869 reaped a rich harvest. Through its doors passed Pavlov, Fick, Sechenov, Bowditch, Kronecker and about 200 other future physiologists. Ludwig's laboratory could lay just claim to many of the first systematic investigations of renal function, hemodynamics, reflex regulation of blood pressure, ventricular fibrillation and the effects of the nervous system on the heart.

It was in this rich environment that MacWilliam was nurtured in the best scientific traditions of German physiology. After completing his studies with Ludwig, MacWilliam visited the University of Bern, where he worked with Hugo Kronecker (4). Both Ludwig and Kronecker had been investigating a newly discovered arrhythmia that often rapidly led to death of the animal. Hoffa and Ludwig had produced this arrhythmia in 1850 in cold-blooded and mammalian hearts by applying strong electric shocks delivered by a "rotations machine" in an attempt to produce tetanus of the heart (6). Muscular contractions did not occur regularly after such stimulation, but became weak, irregular and asynchronous, with ineffective cardiac pumping action and resultant cardiovascular collapse.

The new arrhythmia was called *Flimmern* by Hoffa and Ludwig, *delirium cordis* by Ludwig and *Herz-zittern* by Einbrodt and Kronecker; later it was named *circulating rhythm* by Mines and *circus contraction* and *intervermiform movement* by Garrey (6). Vulpian's terms, *fremissement fibrillaire* and *mouvement fibrillaire*, though more euphonious than the others, did not survive intact in translation. Instead, the arrhythmia is now called *ventricular fibrillation* in the English medical literature. MacWilliam, no doubt, was well familiar with this arrhythmia from the work in Ludwig's laboratory, and he would start his own research on ventricular fibrillation when he returned to Britain.

In 1882, MacWilliam received the MD degree with highest honors. His thesis dealt with the structure of the cardiac and diaphraghmatic fibers in various animals (4). From 1882 to 1886, he acted as assistant to Edward Sharpey-Schafer at University College. Sharpey-Schafer, together with J. G. Romanes, had already made significant contributions to basic concepts in neurophysiology with their work on the nervous system of the medusa; these concepts were later applied to cardiac electrophysiology (7). Under Sharpey-Schafer's tutelage, MacWilliam began extensive investigations on cardiac electrophysiology and the effects of vagal stimulation in the hearts of fish and cold-blooded animals (8). In 1886, MacWilliam's former teacher Stirling left Aberdeen to accept an appointment in Manchester, England. MacWilliam was appointed in his place. The new professor of physiology, who had graduated but 6 years previously, was only 29 years old. Huxley's vision was already being realized.

Experimental Work in Mammals

It was in Aberdeen that MacWilliam did his principal work in laying the foundations of modern cardiovascular research and cardiac electrophysiology. Bowditch at Harvard, Gaskell at Cambridge and others from Leipzig had worked largely on the hearts of the eel and the frog. Experimentation was limited to fish and amphibia out of necessity because it was impossible to maintain the heart of mammals alive for more than a few minutes after removal from the body or after exposure of the thorax. Large animal preparations would deteriorate rapidly because prolonged exposure of the heart and the onset of cardiac arrest would terminate the experiment. It was, therefore, impossible to conduct prolonged experiments that would be physiologically meaningful or clinically relevant. The unanswered question was whether observations made in cold-blooded animals were applicable to mammalian hearts.

One of MacWilliam's greatest contributions was to the solution of the problem of experimentation on the mammalian heart. Animals were kept alive for long periods by preventing cooling with a warm pan and by providing artificial ventilation of the lungs by cannulating the trachea. In the event of a physiologic mishap, the experiment was continued by resuscitating the heart with rhythmic internal massage and the injection of pilocarpine (9,10). These methods were the beginning of a systematic and meaningful approach to successful cardiopulmonary resuscitation.

MacWilliam repeated experiments done in fish and amphibia and was able to demonstrate that the fundamental electrophysiologic observations made in cold-blooded animal hearts corresponded to those in mammals. In two short papers (10,11) in 1888, he demonstrated that the spontaneous rhythmic action of the heart seemed to be of myogenic origin, that the strength of an artificially evoked beat is independent of the strength of the stimulus and that recovery

from ventricular fibrillation can be accomplished by the resuscitative measures just described. He also studied the conduction of the heartbeat from the ostial parts of the great veins to the atria and ventricles and the physiologic relation among these parts of the heart. Therefore, he confirmed work that had been previously done in lower animals by Foster and Dew-Smith, Stannius, Bowditch, Gaskell and others.

Vagal stimulation of the heart. In 1822, Magendie (12) made the major neurophysiologic discovery of the 19th century by distinguishing between motor and sensory nerves. In 1845, the Weber brothers (13) discovered that the vagus—then thought to be a purely motor nerve—actually had an inhibitory effect on the contraction of the frog heart. This unexpected and astonishing discovery opened a new and productive area of research in cardiac physiology. MacWilliam duplicated these experiments on the vagus in the hearts of small mammals, demonstrating that vagal stimulation reduced heart rate and contraction and that inhibition was followed by resumption of the heartbeat, with the order of contraction progressing from the ostial regions to the atria and then to the ventricles. Vagotomy caused cardiac acceleration only when the medullary "cardioinhibitory" (vasomotor) center was active, and this effect was not seen when the center was inactive. By this experiment, MacWilliam clearly understood the principle that the effect of the vagus was not a direct one on the heart, but was dependent on the prevailing level of sympathetic neural tone (10).

With this series of experiments, MacWilliam provided physiologists with meaningful animal models for experimentation and simultaneously bridged the evolutionary gap between the heart of cold-blooded animals and that of mammals. These experimental models, like his concepts, have survived the last 100 years.

After MacWilliam died in 1937 at 80 years of age, one admirer, Hugh MacLean (4), commenting on the importance of his work on the phyletic correlation of physiologic functioning of the heart, remarked that "the ultimate bearing of this epoch-making discovery has influenced modern cardiology to a greater degree, perhaps, than has the work of any other investigator."

Ventricular Fibrillation and Sudden Death

The sudden collapse and instantaneous death of a person had long intrigued and puzzled medical attendants. For centuries, no ready explanation was forthcoming. It was in a classic work in 1889, "Cardiac failure and sudden death," that MacWilliam (2) first proposed the hypothesis that ventricular fibrillation was the mechanism of sudden death in human beings. Until that time and for some time after, it was assumed that sudden death—or "cardiac failure" as it was then commonly called—was due to sudden stoppage of the heart in diastole. MacWilliam (2) wryly summarized the various and sundry causes for sudden death, including events such as "overdistention" or "strain" of the organ, "pressure" on the heart, rupture, vagal inhibition, "abrupt loss of contractile power from failure of the intrinsic mechanism" and "exhausting influences of a more obscure character." In less than three pages, he succinctly outlined the two conditions necessary for the occurrence of sudden death.

Predisposing and precipitating causes of sudden death. The predisposing anatomic substrate, he averred, was an organic lesion consisting of coronary artery disease or degenerative changes in the muscular walls or valves. Predisposing physiologic conditions as well as electrical, mechanical and thermal stimulation may also have affected the myocardium and favored emergence of the fatal arrhythmia. The second condition he defined for the occurrence of sudden death was the specific physiologic derangement—ventricular fibrillation. MacWilliam considered vagal stoppage of the heart, the predominant theory of the time, to be an unlikely culprit in causing sudden death. A year earlier, in a paper (11) communicated to the Royal Society by Michael Foster, he had already noted that a hierarchy of pacemaker function existed in the heart, causing resumption of the heartbeat after vagal stimulation after initial stoppage.

In the clarity of the exposition of his theory that ventricular fibrillation was the cause of sudden death, MacWilliam was bold and brilliant. His own words best describe his conclusions: ". . . sudden cardiac failure does not usually take the form of a simple ventricular standstill in diastole. . .It assumes, on the contrary, the form of violent, though irregular and incoordinated, manifestation of ventricular energy. Instead of quiescence, there is a tumultuous activity, irregular in its character and wholly ineffective."(2).

Mechanism of ventricular fibrillation. MacWilliam had already noted (9) in 1887 that the ventricles contained within them the entire mechanism necessary for the execution of regular coordinated pumping action. Separating the ventricles from the atria physiologically or anatomically by sectioning through the atrioventricular groove proved that the ventricles could function normally, albeit at a slower rate. In such a sectioned heart, fibrillation could still be induced, demonstrating that extrinsic control was not essential for either ventricular contraction or the induction of fibrillation. On the basis of his results, MacWilliam believed that fibrillation was *primarily* the result of changes occurring within the ventricles themselves and not the *direct* result of external neural impulses or interruption of neural traffic to the heart.

These conclusions were somewhat at variance with the views of Kronecker and others, who held that there was a coordinating center in the ventricles for normal cardiac action and that fibrillation arose from some disruption of this center. The alleged evidence for the existence of such a center was that fibrillation could be provoked by piercing a

limited area in the upper third of the interventricular septum with a needle (9). MacWilliam did not hide his skepticism of this theory. Because a weak faradic current insufficient to damage the hypothetical center could cause fibrillation and because complete recovery was the rule in small hearts, it was unlikely that such a center was involved in any way. Furthermore, he knew that there was no histologic evidence for the existence of such a coordinating center for generation of the cardiac impulse within the septum.

MacWilliam was thus the first to recognize that the heart was not only a self-contained electrical unit capable of generating spontaneous rhythmic action, but that it also possessed an inherent capacity for self-electrocution, thus allowing the sudden death of its owner. This was a startlingly novel concept that linked experimental observations with clinical medicine in a striking manner.

Evolutionary Biology and Sudden Death

It is useful to consider the intellectual climate in Britain in MacWilliam's time and the theoretical scaffolding on which he built his theory of sudden death. British physiology, embryology and biology were profoundly influenced by Darwinism and to a greater extent than sciences on the Continent. Darwin's theory of evolution was presented before the Linnean Society in 1858, conjointly with Alfred Russell Wallace's contribution (1). *On the Origin of Species by Means of Natural Selection (14)* was published in 1859, and Darwin's friendships with Huxley and many of the leading biologists and physiologists of his day inevitably influenced thinking and research in physiology. Foster, who spearheaded the renaissance of British physiology from Cambridge, published his influential *Textbook of Physiology* (15) in 1877. It quickly became a major source of the evolutionary outlook in British physiology (15a). The confluence of ideas between Darwin and physiologists such as Foster, Burdon Sanderson, Romanes and Gaskell inspired an evolutionary climate that legitimized physiologic correlations between structure and function in different species (7,16). Darwinian phylogeny was thus being eagerly sought after in British physiology in the late 19th century, with Huxley as its most energetic and skillful proponent.

Throughout MacWilliam's research, one detects the thread of comparative physiology. On the basis of the evolutionary principle of similar structure and function, he noted that ventricular fibrillation was a feature in all warm-blooded animals examined. It would be strange indeed, he reasoned, if humans did not show the same propensity for ventricular fibrillation. This deceptively simple and original theorem was fundamental to the thesis that ventricular fibrillation was the mechanism of sudden death in humans. MacWilliam noted yet another feature of ventricular fibrillation of interest to evolutionary biologists. In small animals such as birds, rabbits and rodents, the arrhythmia often self-terminated. Normal rhythm was reestablished after a brief period of time, and the animal recovered spontaneously (10,11). In slightly larger animals such as the cat, ventricular fibrillation either reverted spontaneously to normal rhythm or it persisted. In larger animals such as the dog, the arrhythmia was invariably fatal because self-termination rarely occurred. He noted that in young mammals (fetal or after birth), spontaneous recovery from ventricular fibrillation was the rule.

The species distinction in the behavior of the arrhythmia is crucial for the acceptance of MacWilliam's hypothesis regarding the cause of sudden death. If the arrhythmia were self-terminating in human beings as it was in smaller mammals and fetal hearts, ventricular fibrillation would be an unlikely factor in sudden death. Although the arrhythmia was not known to occur in human beings, they presumably belonged to the category of larger animals in whom ventricular fibrillation did not abort spontaneously. MacWilliam ingeniously concluded that fibrillation was fatal when it occurred in human beings.

Role of size of the heart. The differences in the behavior of the arrhythmia according to a roughly hierarchical system was unexplained in MacWilliam's time. Depending on the species—and, hence, its approximate position in the evolutionary chain—the size of the heart determined whether ventricular fibrillation was capable of being sustained long enough to cause death. In 1914, Garrey (17) demonstrated that the size of the heart did indeed have a role in sustaining ventricular fibrillation. If the fibrillating ventricle was progressively cut to a surface area of <4 cm^2, fibrillation ceased. This effect was presumably due to lack of a critical tissue mass to sustain reentry of multiple circulating wavefronts.

Autonomic Neural Factors and Sudden Death

In the final portion of his classic paper of 1889 (2), stating his belief that ventricular fibrillation was the cause of sudden death, MacWilliam developed the most interesting and intellectually abstract of his concepts of sudden death. Intrigued by the suddeness of death in an apparently healthy person, he cited Gairdner, who wrote, "It is plainly out of the question to suppose that a chronic, and in its very nature gradually advancing lesion like fatty degeneration or disease of the coronary vessels, is the direct and immediate cause of death which occurs in a moment." (2).

MacWilliam surmised that because the pulse was palpable during most attacks of angina, ventricular fibrillation did not occur as a frequent complication. He realized that fixed coronary disease or pre-existing myocardial or valvular disease alone—while causing symptoms—did not account completely for the occurrence of sudden death. Sudden death, then, may be due to additional and transiently occurring factors that abruptly disrupt electrical stability of vul-

nerable myocardium, thus causing ventricular fibrillation. To support this view he had already noted (9), in 1887, that certain temporary experimental conditions such as exposure of the heart in an open thorax and high temperatures may induce the spontaneous occurrence of ventricular fibrillation. In a paper (18) written more than 25 years later, entitled "Blood Pressure and Heart Action in Sleep and Dreams," he developed the concept that the central nervous system plays a role in sudden death.

Role of the central nervous system. The actions of the nervous system had already been under intense scrutiny since Magendie's discovery of motor and sensory fibers early in the 19th century (12). At the turn of the 20th century, J. N. Langley (18a) had devised a nomenclature for the divisions of the autonomic nervous system, and in 1906, Sherrington (19) published his Silliman lectures at Yale University on the integrative action of the nervous system. MacWilliam drew from these workers and was quick to apply their concepts to the cardiovascular system to explain how sudden death might occur. Although the title of his paper (18) refers to circulatory changes in sleep and dreams, MacWilliam used this opportunity to provide a theoretical framework for the discussion of the integrated action between the autonomic nervous system and the cardiovascular system during a variety of physiologic conditions.

Role of sleep and dreams. In that paper (18), MacWilliam recorded a remarkable series of observations during sleep in human subjects and dogs. He noted that there were two stages of sleep—sound sleep and disturbed sleep. During the former, there was a lowering of blood pressure, heart rate and respiratory rate; during disturbed sleep, there were vivid dreaming, groaning, biting actions and growling in dogs, talking by humans subjects and reflex changes. Vivid dreams, such as those associated with physical exercise or hurrying to catch a train, resulted in pronounced increases in heart rate and blood pressure. He confirmed Hughlings Jackson's observations that movements of large limbs are absent even during dreams of vigorous action (18). He surmised that cortical impulses reached the vasomotor and respiratory centers, while bypassing motor areas for the limbs. MacWilliam may well have been among the first to recognize the principal physiologic features of rapid eye movement (REM) sleep. He noted that heart rate and blood pressure elevations during disturbed sleep were surprisingly more marked than those occurring during mild exercise, such as walking up a flight of 20 stairs. Increases in systolic blood pressure of up to 72 mm Hg and diastolic pressure of up to 30 mm Hg occurred during dreaming as compared with blood pressure measured at rest during the day.

Realizing that these cardiovascular changes "imposed sudden and dangerous demands on the heart," MacWilliam surmised that anginal attacks and sudden death at night may occur during this disturbed phase of sleep, even though the body appears to be in a state of repose. Developing this concept further, he wrote (18): "In a heart susceptible to fibrillation a sudden call on the heart during muscular exertion and excitement in the waking state is often fatal; in the disturbed conditions of sleep and dreaming, a similar mechanism is sometimes brought suddenly and strongly into action—diminution of vagus control and, especially under emotional stress, stimulation of the cardiac sympathetic together with a high blood pressure—conditions which favour ventricular fibrillation."

Role of adrenergic factors. Following T. R. Elliott's description (20) of the cardiovascular actions of adrenaline in 1904, MacWilliam ascribed a possible role for the newly discovered hormone in the provocation of angina and sudden death due to ventricular fibrillation. In commenting on the role of adrenaline in provoking sudden death, he cited the work of Cannon and de la Paz (21) on the cardiovascular response to emotion. MacWilliam favored the view that adrenergic factors evoked during excitement and exercise may excite the heart sufficiently to cause sudden death from ventricular fibrillation. Later investigators (22,23) who developed the concept of *transient risk factors* arising within the nervous system and causing a decrease in the ventricular fibrillation threshold, and the role of acute psychologic stress in provoking sudden death, merely confirmed the hypotheses that MacWilliam had initially advanced. It is a little surprising, however, that in his speculations on the effects of the nervous system on the heart, MacWilliam did not invoke coronary artery spasm as a possible factor in sudden death. The thesis that spasm might play a role in angina was the topic of Sir William Osler's well known Lumlean Lecture (24) in 1910 and must have been known to MacWilliam.

Electrical Resuscitation of the Heart

MacWilliam was always keenly aware of the possible clinical relevance and applications of his work. In 1914, at the annual meeting of the British Medical Association in Aberdeen, MacWilliam presented evidence that sudden death may indeed occur in human beings as a result of ventricular fibrillation (4). He showed that sudden death during chloroform anesthesia was a consequence of this arrhythmia and could not be attributed to respiratory failure as the Hyderabad Commission (4) had concluded. MacWilliam produced evidence that when this agent was slowly and carefully administered, such deaths were prevented. This discovery was highly significant because ether and chloroform were the principal anesthetic agents then being administered, the latter having rapidly become the agent of choice.

There had been great interest in human resuscitation during the preceding 100 years, but little progress had been made. MacWilliam had, as described, kept animals alive for long periods of time by vigorous resuscitative measures. It is surprising, therefore, that he did not mention the termination

of ventricular fibrillation by electric shock in any of his major papers. He could not have been completely unaware of other published reports on the uses of electricity for resuscitation. Administration of electric shocking for the most unlikely ailments was then in great vogue, and was used freely by clinical practitioners and charlatans alike. There were at least two reports on the effects of successful resuscitation in animals and humans using Leyden jar discharges—that of Abilgaard in 1775 and by a certain Mr. Squires a year earlier (25). The Swiss researchers Prevost and Battelli (25) reported in 1899 that low currents provoked ventricular fibrillation and that strong discharges terminated this arrhythmia. MacWilliam's silence on this important subject is puzzling.

Electrical treatment of asystole. MacWilliam did, however, comment on the electric treatment of asystole. In yet another paper (26) in 1889, which he boldly entitled "Electrical stimulation of the heart in man," he advanced possible modes of treatment for "heart failure." He wrote (11,26) that by a series of induction shocks, "artificial excitation might be useful in rousing into action a heart that has been arrested by a temporary cause; for example, by inhibitory impulses profoundly depressing the rate and force of its action, or causing it to stand still in diastole." He was careful to point out, however, that application of a strong current would cause ventricular fibrillation, especially in a heart compromised by metabolic or structural alterations.

MacWilliam had, at the time of that writing, heard of von Ziemssen's unusual experiments in Munich in 1880 in which a woman's heart was stimulated with electrical pulses with no apparent harm (27). This extraordinary case was that of Catharina Serafina, a 42 year old Silesian peasant, who had an endochrondoma of the chest wall surgically removed. The anterior portions of the second to the sixth ribs were excised, causing collapse of the lung and exposing the heart through a 9 × 11 cm hole. Through this hole, von Ziemssen observed the contraction of the atria and ventricles and the effects of digital pressure on various parts of the heart and great vessels. Subsequently, more interesting and dangerous experiments were done with electrical stimulation. Strong currents could control the rhythm and frequency of cardiac pulsation. Each stimulation was "followed by a complete and perfect systole of both ventricles" and rates as high as 140 beats/min were achieved. It was, indeed, extremely fortunate for Catharina Serafina that her heart did not develop ventricular fibrillation because she would certainly have come to an untimely end.

This experiment, as well as his own work in 1888 (10), suggested to MacWilliam that rhythmic cardiac contraction might be accomplished by a periodic series of single induction shocks. He believed that this interrupted sequence of shocks would avoid the risk of provoking ventricular fibrillation. He did not then know of the vulnerable period of ventricular repolarization, during which time a critically placed stimulus during the cardiac cycle would cause ventricular fibrillation. This window of vulnerability of the ventricle when fibrillation could be provoked would be described by Mines (28) in 1914 and rediscovered later by de Boer (29) and Wiggers and Wegria (30). MacWilliam's recommendations for external cardiac pacing were all but forgotten until 1935 when Hyman (31) attempted to pace the human heart and Zoll (32) introduced successful external cardiac pacing by using his basic principles.

MacWilliam and Contemporary Cardiology

Sir Thomas Lewis, the leading British cardiologist in the early part of this century, said that MacWilliam's hypothesis regarding ventricular fibrillation as the cause of sudden cardiac death was nothing more than "brilliant for his time" (4). At a time when theories abounded on the origin of the heartbeat, MacWilliam had, by experimentation, identified accurately how the heart functioned as an electromechanical pump and determined how neural and other influences modified the heartbeat. By a series of stochastic deductions, he was able to extrapolate into the unknown, turning an experimental curiosity into a credible hypothesis for a clinical reality. His remarkable series of linked hypotheses was advanced into a working theory in the middle of this century, guiding epidemiologic field studies and spurring experimental and clinical research on sudden death from ventricular fibrillation.

The successful development of human resuscitation by defibrillation and cardiac pacing during the 1940s, 1950s and 1960s by Wiggers, Kouwenhoven, Zoll and Lown and their respective coworkers (23,32–34) remains one of the major accomplishments in clinical medicine today. Their work bears ample testimony to the value of the integrated series of basic physiologic concepts advanced by John MacWilliam exactly 100 years ago.

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*In early publications, MacWilliam spelled his name McWilliam.