# PREFACE

There are a number of excellent books on molecular biology, single-channel electrophysiology, animal experimentation, and clinical electrophysiology. However, the past decade has seen an explosion of knowledge and radical changes in our understanding of ventricular repolarization as an integral part of the cardiac electrophysiologic matrix; a topic which, until now, has not been covered in depth. *Cardiac Repolarization: Bridging Basic and Clinical Science* presents comprehensively the latest developments in the field of cardiac electrophysiology with a focus on the clinical and experimental aspects of ventricular repolarization, newly discovered clinical repolarization syndromes, electrocardiographic phenomena, and their correlation with the most recent advances in basic science.

Repolarization has distinct adaptive mechanisms that are responsible for maintenance of electrophysiological equilibrium and electrical stability of the heart under normal and pathophysiological conditions. Both congenital and acquired abnormalities of ventricular repolarization have recently received significant recognition because these are major contributors of life-threatening cardiac arrhythmias and are an important target for antiarrhythmic drugs and interventions. We have aimed to provide unique prospective views on ventricular repolarization by emphasizing the clinical and basic aspects of physiology and pathophysiology in conjunction with new clinical findings and research discoveries. The authors have provided a thought-provoking and enlightening review of the latest research and clinical accomplishments in their areas of expertise. Each chapter is outlined with objectives, key points, current perspectives, and recommendations for future investigations. Each chapter includes established and evidence-based knowledge, the authors' personal opinions, areas of controversy, and future trends. We aimed to provide a contemporary and succinct distillation of the current status of cardiac repolarization. Although some of the areas are highly subspecialized, this book has been designed for a broad audience ranging from medical and graduate students to clinicians and scientists.

*Cardiac Repolarization: Bridging Basic and Clinical Science* is organized so as to make the large volume of rapidly evolving information understandable and easy to assimilate, with each section focusing on a theme of cardiac repolarization. The spectrum of ventricular repolarization, historical milestones of electrical signal recording, and their relevance to clinical arrhythmias and sudden cardiac death syndromes are presented as an introduction. Part II focuses on the theme of basic mechanisms underlying ventricular repolarization. In addition to an overview of electrophysiology, pharmacology, and molecular biology underlying ventricular repolarization, basic mechanisms have been integrated with specific disease conditions, including heart failure, ischemia, long QT syndrome, and Brugada syndrome. The theme of Part III includes clinical physiology and pathophysiology of ventricular repolarization; state-of-the-art information on human cardiac repolarization with an emphasis on clinical application; challenges and clinical relevance of the dynamic interactions of neurohumeral and pharmacological factors; and

a peek into the future of antiarrhythmic drug development based on molecular and electrophysiological properties. Part IV of the book provides a comprehensive review of the clinical presentation and management of specific cardiac repolarization conditions, including early repolarization and short QT interval, Brugada syndrome, long QT syndrome, and sudden infant death syndrome.

The editors of *Cardiac Repolarization: Bridging Basic and Clinical Science* wish to recognize the significant contribution made by all of the authors. The book is the result of a collaboration that has brought together the skills and perspectives of researchers, scientists, and clinicians. We also wish to thank all of our mentors, without whom the work presented in the book would not have been realized. Finally, we are grateful to our colleagues, trainees, and students for stimulating interactions that have served as the basis for many innovative ideas and investigations.

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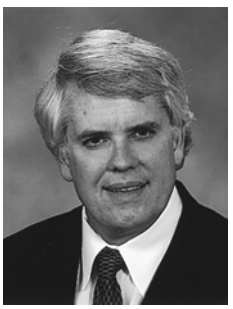

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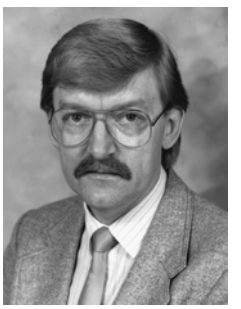

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# 2 Historical Milestones of Electrical Signal Recording and Analysis

*Thorsten Lewalter, MD*
*and Berndt Lüderitz, MD*

***CONTENTS***



## HISTORY OF THE HUMAN ELECTROCARDIOGRAM AND VENTRICULAR REPOLARIZATION

### *The Human Electrocardiogram*

Aside from the discovery of the cardiac conduction system (Table 1) and advancements in the electrotherapy of cardiac arrhythmias (Table 2), the development of electrocardiography was the key issue for a more detailed understanding of arrhythmogenesis as a cause and correlate of cardiac disorders (Table 3). After the first documentation of a cardiac action potential by *Rudolph von Koelliker* and *Heinrich Müller* in 1856, two decades later *Augustus Desiré Waller* (Fig. 1) recorded the first human electrocardiogram. After qualifying as a medical doctor Waller joined the department of physiology at the University of London where he studied in *John Burdon Sanderson's* laboratories the electrical activity of the excised mammalian heart. In 1884 he was appointed lecturer in physiology at St. Mary's Hospital London where he used a capillary electrometer, an instrument invented 15 yr earlier by the French scientist *Gabriel Lippmann*, to record cardiac potentials in animals (Fig. 2). In 1887, he was able to obtain the first human electrocardiogram from the body surface and published his findings in the *Journal of Physiology*: "A demonstration on man of electromotive changes accompanying the hearts beat *(45)*." Waller also proved that the electrical phenomenon preceded the muscle contraction, thus excluding the possibility that the recorded activity was only an artifact. Furthermore, he recognized that it was not essential for the recording that the electrodes

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**Table 1**
**Discovery of the Sinus Node and the Cardiac Conduction System**

| | | |
|---|---|---|
| 1845 | Purkinje fibers | J.E. Purkinje *(1)* |
| 1865/1893 | Bundle of Kent | G. Paladino and A.F.S. Kent *(2)* |
| 1893 | Bundle of His | W. His, Jr. *(3)* |
| 1906 | AV node | L. Aschoff and S. Tawara *(4)* |
| 1906/1907 | Wenckebach bundle | K.F. Wenckebach *(5)* |
| 1907 | Sinus node | A.B. Keith and M.W. Flack *(6)* |
| 1916 | Bachmann bundle | J.G. Bachmann *(7)* |
| 1932 | Mahaim fibers | I. Mahaim *(8)* |
| 1961 | Bundle of James | T.N. James *(9)* |

**Table 2**
**Historical Perspectives on Electrotherapy of Cardiac Arrhythmias**

| | |
|---|---|
| 1580 | Mercuriale, G. (1530–1606): Ubi pulsus sit rarus semper expectanda est syncope *(10)* |
| 1717 | Gerbezius, M. (1658–1718): Constitutio Anni 1717 a.A.D. Marco Gerbezio Labaco 10. Decem. descripta. Miscellanea Emphemerides Academiae Naturae *(11)* |
| 1761 | Morgagni, G.B. (1682–1771): De sedibus et causis morborum per anatomen indagatis *(12)* |
| 1791 | Galvani L., (1737–1798): De viribus electricitatis in motu musculari commentarius *(13)* |
| 1800 | Bichat, M.F.X. (1771–1802): Recherches physiologiques sur la vie et la mort *(14)* (Physiologic study on life and death) |
| 1804 | Aldini G. (1762–1834): Essai theorique et experimental sur le galvanisme, avec une serie d'experiences faites en presence des commissaires de l'institut national de France, et en divers amphitheatres de Londres *(15)* (Theoretical and experimental essay on galvanism with a series of experiments conducted in the presence of representatives of the National Institute of France at various amphitheatres in London) |
| 1827/1846 | Adams R. (1791–1875); Stokes, W. (1804–1878): Cases of diseases of the heart accompanied with pathological observations; Observations of some cases of permanently slow pulse *(16,17)* |
| 1872 | Duchenne de Bologne, G.B.A. (1806–1875): De l'ectrisation localisée et de son application à la pathologie et à la thérapeutique par courants induits et par courants galvaniques interrompus et continues *(18)* (On localized electrical stimulation and its pathological and therapeutic application by induced and galvanized current, both interrupted and continuous) |
| 1882 | von Ziemssen, H. (1829–1902): Studien über die Bewegungsvorgänge am menschlichen Herzen sowie über die mechanische und elektrische Erregbarkeit des Herzens und des Nervus phrenicus, angestellt an dem freiliegenden Herzen der Catharina Serafin *(19)* (Studies on the motions of the human heart as well as the mechanical and electrical excitability of the heart and phrenic nerve, observed in the case of the exposed heart of Catharina Serafin) |
| 1890 | Huchard, H.: La maladie de Adams-Stokes (Adams-Stokes Syndrome) |
| 1932 | Hyman, A.S.: Resuscitation of the stopped heart by intracardial therapy. II. Experimental use of an artificial pacemaker *(20)* |
| 1952 | Zoll, P.M.: Resuscitation of heart in ventricular standstill by external electrical stimulation *(21)* |

*(Continued)*

Table 2 (*Continued*)
Historical Perspectives on Electrotherapy of Cardiac Arrhythmias

| | |
|---|---|
| 1958 | Elmquist, R., Senning A.: An implantable pacemaker for the heart *(22)* |
| 1958 | Furman S., Robinson G.: The use of an intracardiac pacemaker in the correction of total heart block *(23)* |
| 1961 | Bouvrain, Y., Zacouto, F.: L'entrainment électrosystolique du coeur *(24)* (Electrical capture of the heart) |
| 1962 | Lown, B. et al.: New method for terminating cardiac arrhythmias *(25)* |
| 1969 | Berkovits, B.V. et al.: Bifocal demand pacing *(26)* |
| 1972 | Wellens, H.J.J. et al.: Electrical stimulation of the heart in patients with ventricular tachycardia *(27)* |
| 1975 | Zipes, D.P. et al.: Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium *(28)* |
| 1978 | Josephson, M.E. et al.: Recurrent sustained ventricular tachycardia *(29)* |
| 1980 | Mirowski, M. et al.: Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings *(30)* |
| 1982 | Gallagher, J.J. et al.: Catheter technique for closed-chest ablation of the atrioventricular conduction system: A therapeutic alternative for the treatment of refractory supraventricular tachycardia *(31)* |
| 1982 | Scheinman, M.M. et al.: Transvenous catheter technique for induction of damage to the atrioventricular conduction system *(32)* |
| 1982 | Lüderitz, B. et al.: Therapeutic pacing in tachyarrhythmias by implanted pacemakers *(33)* |
| 1985 | Manz, M. et al.: Antitachycardia pacemaker (Tachylog) and automatic implantable defibrillator (AID): Combined use in ventricular tachyarrhythmias *(34)* |
| 1987 | Borggrefe, M. et al.: High frequency alternating current ablation of an accessory pathway in humans *(35)* |
| 1988 | Saksena, S., Parsonnet, V.: Implantation of a cardioverter-defibrillator without thoracotomy using a triple electrode system *(36)* |
| 1991 | Jackman, W.M. et al.: Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current *(37)* |
| 1991 | Kuck, K.H. et al.: Radiofrequency current catheter ablation of accessory pathways *(38)* |
| 1994 | Daubert, C. et al.: Permanent atrial resynchronisation by syncronous bi-atrial pacing in the preventive treatment of atrial flutter associated with high degree interatrial block *(39)* |
| 1994 | Cazeau, S. et al.: Four chamber pacing in dilated cardiomyopathy *(40)* |
| 1995 | Camm, A.J. et al.: Implantable atrial defibrillator *(41)* |
| 1997 | Jung, W. et al.: First worldwide implantation of an arrhythmia management system *(42)* |
| 1998 | Haissaguerre, M. et al.: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins *(43)* |
| 1999 | Josephson, M. et al: Hybrid pharmacologic and ablative therapy: a novel and effective approach for the management of atrial fibrillation *(44)* |

are applied to the subject's chest, he wrote: "if the two hands or one hand and one foot be plunged into two dishes of salt solution connected with the two sides of the electrometer, the column of though less than when the electrodes are strapped to the chest." Waller demonstrated his recording technique at the First International Congress of Physiologists in Basel, Switzerland 1889 where young researchers like *William Bayliss, Edward Star-*

**Fig. 1.** Augustus Desiré Waller (1856–1922) with his laboratory dog named Jimmie. Augustus Desiré Waller was born in Paris as the son of the celebrated British physiologist Augustus Volney Waller, discoverer of the Wallerian degeneration of nerves. After qualifying in medicine at Aberdeen, Scotland and post-graduate studies under Carl Ludwig in Leipzig and John Burdon Sanderson in London he became lecturer in physiology at St. Mary's Hospital in London in 1884. He was Fellow and Croonian lecturer of the Royal Society of London and Laureat of the Institute of France and awarded the Montyon Medal of the French Academy of Science. A.D. Waller is buried in Finchley cemetery, London.

**Table 3**
**Chronology of Electrocardiography**

| | | |
|---|---|---|
| 1887 | First human ECG | A.D. Waller *(45)* |
| 1902 | Surface lead ECG | W. Einthoven *(46)* |
| 1906 | Esophageal ECG | M. Cremer *(47)* |
| 1933 | Unipolar chest wall leads | F.N. Wilson *(48)* |
| 1936 | Vector electrocardiography | F. Schellong *(49)* |
| 1938 | Small triangle F" (RA, LA, RL) | W. Nehb *(50)* |
| 1942 | Unipolar amplified extremity leads | E. Goldberger *(51)* |
| 1956 | Corrected orthogonal lead systems | E. Frank *(52)* |
| 1960 | Intracardial leads | G. Giraud and P. Puech *(53)* |
| 1969 | His bundle ECG | B.J. Scherlag *(54)* |

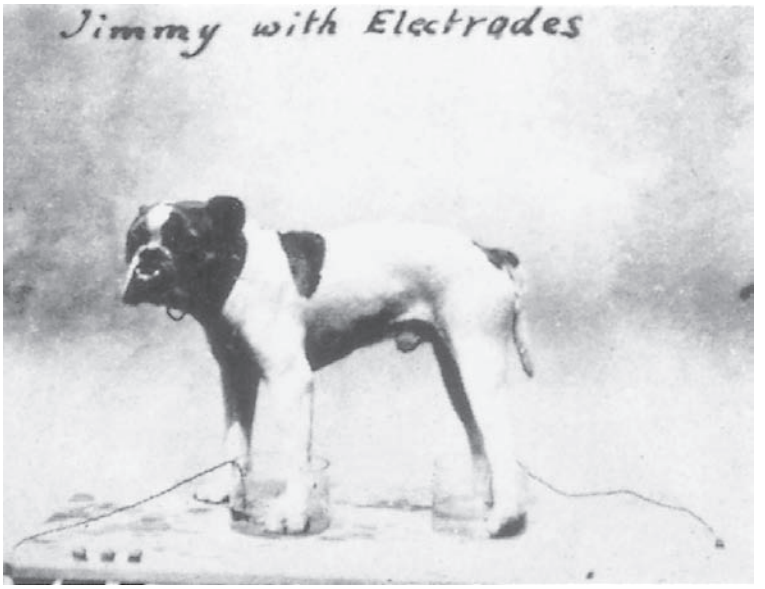



**Fig. 2.** Dog "Jimmie" on the Waller table. Waller's experiments and demonstrations were in part done with his pet bulldog "Jimmie" who was trained to stand quietly with two legs in pots of normal saline.

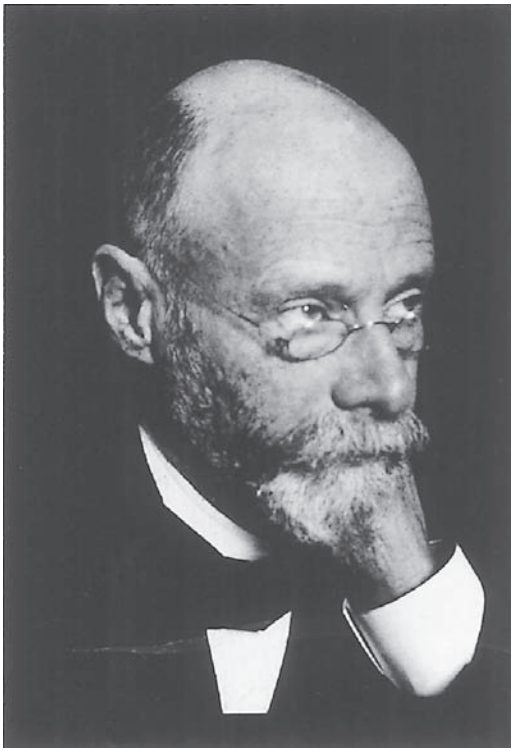


**Fig. 3.** Willem Einthoven (1860–1927) was born on May 21, 1860, the son of a military doctor in Semarang on the island of Java. After the death of his father, the family returned to the Netherlands in 1870, where Einthoven finished school and started medical school at the University of Utrecht in 1879. There he earned his doctorate in 1885. The same year he became a professor of physiology and histology at the University of Leiden. Einthoven held that position until his death on September 28, 1927.

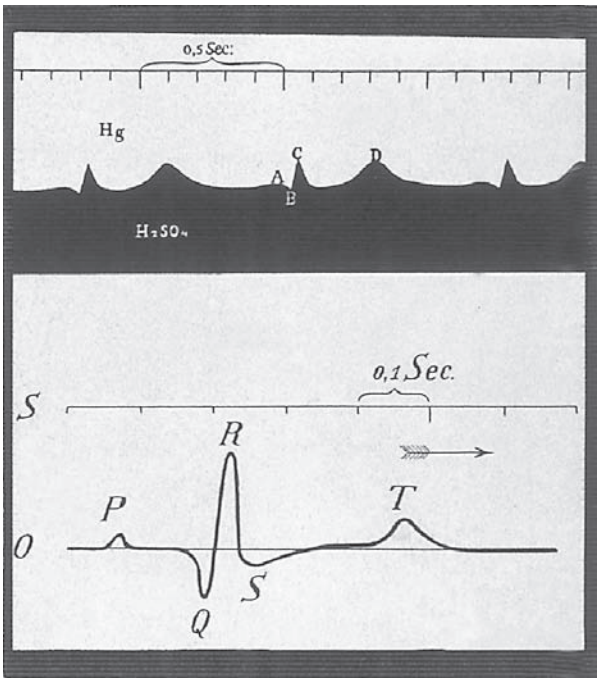



**Fig. 4.** Einthoven's first ECG tracings. Recording of an ECG with A, B, C and D wave using a capillary electrometer (upper registration). The lower ECG registration is Einthoven's first published electrocardiographic tracing using a string galvanometer and a different nomenclature with P, Q, R, S, and T wave.

*ling*, and *Willem Einthoven* were in the audience. *Willem Einthoven* (Fig. 3), a Dutch physiologist was stimulated by the presentation of Waller to further investigate cardiac electrical activity. Owing to the poor frequency response of the Lippmann capillary electrometer, Einthoven tried to refine this method for the application in cardiac electrophysiology. Using complex mathematical and physical maneuvers he succeeded in recording higher frequency curves and described the results in his first paper on the subject in 1895 *(55)*. Initially Einthoven identified four distinct waves on the electrocardiogram (Fig. 4, A–D). However, he finally turned to another technical approach and modified the string galvanometer, an apparatus recently and independently invented by the French physicist *Arsène D'Arsonval* and the engineer *Clement Ader (56)*. Einthoven's string galvanometer and his first recording were described in 1902 in a "Festschrift" for the Dutch physician Samuel Rosenstein (Fig. 4) *(57)*. In the following years he published several papers coming from his early experiences in recordings from 6 persons to a first structured overview about normal and abnormal electrocardiograms in patients from the University Hospital Leiden including atrial fibrillation, ventricular premature contractions, ventricular bigemini, and atrial flutter *(58–60)*.

Even though Einthoven's 600-pound apparatus was large and cumbersome, clinical researchers like *Thomas Lewis* quickly started to use it for the study and characterization of disorders in cardiac impulse formation and conduction including measurements of the myocardial depolarization and repolarization (Fig. 5). Parameters like PQ-, QRS- or QT-interval were investigated and in part identified as rate dependent *(61)*. *Bernhard*

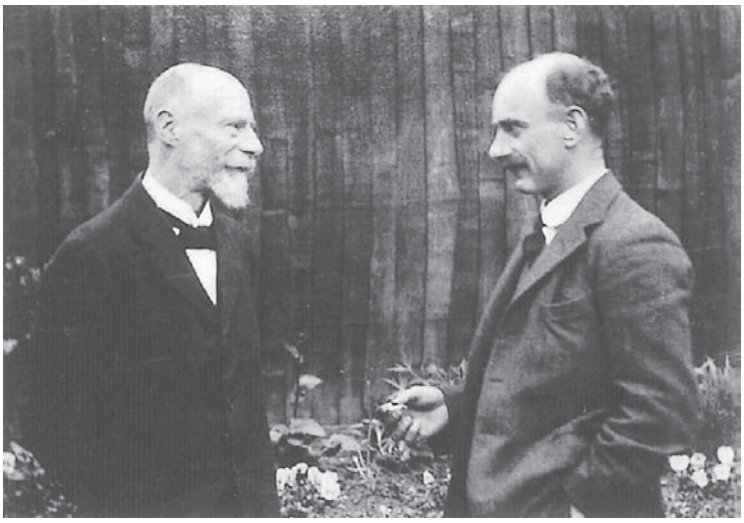


**Fig. 5.** Willem Einthoven and Sir Thomas Lewis in 1921.

**Fig. 6.** Dirk Durrer (1918–1984).

*Lüderitz* for example analyzed in 1938 the QRS duration in relationship to the actual heart rate in 500 electrocardiograms in control subjects *(62)*.

A more detailed approach to arrhythmias became available with the introduction of invasive electrophysiologic procedures which base as a heart catheter technique on the historical maneuver performed by *Werner Forssmann (63)*. Following this pioneer, *Scherlag* described the first intracardiac catheter recordings of the His-bundle in 1969 *(64)*,

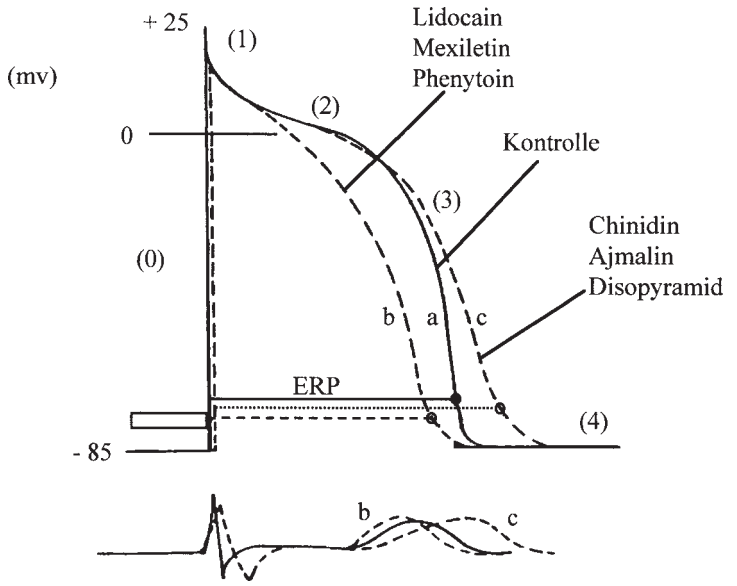



**Fig. 7.** Antiarrhythmic drug effects on the ventricular action potential. Effects of various antiarrhythmic drugs on the ventricular action potential. The unbroken line (a) represents the control state. The circles indicate the level of repolarization at which the fiber becomes reexcitable (ERP = effective refractory period). Action potential duration and the QT-interval are prolonged in b under the effect of Quinidine or Procainamide and shortened when exposed to Lidocain (c) *(73–75).*

whereas *Dirk Durrer* and *Henrick JJ Wellens* were the first who executed programmed stimulation in men (Fig. 6) *(65,66)*. The programmed stimulation technique has in first-line been used to induce ventricular tachycardia and to elucidate the mechanisms of tachycardias in the Wolff-Parkinson-White-Syndrome *(67)*. Electrophysiologic testing was then more and more used to guide pharmacological therapy and to delineate the electrophysiologic effects of drugs on the normal and diseased myocardium *(68)*. The registration of the action potential in the experimental laboratory and in the intact human heart via catheter technique did substantially change our mechanisms in cellular de- and repolarization *(69–71)*, antiarrhythmic drug effects (Fig. 7) *(72–75)*, and arrhythmogenesis *(76,77)*.

## *History of Repolarization*

In the late 18th century the Italian scientist *Felice Fontana* described a phenomenon later called the refractory period while he was investigating irregular impulses of the heart *(78)*. Subsequently, *Moritz Schiff*, a German physiologist (Fig. 8), reported in 1850 that a strong electrical stimulus that has been delivered during the late refractory period of cardiac muscle could induce a contraction. Confirmation of these findings was achieved by *Hugo Kronecker* and the French physiologist *Etienne Jules Marey*, who performed a first documentation of phenomenons like premature ventricular beats using a polygraph recording of the radial and apical impulse simultaneously *(79)*. Schiff's, Kroneckers's, and Marey's experiments have been completed by the work of *Anton Carlson*, an American physiologist, who established the still accepted concept of absolute and relative

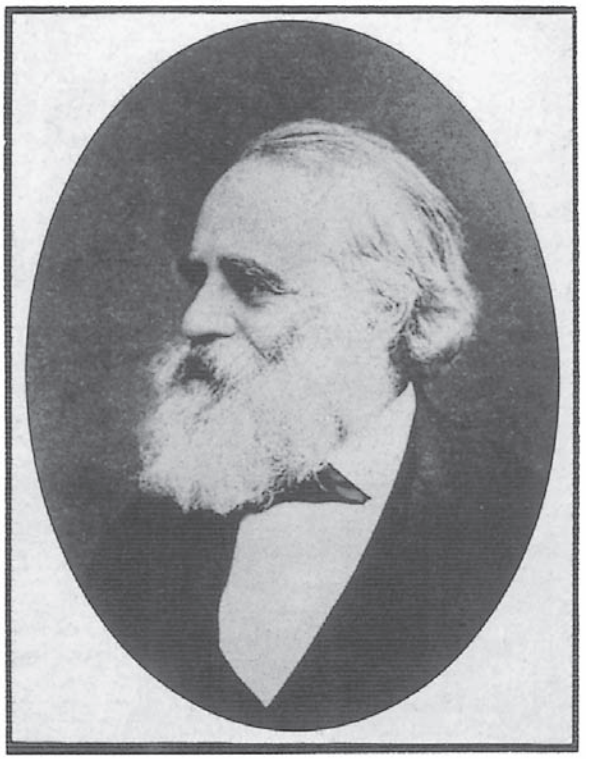


**Fig. 8.** Moritz Schiff (1823–1896).

refractory periods in cardiac tissue *(80)*. In 1920 *Bazett* described the relationship between rate and the duration of the QT-interval in 39 normal subjects *(81)*. He summarized, that the QT interval varies with the square root of the cycle length:

$$QT\,(s) = k(_{constant}) \times \sqrt{R\text{-}R}\,(s)$$

The constant k has been fixed to 0.37 in men and 0.4 in women by *Bazett*. Later on *Shipley* and coworkers changed these values to 0.397 and 0.415 respectively after investigating 200 normal subjects *(82)*. Today, the Bazett calculation is generally used as $QT_c = QT\sqrt{R\text{-}R}$. Thus the $QT_c$-interval is corrected or normalized to the QT interval at a heart rate of 60 beats/min. Several attempts have been made since to modify or substitute the Bazett calculation to gain a still better expression of the cardiac physiology. *Fridericia* for example proposed a cube root formula in 1920 after analyzing 50 normal subjects where $QT = k(_{constant}) \times \sqrt[3]{R\text{-}R}$ *(82)*. However, comparing the cube root formula to the normal range of the QT interval, this calculation gives too short intervals at low rates and too long intervals at high rates. Subsequently, *Ashman* proposed a logarithmic formula in 1942 with $QT = k_1 \times \log (10 \times [R\text{-}R + k_2])$ with the disadvantage of this type of calculation again exhibiting too low intervals at low heart rates *(83)*. A straight-line formula has also been discussed by various investigators *(84–88)*, however the Bazett calculation is still the most widely accepted. It has also been Ashman who investigated the relationship of heart rate and the refractory period; he described first that aberration can be induced by prolongation of the preceding cycle, an observation which is commonly referred to as the Ashman phenomenon *(89)*.

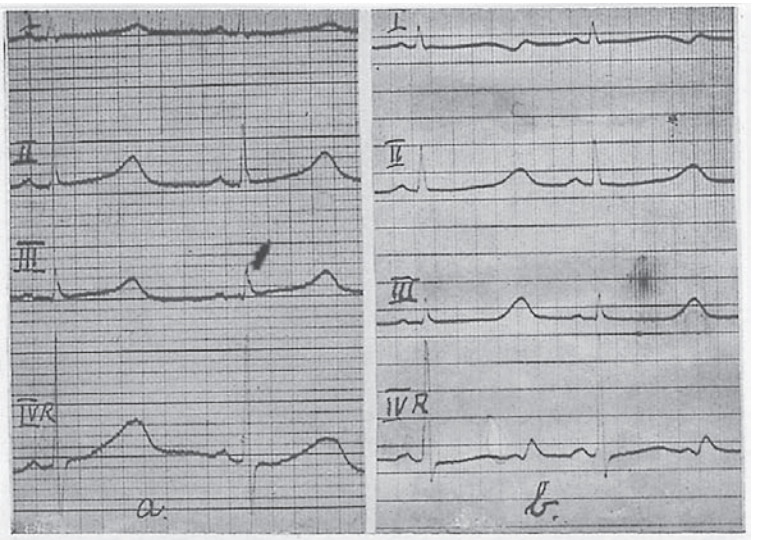



Fig. 1.—Tormod J. (*a*) ECG July 20, 1953, during rest. Leads I, II, III, IV R. Q-T = 0.50 sec. R-R = 0.88 sec. (*b*) ECG July 20, 1953, after stair-running. Leads I, II, III, IV R. Q-T = 0.60 sec. R-R = 0.86 sec.

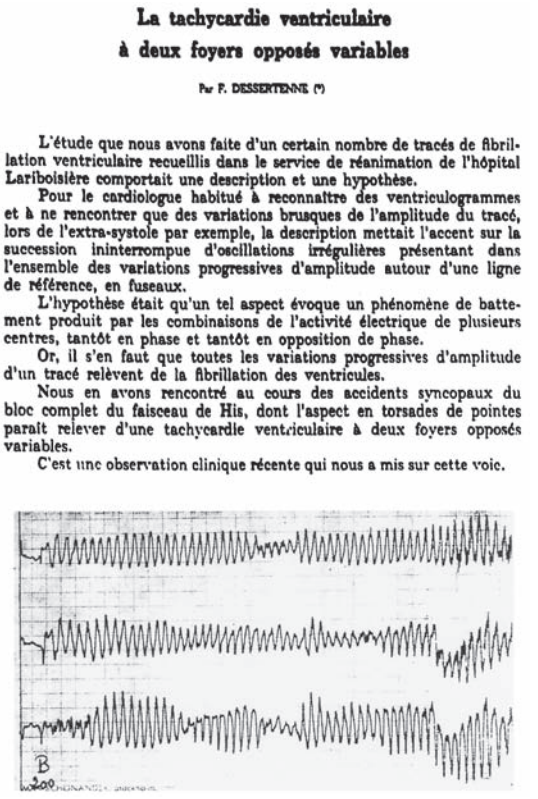
**Fig. 9.** Jervell and Lange-Nielsen syndrome. A combination of deaf-mutism and a peculiar heart disease has been observed in 4 children in a family of 6. The parents were not related, and were, as the other 2 children, who otherwise seemed quite healthy and had normal hearing. The deaf-mute children, who otherwise seemed quite healthy, suffered from fainting attacks "occurring from the age to 3 to years. By clinical and roentgen examination, which was performed in 3 of the children, no signs of heart disease could be discovered. The electrocardiograms, however, revealed a pronounced prolongation of the QT interval in all cases. Three of the deaf-mute children died suddenly at the ages of 4, 5, and 9 years respectively."

Reproduced from Jervell A, Lange-Nielsen F: Congenital deaf mutism, functional heart disease with prolongation of the QT interval, and sudden death. Am Heart J 1957;54:59–68 with permission.

*Lepeschkin* and *Surawicz* described in 1952 QT interval differences among the 12 leads of the surface ECG as a possible expression of spatial inhomogeneity of ventricular repolarization *(90)*. However, it lasted until the mid-80s until systematic investigations of the spatial inhomogeneity of repolarization were performed: *Mirvis* and colleagues studied the difference between the longest and shortest QT interval using body surface mapping in normals and patients after myocardial infarction *(91)*. The term "QT dispersion" as an expression of regional differences in myocardial repolarization has been established in clinical cardiology by *Ronald WF Campbell* and coworkers *(92)*. Even if in our days the relevance of the QT dispersion for clinical decision making is very limited owing to methodological problems and contradicting study results, it served as an important step for a better understanding of the spatial aspects of repolarization.

## HISTORY OF THE "LONG QT SYNDROME" AND "TORSADES DE POINTES" TACHYCARDIA

The *long QT syndrome* is characterized by QT interval prolongation and syncope or sudden cardiac death owing to ventricular tachyarrhythmias. The congenital form can either be familial or idiopathic *(93,94)*. The familial type consists of two subgroups:



La tachycardie ventriculaire
à deux foyers opposés variables

Par F. DESSERTENNE (*)

L'étude que nous avons faite d'un certain nombre de tracés de fibrillation ventriculaire recueillis dans le service de réanimation de l'hôpital Laribolsière comportait une description et une hypothèse.

Pour le cardiologue habitué à reconnaître des ventriculogrammes et à ne rencontrer que des variations brusques de l'amplitude du tracé, lors de l'extra-systole par exemple, la description mettait l'accent sur la succession ininterrompue d'oscillations irrégulières présentant dans l'ensemble des variations progressives d'amplitude autour d'une ligne de référence, en fuseaux.

L'hypothèse était qu'un tel aspect évoque un phénomène de battement produit par les combinaisons de l'activité électrique de plusieurs centres, tantôt en phase et tantôt en opposition de phase.

Or, il s'en faut que toutes les variations progressives d'amplitude d'un tracé relèvent de la fibrillation des ventricules.

Nous en avons rencontré au cours des accidents syncopaux du bloc complet du faisceau de His, dont l'aspect en torsades de pointes paraît relever d'une tachycardie ventriculaire à deux foyers opposés variables.

C'est une observation clinique récente qui nous a mis sur cette voie.

**Fig. 10.** Torsades de pointes tachycardia. Dessertenne first described this form of polymorphic tachycardia in 1966 when he observed this rhythm disorder in an 80-year old female patient with complete AV block *(46).*

1. The Jervell and Lange-Nielsen which is associated with deafness.
2. The Romano-Ward syndrome with normal hearing. Two classical descriptions of these functional, hereditary syncopal cardiac disorders exist *(95–98).*

*Jervell and Lange-Nielsen Syndrome.* In 1957 *Anton Jervell* and *Fred Lange-Nielsen* described a case of syncopal arrhythmia and QT prolongation combined with a profound congenital deafness in a Norwegian family with six children *(95)*. Four of the children were deaf-mutes, suffered from syncopal episodes with loss of consciousness and demonstrated a clear QT interval prolongation on their surface electrocardiograms (Fig. 9). Three of the four children with the disease died suddenly. Interestingly the parents of those children were healthy as an indicator for the recessive genetics in the Jervell and Lange-Nielsen syndrome.

*Romano-Ward Syndrome. Cesarino Romano* was born in Voghera, Italy in 1924. After his study of medicine at the University of Pavia, he worked in pediatrics at the University of Genoa. In 1961 he became a professor for pediatrics and later he served as the director of the First Pediatric Department and the Scientific Institute of the Pediatric Clinics at the University of Genoa. Among numerous publications dealing with hereditary hypothyroidism, cystic fibrosis, and cardiac disorders, he described in 1963 an inherited functional syncopal heart disorder with prolonged QT interval in a 3-mo-old female patient

("Aritmie cardiache rare dell'eta'pediatrica") *(96)*. Two brothers of his patient had exhibited the same symptoms and died suddenly at a young age. Independently of Romano, *Owen Conor Ward*, professor for clinical pediatrics at the University of Dublin, published one year later a work in Ireland entitled "*A New Familial Cardiac Syndrome in Children*." He also described syncopal attacks and a prolonged QT interval in both a young female patient and her brother *(97)*. Ward was born in Monaghan, Ireland on August 27, 1923. After completing St. Macarten's College in Monaghan, Ward studied medicine at the University College of Dublin where he passed his examinations in 1947. After his internship in various Irish hospitals, Ward specialized in pediatric medicine in 1949 and earned his doctorate in 1951 with a thesis on hypoglycemia in neonates. After that, Ward worked for a few years in a Dublin pediatric clinic. In 1972, he was made a professor of clinical pediatrics at the University of Dublin, where he has served as first professor for pediatrics since 1983.

The typical arrhythmia of patients with congenital or acquired long QT syndrome is the *torsades de pointes tachycardia*. This specific form of a dangerous polymorphic ventricular tachyarrhythmia is characterized by a repetitive change of the main QRS vector during tachycardia in the presence of a prolonged repolarization. *Dessertenne* first described the torsades de pointes morphology in an 80-yr-old female patient with intermittent AV block (Fig. 10) *(99)*. The cause of her recurring syncopal episodes was the torsades de pointes tachycardia rather than the bradycardia, as it has primarily been suspected. Dessertenne himself suggested in his description that two competing foci were responsible for the typical torsades de pointes morphology. This hypothesis has been tested in experimental animal studies, one using a porcine Langendorff heart technique by *Christoph Naumann d'Alnoncourt* and *Berndt Lüderitz* and in a canine heart *in situ* experiment from *Gust H Bardy* and *Raymond E Idecker (100,101)*. In both studies pacing from the left and right ventricular site at a similar but periodically changing rate resulted in an electrocardiogram with torsades de pointes configuration.

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