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DIALOGUES

ELECTROPHYSIOLOGY: from Galvani's frog to the implantable defibrillator

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In contrast to William Harvey's understanding of the pump function of the heart, published in 1628, recognition of the rhythmic function of the heart is traceable to man's earliest history, including the literature of ancient China and the Bible. Yet only in the 1700s was the wherewithal developed to gain insights into the mechanisms responsible for the heartbeat. Among others, Franklin, Galvani, and Volta planted the seeds of electrophysiology, while Einthoven's invention of the electrocardiogram in the early 1900s provided the trunk from which the field of arrhythmology could grow. Within a mere 100 years of Einthoven's invention noninvasive and invasive electrophysiologic diagnostics and therapeutics grew rapidly, expanding into the fields of pharmacology and, especially devices.

Keywords: electrophysiology; electrocardiography; arrhythmia; atrioventricular conduction block; cardioverter-defibrillator

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The tree trunk for electrocardiography and arrhythmias is Willem Einthoven *(Figure 1)*,[1] who invented the ECG. Following his discovery, the work of early experimentalists like Wenckebach, Lewis, and Scherf, and basic scientists like Mayer, Mines, and Garrey facilitated the growth of a field that has known extraordinary success in diagnosing and treating cardiac disease. Yet, there can be no tree without a seed, and it is with seeds that we will start...

THE SEEDS

The recognition of electrical phenomena is as old as ancient China and Greece: Thales of Miletus (c 624 – c 545 BC) noted that amber rubbed with wool attracts light objects; amber is important to electricity as its ancient Greek name is ἤλεκτρον, (electron). Although Thales could not find any immediate use for his discovery, he clearly wanted it to go down in history: "I will be sufficiently rewarded if when telling it to others you will not claim the discovery as your own, but will say it was mine."[2] In 1994, the Greek government commemorated Thales' discovery on a postage stamp *(Figure 2, next page)*.

The first English-language use of "electricity" as a medical term is generally attributed to Sir Thomas Browne, who discussed the medical properties of the lodestone in 1646. "Electricity" debuted as a scientific term in 1690: while Shakespeare labored over Hamlet, his countryman, William Gilbert, published *De Magnete,* in which he postulated a relationship between electricity and magnetism. Had Thales, Browne, and Gilbert not co-conspired over the centuries, we assume the electrocardiogram would have been differently named. In 1752, Benjamin Franklin reported his kite experiment, a landmark in research on electricity that led to the invention

Figure 1. *Willem Einthoven in 1906.*

Reproduced from reference 1: *Snellen HA.* Willem Einthoven, Father of Electrocardiography. *Dordrecht, The Netherlands: Kluwer; 1995. Copyright © 1995, Kluwer*

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of the lightning rod. Although others replicating Franklin's experiment had the ill fortune to be electrocuted, Franklin survived, much to the benefit of the American Revolution, French parlors, and numerous biographers. Importantly, Franklin also proposed the concept of positive and negative charges, laying a cornerstone in our library of electrical phenomena.

In 1791, a year after Franklin's death, Luigi Galvani published *De Viribus Electricitatis in Motu Musculari Commentarius.* Among his discoveries was that frogs' legs twitched during metallic contact between muscle and crural nerve. Whether his initial insight derived from a laboratory assistant's chance juxtaposition of scalpel and muscle or an accident in Galvani's kitchen as his wife prepared frogs' legs for supper is uncertain. Not at all uncertain were subsequent experiments leading to Galvani's conclusion that animal electricity is generated via an animal electric fluid. He considered the greatest sources to be brain and nerve. Given his understanding that an electrical stimulus precedes muscle contraction, Galvani might be considered the first electrophysiologist.

Galvani's contemporary, Alessandro Volta, viewed electricity differently. He juxtaposed discs of copper and zinc, each pair separated from the next by saline-moistened cardboard, to build a "Voltaic pile," and demonstrated the generation of charge in various ways: touching one finger to each end of the pile caused a tingle; applying tongue and finger elicited taste, finger and ear, a buzz. He concluded that electricity was derived from metal, and interpreted Galvani's experiment (which Volta replicated) as demonstrating that the frogs' legs were an electroscope rather than a source of electricity.

Figure 2. *Thales of Miletus and his amber experiment: Greek commemorative stamp.*

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Subsequently, many contributors improved on the production of sources of electricity and/or means for recording the contractions of and signals generated by muscles. Noteworthy is Matteucci's demonstration of an electrical current associated with each heartbeat (1842), Dubois-Raymond's description of action potentials related to the heartbeat (1843), and Burden Sanderson and Page's recording of two phases of the heartbeat (1878, 1884).

Burden Sanderson and Page made their recordings thanks to Gabriel Lippmann's development of the capillary electrometer in 1872. The principle on which it was based was the change occurring in surface tension at a mercury/sulfuric acid interface in a capillary tube *(Figure 3A)*[1] as potential difference varied between the liquids. In Lippmann's electrometer, a droplet of mercury resided in the capillary, sensitive to and moving with very small changes in the electrical field. An important modification was provided by Étienne Jules Marey, who used the movement of mercury to deflect a beam of light, enabling photographic recording.

In the late 1880s, Augustus Waller used Lippmann's capillary electrometer to record electrical potentials from animals (notably, his bulldog, Jimmy, immortalized in an early photographic plate, standing in four pans of water) and humans. Why Einthoven rather than Waller is commemorated as the father of electrocardiography in part relates to the technical advances Einthoven developed and in part to Einthoven's recognition of the clinical applicability of electrocardiography. Indeed, in 1893, Einthoven was already presenting to Dutch audiences examples of the future clinical applicability of both electrocardiography and phonocardiography.[1] In contrast, Waller had stated "I do not imagine that electrocardiography is likely to find any very extensive use in the hospital. It can at most be of rare and occasional use to afford a record of some rare anomaly of cardiac action."[3]

THE TRUNK

According to contemporaries, including Sir Thomas Lewis and the Nobel Prize committee, Einthoven invented the ECG. Understanding who coined the term "electrocardiogram" is more challenging. Waller credited Einthoven, and the printed record supports Waller's contention. In 1912, Einthoven used the word "electrocardiogram" in print for the first time, but attributed the term to Waller.[4] However, Waller never used the term in a publication until 1917.[5] According to still another source, Einthoven coined the term, but then attributed it to Waller as a sign of respect.[6] Have there been any such signs of generosity of late?

Regardless of who was being generous to whom, history has come to consider Einthoven the "trunk" of modern electrocardiography. The reasoning was summarized by Carl Wiggers as follows:

> In 1889, A. Waller had reported that electrical currents generated during the heart beat could be tapped from the body surface and recorded by capillary electrometer. Human elec-

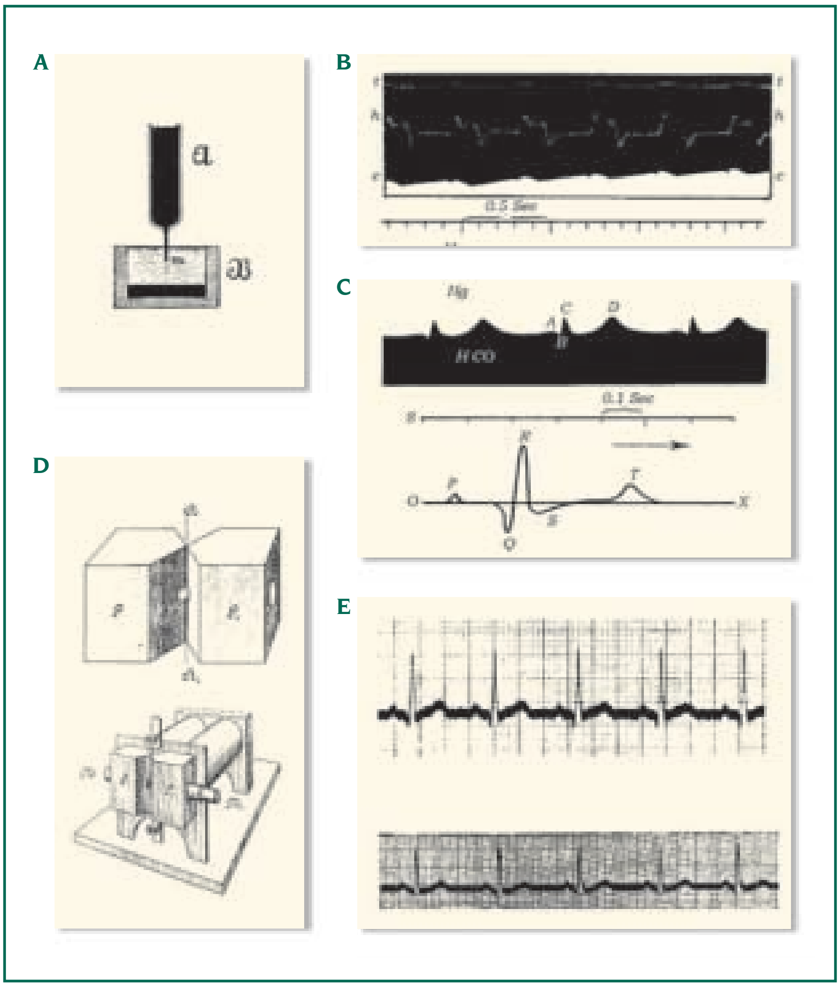

Figure 3. *Evolution of the ECG.* ***Panels A, B, C,*** *relate to Lippmann's capillary electrometer.* ***Panel A:*** *($\mathfrak{A}$) Mercury reservoir ending in glass capillary: upper half filled with mercury. ($\mathfrak{B}$) Lower half of capillary and reservoir, both filled with sulfuric acid.* ***Panel B:*** *Waller's cardiogram: t = time; h = external pulsation from heartbeat; e = electrical activity of heart;* ***Panel C:*** *Einthoven's recording using capillary electrometer.* ***Upper:*** *A, B, C, D waves;* ***Lower:*** *mathematically corrected waves, now designated PQRST.* ***Panel D:*** *String galvanometer:* ***(upper)****, poles $\mathfrak{P}$ and $\mathfrak{P}_1$ of electromagnet and aperture for string $\mathfrak{A}$-$\mathfrak{A}_1$. Note holes for viewing via microscopes:* ***(lower)*** *electromagnet with string in place and two microscopes:* ***Panel E:*** *Einthoven's ECG recordings. See text for discussion.*

Reproduced from reference 1: *Snellen HA.* Willem Einthoven, Father of Electrocardiography. *Dordrecht, The Netherlands: Kluwer; 1995. Copyright © 1995, Kluwer.*

> trocardiography may thus be said to have been born in Oxford, England. However, since Waller went to great pains to rule out any possible clinical application of the procedure, this proved to be a stillbirth. Waller's conclusion need not surprise us if we view again the wholly unsatisfactory character of his records—it is at this point that we gain a good insight into Einthoven's genius—a human trait that Carlyle has defined as 'the ability to take infinite pains.[7]

Who was Einthoven, where did he come from, what exactly did he do? A good source of information was his student, H. A. Snellen, whose biography of Einthoven[1] we summarize here. Einthoven's ancestry is traceable to the mid 1700s when a Jewish merchant, David Joseph, left the Rhineland to settle in Eindhoven, Holland. At times he used the name Enthoven, then a common practice to denote place of origin. When the Napoleonic Code required all persons to take a last name, David Joseph's grandsons chose different routes: one selected as family name, Hoven, the other, Einthoven. Salomon Jurdan Einthoven (Willem's grandfather-to-be), a surgeon, moved to Groningen, joined the Dutch Reformed Church and married the daughter of the professor of physics and astronomy at the university. Their son, Jacob entered government service as a military physician in the Dutch East Indies and then became town physician in Semarang, Java, where Willem Einthoven was born.

Jacob Einthoven died when Willem was six, and his mother took the family back to Holland. They settled in Utrecht where Einthoven studied classical languages and then medicine. While preparing for a career in ophthalmology and a return to the Dutch East Indies, he studied with Herman Snellen (the grandfather of Einthoven's biographer) and Franz Donders, and in 1885 obtained his doctoral degree with a thesis on *Stereoscopy through differences in color.* The quality of his thesis brought him the professorship and chair in physiology at Leiden in 1886, at age 25.

Einthoven's initial research focused on vision and on respiration. However, when his brother-in-law, Willem de Vogel, commenced doctoral research at the laboratory in 1891, Einthoven gave him a choice of subjects and de Vogel selected cardiac electrical activity. Waller and Bayliss and Starling had already published their own (personal) cardiograms using Lippmann's capillary electrometer. Their recordings were marred by the slow voltage/time course of the device, reflecting the friction and the inertia of the mercury in the column, and the presence of only two deflections *(Figure 3B),*[1]. By 1902, Einthoven had improved the sensitivity of the Lippmann device such that four deflections were visible (labeled A, B, C, D) in a recording from both upper extremities *(Figure 3C, upper).*[1] Einthoven also modified a method originally described by Burch for skeletal muscle studies to correct his recordings mathematically *(Figure 3C, lower).*[1] He now designated the wave forms PQRST. The reasons for the change in nomenclature were first, to avoid confusion between uncorrected and corrected records and second, to permit addition of further letters should earlier or later waveforms be discovered.

As good as the capillary electrometer had become, it was still slow and the requirement for mathematical correction of each waveform too labor-intensive for widespread clinical application. Hence, Einthoven adapted a galvanometer invented by Deprez and d'Arsonval. Whereas earlier galvanometers incorporated a magnetized needle that moved when current flowed through a wire coil, Deprez and d'Arsonval designed a fixed magnet and a coil that could move within the field. A pointer attached to the coil moved over a calibrated scale, providing the recording. The result was a rapid enough trace, but one not sufficiently sensitive to record the ECG. This required Einthoven to make a variety of changes in the weight and operation of the coil; his ultimate design used a thin quartz wire coated with silver or gold placed between the poles of an electromagnet. The quartz was made thin enough (initially about 3 microns) by melting it, fixing one end to an arrow and then shooting this with a bow.

Each pole of the electromagnet was perforated such that the string could be illuminated and visualized using two microscopes *(Figure 3D).*[1] Einthoven noted that this was not the first use of a string in an electric field: in 1897, Ader had reported such a device. This was used as a receiver for transatlantic communication of code, was never intended for use as a galvanometer, and had only 1/100 000 the sensitivity of Einthoven's device. Indeed, the signals recorded by Einthoven in 1902-1906 *(eg, Figure 3E)* are readily recognizable and interpretable via today's ECG standards.

Einthoven reported the development of the string galvanometer in 1901[8] and ECGs were published in 1903.[9] The technical advances the string galvanometer afforded over the capillary electrometer in fidelity and speed are evident in *Figure 4.*[8,10] To harness the string galvanometer's clinical potential, a one-mile telephone cable was laid underground, connecting Einthoven's laboratory to the Leiden Academic Hospital. This permitted the recording of "telecardiograms"[11] and diagnosis of arrhythmias. Regrettably, the cooperation between research laboratory and clinical unit was short-lived: this has been variously attributed to the clinicians' jealousy of the scientists' ability to diagnose extrasystoles even before the clinicians were aware of them, and their additional dismay that in an enterprise whose cost was to be equally divided, the credit accrued largely to Einthoven.

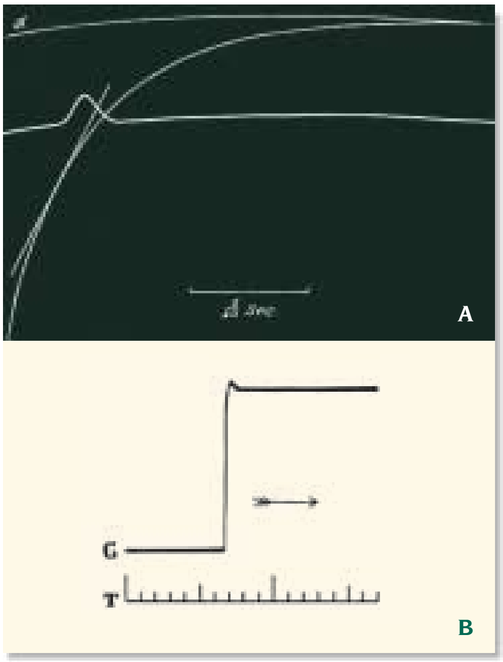

Figure 4. *Response rates of the capillary electrometer (A) and the string galvanometer (B) to a sudden voltage step. The inertia of the mercury column* (see Figure 3A) *is such that the curve recorded by the electrometer shows a slow response as compared to the string galvanometer. In the lower tracing, each vertical time mark (T) = 0.01 second.*

Reproduced from reference 10 (A): *Schäfer EA.* Textbook of Physiology. *Edinburgh, UK: Young J. Pentland; 1900. Copyright © 1900, Young J. Pentland.* ***And from reference 8 (B):*** *Einthoven W. Un nouveau galvanomètre [A new galvanometer].* Arch Neerl Sci Exactes Nat (Ser 2). *1901;6: 625-633. Copyright © 1901, Royal Holland Society of Science and Humanities.*

With this linkage lost, a major boost to the investigative and clinical application of string galvanometry came via a contact made by Thomas Lewis. In 1908, Lewis asked Einthoven for a reprint of the "telecardiogram" paper[11] that had impressed him for a variety of reasons, likely including Einthoven's recordings of ventricular hypertrophy, U waves, ventricular premature depolarizations, bigeminy, atrial flutter, and heart block. As for Einthoven, he assessed the value of his device as follows in a 1922 letter to Lewis (as quoted by Snellen[12]) "An instrument takes its true value not so much from the work it possibly might do, but from the work that it really does."

There is not the space to write more about Einthoven's research. Following his invention and perfection of the string galvanometer, he continued to investigate the relationship between cardiac electrical and mechanical activity. He was awarded the Nobel Prize in 1924, and in 1927 died of cancer. We conclude this section with a Carl Wiggers quote from Einthoven, a few words that cut to the core of our profession: "The truth is all that matters: what you or I may think is inconsequential."

INTRODUCTION TO THE BRANCHES

Before discussing the major branches of electrocardiography/arrhythmias, there are several milestones to be noted. In 1920, Hubert Mann described an electrocardiographic analysis, the "monocardiogram," that evolved into the vectorcardiogram. Also in 1919, James Herrick published the first ECG of a myocardial infarction in a patient. In 1930 and 1932, respectively, Frank Wilson, Charles Wolferth, and Francis Wood described the use of chest leads, and in 1934, Wilson described his central terminal, which, used as a reference, permitted the unipolar limb leads to be recorded. Finally, in 1942, Emanuel Goldberger added the augmented unipolar limb leads to Einthoven's original three leads and to the six chest leads of Wilson and of Wolferth and Wood, providing the 12-lead ECG that is used to this day.

The advances in electrocardiography were accompanied by a renaissance in all areas of electrophysiology, which has grown by moving across disciplines, resulting in further discoveries throughout the twentieth century. Major advances include Tawara's description of the atrioventricular (AV) node (1906), Keith and Flack's description of the mammalian sinoatrial (SA) node (1907), Mines' descriptions of reentry (1913, 1914), Graham, Ling, and Gerard's invention and use of the glass microelectrode (1946,1949), Hodgkin and Huxley's voltage clamp of the squid axon (1940s), Alanis et al's registration of electrical activity of the His bundle (1958), Scherlag et al's His bundle catheter recordings in humans (1968); Neher and Sakmann's development of the patch clamp (1978), Numa's use of gene cloning to describe the molecular structure of voltage-gated ion channels and provide new insights into structure-activity relationships (1980s-90s), and MacKinnon's description of structure of a *Saccharomyces* (yeast) potassium channel (1998). While each development has been of signal importance, one could reasonably argue that with the exception of Mines, Alanis, and Scherlag, the direct contributions of the individuals mentioned were primarily focused on a different area of interest and only secondarily impacted on the field of arrhythmias and electrocardiography.

THE FIRST BRANCHES—THE FIRST HALF OF THE TWENTIETH CENTURY

Here, we include persons whose work and in some cases personalities dominated the development of basic and clinical electrophysiology: Karel Wenckebach, George Ralph Mines, Thomas Lewis, Frank Wilson, and David Scherf.

Karel Wenckebach

Karel Wenckebach *(Figure 5)* was born in The Hague and raised and educated in Utrecht, earning his medical degree in 1888. His initial research interest was embryology, but color blindness limited his interpretations of histologic stains and this disability led him to physiology. In 1891, he entered clinical practice, becoming interested in irregularities of the heartbeat. He resumed the study of physiology in Utrecht in 1896.

Figure 5. *Karel Wenckebach.*
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In 1898, Wenckebach described extrasystoles, and, in 1899, a unique periodicity in a patient's pulse. Aided by his mentor, Theodor Engelmann, Wenckebach studied this periodicity in frog heart in which both the atrial and ventricular pulses could be recorded simultaneously and the time between pulses measured using a tuning fork. We emphasize that these painstaking and accurate studies were performed before the ECG had been invented (Wenckebach described his periodicity using smoked drum kymograph tracings of jugular venous and carotid pulsations) and before the SA and AV nodes had been structurally identified.

However, once Einthoven developed his string galvanometer, Wenckebach used it in 1906 to demonstrate the progressive prolongation of the PR interval that precedes the dropped beat in what is now called Wenckebach periodicity.

In 1901, Wenckebach was named chair of medicine at the University of Groningen. His 1903 book, *Die Arhythmie als Ausdruck Bestimmter Funktionsstörungen des Herzens [Arrhythmia as the Expression of Specific Function Disorders of the Heart],* became a classic. From 1911-1914, he chaired the department of medicine at the University of Strasbourg and from 1914-1929 held the chair in medicine at the University of Vienna. He died in Vienna in 1940.

George Ralph Mines

Born in 1886, Mines *(Figure 6)* trained in physiology at Cambridge, was appointed to the chair in physiology at McGill at age 29, and was found dead in his laboratory shortly thereafter, apparently the victim of self-experimentation. Mines and his contemporary, Walter Garrey, pioneered the study of reentry, and both were inspired by Andre Mayer's studies (1906, 1908) of ring-like structures cut from the muscular tissue of the subumbrella of the jellyfish *Scypho-medusa cassiopeia.* Mayer used mechanical stimulation and photographic plates, respectively, to induce and record a contraction wave that continued to circulate: "…upon momentarily stimulating the disk in any manner, it suddenly springs into rapid, rhythmical pulsation so regular and sustained as to recall the movement of clockwork."[13]

Mines and Garrey noted independently in 1914 that for the initiation of reentry, an area of unidirectional block must be present. Mines' experiment was performed on a ring-shaped preparation cut from dogfish auricle.[14] Normally, a stimulus induced two contraction waves that traveled in opposite directions, meeting on the far side of the ring, where they were extinguished. However, he repeated

Figure 6. *George Ralph Mines. © Physiological Laboratory, Downing Street, Cambridge, UK.*

> …the stimulus at diminishing intervals and after several attempts started a wave in one direction and not in the other. The wave ran all the way around the ring and continued to circulate going around about twice a second. After this had continued for two minutes extra stimuli were thrown in. After several attempts the wave was stopped.[14]

Not only did Mines describe unidirectional block here, but provided an observation that came to underlie antitachycardia pacing.

Mines also described the relationship between conduction velocity and refractory period, pointing out that reentrant arrhythmias are more likely to occur "when conduction velocity is low and refractory period duration is short."[15] He also recognized the need to differentiate reentry from other mechanisms:

> The chief error to be guarded against is that of mistaking a series of automatic beats originating in one point of the ring and traveling round it in one direction only owing to complete block close to the point of origin of the rhythm on one side of this point… Severance of the ring will obviously prevent the possibility of circulating excitations, but will not upset the course of a series of rhythmic spontaneous excitations unless by a rare chance the section should pass through the point actually initiating the spontaneous rhythm.[14]

Mines' prescience was perhaps best illustrated when he linked his experiments on reentry in the ring-like structures to his understanding of Kent's work, stating "in light of the new histological demonstrations of Stanley Kent that the muscular connection between auricles and ventricles in the human heart is multiple… supposing that for some reason an impulse from the auricle reached the main AV bundle, but failed to reach its "right lateral" connexion. It is possible then that the ventricle would excite the ventricular end of this right lateral connexion, not finding it refractory as it normally would at such a time. The wave spreading then to the auricle might be expected to circulate around the path indicated."[14]

Mines added that the rhythm might become self-sustaining and in so doing would provide "…a type of rhythm known to occur both under experimental conditions and in disease."[14]

In fact, Mines described the Wolff-Parkinson-White (WPW) syndrome 16 years before the authors whose name it bears reported that selfsame arrhythmia. And many investigators who followed failed to link Mines' seminal observations to the mechanism of the arrhythmia. Not until the 1960s was the record set straight, based on the work of the Durrer group in Amsterdam and the Sealy group in Durham.

A fitting comment on the failure of so many authors to recognize Mines' discovery and the pivotal role it played in our knowledge of arrhythmias was that attributed to Carl Wiggers, "To enjoy the thrill of discovery, don't go to the library."

Thomas Lewis

Thomas Lewis *(Figure 7)* was born in 1881, studied medicine at University College, Cardiff, and University College Hospital, London, and joined the staff of the London Chest Hospital in 1907. In 1909, James MacKenzie persuaded Lewis to become the founding editor of the *British Heart Journal* (now *Heart*), the journal that published most of his subsequent research.

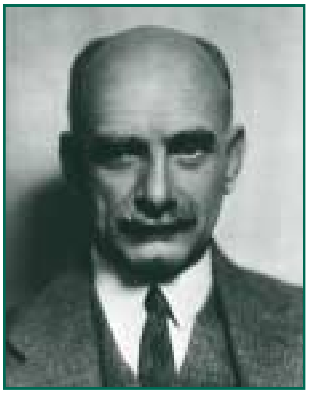

Figure 7. *Sir Thomas Lewis.*
© Wellcome Library.

We have already mentioned Lewis' letter to Einthoven in 1908, asking for a reprint of the telecardiogram manuscript. This communication marked the onset of a lifelong friendship between the two.[12] It also marked the beginning of Lewis' efforts to record not only the ECG, but the sequence of activation that occurred in the heart during cardiac arrhythmias. The coming of the Great War postponed some experiments by a few years, and Lewis published his first atrial mapping experiments in 1920. This paper was a watershed in his thinking, for the following reason: although Mines and Garrey had independently described circus movement in great detail, Lewis was not initially a devotee of the circus movement concept. Rather, he "leaned to the view that irritable foci in the muscle underlay tachycardia and fibrillation," a view he restated in his book *The Mechanism and Graphic Registration of the Heart Beat* (Lewis 1920). Nonetheless, he published an addendum dated May 1920, as follows:

> In observations recently completed and as yet unpublished, we have observed much direct evidence to show that atrial flutter consists essentially of a single circus movement… the hypothesis which Mines and Garrey have advocated now definitely holds the field.

Yet, after 1920, Lewis' interest in electrocardiography waned, and he began to study the peripheral circulation. His professed to being "weary of being tied to an instrument… the 'cream was off'… there were no new things to be discovered in the field of electrocardiography."[12] Lewis' 1933 book, *Diseases of the Heart,* paid only passing attention to the ECG.

Lewis was knighted in 1921, suffered his first myocardial infarct in 1927, remained active despite advancing coronary artery disease, and died of a myocardial infarction in 1945.

Frank N. Wilson and David Scherf

Although they never worked together and in fact had different viewpoints and different approaches to electrocardiographic and arrhythmia research, we consider Wilson and Scherf together as they were not only unique scientists, but important transitional figures. Both were born in the same decade (Wilson in 1890 in Michigan, Scherf in 1899 in the Austro-Hungarian Empire) Wilson died in 1952, Scherf in 1977. Wilson received his MD degree from the University of Michigan in 1913. He obtained a string galvanometer in 1914, and commenced a lifetime of electrocardiographic and vectorcardiographic research. Thomas Lewis was a major influence on Wilson, not only because of Lewis' eminent position in electrocardiography at the beginning of Wilson's career, but also because he was the commander of the English rehabilitation hospital at which Wilson was stationed during World War I. In the 1920s to early 1930s, Wilson's research into bundle branch block, ventricular hypertrophy, body surface distribution of electrical potentials, the ventricular gradient, and electrocardiographic theory culminated in his introduction of precordial leads into electrocardiography. Not only was he the leading electrocardiographic researcher of his time, but he was also a bridge between the early scientists in the field (Einthoven and Lewis) and the practitioners of modern electrocardiography.

Scherf graduated from the University of Vienna Faculty of Medicine, where he studied under Wenckebach. On the ascendancy of fascism, he moved to New York, where he chaired the Cardiology Division at New York Medical College until his retirement. He then remained active in teaching, especially in New York, where he was a source of inspiration to, among others, Brian Hoffman, Paul Cranefield, and their students. Scherf was both an outstanding animal experimentalist and an early "translational scientist" carrying his experimental work to the bedside. In 1932, he and Holzmann suggested the short PR interval and delta wave of WPW syndrome were likely the result of conduction through an accessory pathway. Earlier, he had described Wenckebach periodicity in the bundle branches, and made a number of observations regarding functional longitudinal dissociation. He had a long interest in parasystole and performed a number of thought-provoking experiments relating to focal origin of ectopic impulses and of atrial fibrillation. His numerous publications were capped by his coauthorship with Adolf Schott of *Extrasystoles and Allied Arrhythmias,* whose second edition, in 1973, remains a classic reference.

NEW GROWTH: BEGINNING OF THE MODERN ERA OF ARRHYTHMOLOGY

The individuals we discuss were not only outstanding investigators in their own right, but were recognized in an informal survey (see acknowledgements) as founders of the modern schools of arrhythmology. In selecting them we have deliberately not listed those whose contributions might have been thought of as largely clinical (eg, Louis Katz, Alfred Pick, Richard Langendorf, Mauricio Rosenbaum) or largely in the basic sciences (eg, Denis Noble). Rather, these are all individuals who have “bridged the gap,” between that which is basic and that which is clinical. The only possible exception to the statement regarding bridging the gap is Silvio Weidmann, who, in a field of godfathers, is generally considered the “capo di tutti capi.” In addition to Weidmann, we include Gordon Moe, Brian Hoffman (partnered with Paul Cranefield) and Dirk Durrer.

Silvio Weidmann

Swiss-born Weidmann (1921-2005; *Figure 8*) worked in the department of physiology of the University of Berne from 1951 to 1986, and chaired it from 1968-1986. Although his interest was basic physiology rather than electrocardiography/arrhythmias, his studies were central to the development of approaches that translate basic to clinical research. Weidmann’s direction in science was crystallized during a visit to the laboratory of Alan Hodgkin in Cambridge in 1948. (Hodgkin shared the 1963 Nobel Prize with Andrew Huxley and John Eccles for their work on the ionic mechanisms underlying neuronal action potentials). Hodgkin had learned how to pull glass microelectrodes from Gilbert Ling in Chicago, and refined the recording technique. He told Weidmann: “Here is a powerful tool. Prod around in nature, but keep skeletal muscle reserved for me.”[16] Weidmann later wrote: “A remark by Hodgkin, in 1949, is still in my ears: You can now rediscover the whole of cardiac electrophysiology.”[16] In retrospect, some of Weidmann’s contributions might be called rediscoveries, such as the confirmation that the cardiac action potential has an overshoot, which had been proposed by Engelmann et al in 1873,[17] but his originality and the elegance of his techniques make him one of the founding fathers of cardiac cellular electrophysiology. He and Edouard Coraboeuf from the Sorbonne were the first, in 1949, to record transmembrane potentials of cardiac fibers with microelectrodes. Among Weidmann’s subsequent contributions, the most important are probably the demonstration that the availability of the rapid inward sodium current is dependent on the level of the membrane potential, the cable analysis of ventricular muscle, and, above all, the proof that the heart functionally behaves as a syncytium. In the latter study, Weidmann showed, by measuring the diffusion of radiopotassium, that the intercalated disk has a low resistance, allowing the longitudinal flow of ions, and other small molecules, from cell to cell.

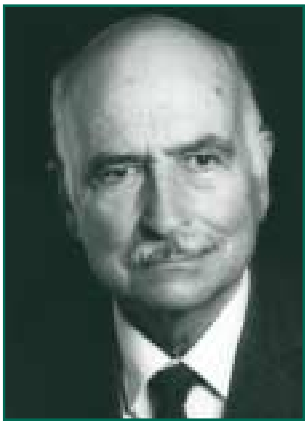

Figure 8. *Silvio Weidmann in 2001. © Universität Bern*

Dirk Durrer

Dirk Durrer *(Figure 9)* was born in 1918 in the Netherlands, and died in 1984 in Amsterdam. In 1957, he became the first professor of cardiology at the University of Amsterdam. One of Durrer’s enduring characteristics was his insistence on bridging basic and clinical science. A key element in his career was his collaboration with the physicist L. H. van der Tweel. In the early 1950s, van der Tweel designed and built a 4-channel oscilloscope, allowing photographic recordings of extracellular electrograms. In articles published in the *American Heart Journal* in 1953 and 1954, Durrer and van der Tweel described the spread of activation in the canine left ventricular wall, and settled the question of which deflection in both unipolar and bipolar electrograms reflects local activation.[18] Further contributions included the 1961 demonstration of delayed, fractionated activity, proving the persistence of electrical activity in a healed infarct, and intraoperative mapping in 1967, identifying the earliest excited epicardial area in a patient with WPW syndrome.[19] Perhaps the most influential paper is the 1967 study on the role of electrically induced premature beats on the initiation and termination of tachycar-

Figure 9. *Dirk Durrer.*

Reprinted from: A tribute to Dirk Durrer. Int J Cardiol. *1984;6: 749-773. Copyright © 1984, Elsevier Science.*

dias in patients with WPW syndrome.[20] Independently, the group of Philippe Coumel and Robert Slama in Paris published in the same year another study on the use of electrical stimuli to investigate arrhythmia mechanisms in patients.[21] These two papers mark the beginning of the era of programmed electrical stimulation, and form the seeds of another formidable tree.

Gordon K. Moe

Gordon Moe was awarded his PhD degree from the University of Minnesota in 1940, trained with Carl Wiggers at Case Western Reserve University, and subsequently received the MD degree at Harvard. From 1943 to 1950, he was on the faculty of the University of Michigan, where his career overlapped that of Frank Wilson. The remainder of Moe's academic career was first at the State University of New York at Syracuse and then, from 1960 until his death in 1989 as Director of Research at the Masonic Medical Research Laboratory in Utica, New York. Moe's major contributions to research on arrhythmias were in our understanding of reentry. He conceived of the multiple wavelet hypothesis, which explored the interaction of reentrant circuits in fibrillating chambers. He brought to this work not only a keen understanding of physiology, but of modeling as well. This carried over to his research on other conduction abnormalities such as reflection as well as to abnormalities of impulse initiation. The work of the Moe laboratory on delayed afterdepolarizations in the early 1970s was concurrent with that of the Hoffman laboratory on the same phenomenon. The net result of both laboratories' efforts was the understanding that arrhythmias not only are caused by abnormal automaticity or abnormal conduction, as had been the gospel until then, but that afterdepolarizations and resultant triggered activity were important as well. Both laboratories were to acknowledge the root of this work in earlier studies by Segers and by Bozler in the late 1930s and early 1940s as well as the major contributions of David Scherf and associates to our clinical understanding of triggered activity.

Brian F. Hoffman

Brian Hoffman received his MD degree from the Long Island College of Medicine in 1947 and joined the faculty of the department of physiology of the SUNY Downstate Medical Center in 1949. In 1963, he was appointed Professor and Chairman of Pharmacology at Columbia University, a position he held until his retirement in 1995. Hoffman's cellular electrophysiologic studies of sinus node characteristics and AV conduction are among the significant early experiments that demonstrated the function of these sites in the conduction system. In his laboratory, techniques for His bundle recording and pacing and the means for extracellular recording of electrical activity were developed to a point where his former student, Benjamin Scherlag, working with Anthony Damato, could consistently record His bundle activity in human subjects[22] (independent work on the subject was earlier reported by Paul Puech and associates). With several colleagues, notably Paul Cranefield, Hoffman described cellular mechanisms by which slow conduction, summation, and reentry could occur in small bundles of cardiac fibers. Prior to these studies, reentry had a sound basis experimentally (ie, it had been studied extensively in nonmammalian and to a lesser extent in mammalian tissue), but the cellular mechanisms that permitted it to occur in the intact heart had not been recognized. Hoffman also worked extensively in the field of antiarrhythmic pharmacology, contributing importantly to our information in that arena. His 1960 book, *Electrophysiology of the Heart,* coauthored with Paul Cranefield, remains one of the classic publications in electrophysiology.

AND NOW THE FOREST....

A little-known byproduct of the Vietnam War was the impetus it gave to clinical electrophysiology in the United States, when many who became leaders in clinical electrophysiology spent their military service time in the US Public Health Service, in the clinical laboratory of Anthony Damato in Staten Island. The worldwide growth of the field has been to a degree that Einthoven predicted, but that would have amazed Waller and even Lewis. The application of electrophysiologic techniques to the development of pacemakers and cardioverter-defibrillators—based in large part on the work of Zoll, Mirowski, Lown, and others—and the impressive benefits these inventions have brought to society are now readily appreciated. It is estimated that nearly 1 000 000 devices per year are implanted worldwide annually, each with the potential to save and prolong a life. This observation permits us to come full circle and to conclude with a quote from Einthoven's Nobel Prize lecture. His words not only say much about Einthoven, the man, but say so much about our scientific discipline, its core, and the people in it:

> A new chapter has been opened in the study of heart diseases, not by the work of a single investigator, but by that of many talented men, who have not been influenced in their work by political boundaries and, distributed over the whole surface of the earth, have devoted their powers to an ideal purpose, the advance of knowledge by which, finally, suffering mankind is helped.

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