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Editorial

Defibrillation of the Ventricles

PROBABLY many can recall the retort that Faraday, the discoverer of faradic electricity, is supposed to have made when a lady of culture inquired what good his discovery could be to mankind. "Madam, what good is a baby?" According to some authorities this sage reply should be credited to Benjamin Franklin, but, regardless of origin, the story stresses the generally accepted dictum that every basic research has the potentiality of developing into useful channels.

In accordance with this philosophy, the American Heart Association has accepted the principle that the greatest hope for reduction of human suffering and for prolongation of life lies in the extension of basic knowledge of the circulation. The generous support of basic research and the launching of this journal are designed to motivate this concept. Many instances could be cited in which basic discoveries during the past half century, originally prompted by the "search of truth for truth's sake," have become the basis of practical advances in cardiology. However, no more dramatic example exists than the resuscitation of the virtually dead by the process of ventricular defibrillation.[1] As an example, more than 20 instances of successful human defibrillation have been reported by surgeons who have participated in a Training Course for Cardiac Resuscitation sponsored by the Cleveland Area Heart Society during the past two years.

The narration of basic discoveries that have led to such achievements is usually cursory, prosaic, and devoid of human interest. Consequently, neither the novice in experimental research nor the practitioner who benefits by it appreciates the incentive that drives investigators in their pursuit of basic knowledge. It therefore seems appropriate that investigators who have been behind the scenes in some instances and witnessed performances in other cases, should occasionally share some of these experiences with the present generation.

Not every research is projected because of a zeal to discover a new basic fact. Some investigations are designed for the purpose of improving technics or apparatus; others, again, must be instituted in order to surmount biologic obstacles that nature has designed to thwart disclosure of her secrets. Such a motive has stimulated and maintained the writer's interest in ventricular fibrillation ever since he first witnessed the phenomenon in 1903. The occasion arose while he was a student assistant to Cushny in Ann Arbor. The experiments then in progress involved injections of digitalis in dogs, repeated until the exposed heart fibrillated. To Cushny these were more than experiments pertaining to the pharmacology and toxicology of cardiac glucosides; they were part of his consistent program to unravel the mystery of cardiac irregularities.[2, 3] Cushny was an experimenter who never neglected the power of observation in connection with graphic registrations. He called the attention of his assistants to the irregular undulating appearance of the fibrillating heart and the palpatory sensation resembling a handful of wriggling worms. Subsequent experience has taught us, however, that such a vermicular appearance and sensation is not necessarily descriptive of ventricular fibrillation induced by

electric shock or coronary occlusion. Indeed, the process evolves through stages which, on the basis of appearance, palpation, and electrographic changes, have been characterized as tachysystolic, undulatory or convulsive, tremulous or quivering, and atonic.[4]

Circa 1907, a study of the coronary vasomotor mechanism was started which involved the use of isolated cats' hearts perfused with Locke's solution by the Langendorff method. As is well known to all who have used such preparations, the experiments are often terminated abruptly by development of ventricular fibrillation. Under such circumstances a tyro in investigation turns to his more experienced chief for counsel and advice. Warren P. Lombard, a pupil of Carl Ludwig, pointed out that the latter had given the first description of ventricular fibrillation produced by rapidly repeated electrical stimulation.[5] However, subsequent search of the literature revealed that it had been previously described by Erichsen[6] following coronary ligation in the dog.*

Having then recently returned from a meeting of the International Physiological Congress at Heidelberg, Lombard related that he had witnessed a demonstration by Hering[7] in which ventricular fibrillation in a perfused heart was arrested promptly by adding an excess of potassium to the perfusion fluid; and that normal beats gradually redeveloped as soon as the perfusate had washed out the excess potassium. A few personal trials showed that the revival by this procedure is so dramatic that it has remained a standard laboratory experiment or demonstration for our students for over 40 years. The immediate technical advantage was that the experiments on perfused hearts could be continued after such defibrillation, but the broader implication took root that ventricular fibrillation is not an irreversible process. However, another 20 years were to pass before we began to think of the possibility of utilizing this technic as a means of reviving fibrillating hearts in situ. The frequency of human death by accidental electrocution, after coronary occlusion, or during surgical operation was still not appreciated during that period. Also it seems to be a biologic fact that new basic discoveries are doomed to remain in a cocoon stage for a considerable time and only metamorphose slowly to a stage at which the idea is born that they have a practical value.

When, a little later, studies on the coronary circulation involved the dog's heart in situ the incidence of ventricular fibrillation during preparation of coronary vessels again became a real hindrance. In such periods of frustration it is always a happy event when a young investigator is able to obtain the advice of an experienced master. It was my good fortune to make the acquaintance of W. T. Porter of Harvard, an acknowledged master of meticulous experimental technic. Differences in age and experience do not hinder the development of bonds of friendship among investigators interested in similar fields. Discussions with Porter centered upon precautions in preparing coronary vessels which might prevent fibrillation, and ways in which it might be terminated should it develop. It was Porter's firm belief that the phenomena of fibrillation is not due to the effect of mechanical injury, for, in his experience, preparation of coronary arteries, per se, never produces a serious disturbance of heart action. Despite this emphasis on meticulous technic, the fact remains that occasionally premature systoles evoked during operative procedures on the heart do progress into fibrillation.

With regard to the reversibility of ventricular fibrillation, Porter's views are ably summed up in the American Textbook of Physiology[8]: "The [perfused] dog's heart can be recovered

* Experimental coronary ligation had been performed by many investigators between 1698 and 1881, the years when Cohnheim and von Schulthess-Rechberg performed their experiments, so often quoted as demonstrating the terminal nature of coronary arteries. The descriptions of those investigators merely recorded the fact that coronary occlusion leads to cardiac arrest and are therefore inexact in that they ignore a long preceding period of fibrillation. Or the investigators described abrupt cessation of the heart beat followed by fibrillation lasting 40 or 50 seconds, which is also incorrect, because no period of cardiac arrest precedes the fibrillation, the duration of which is apt to be 40 or 50 minutes. These are merely examples of failure on the part of the experimenters to observe or record accurately data which are apparently only incidental to the objective of an experiment.

by cooling the ventricles until all traces of fibrillation have disappeared and then bringing the heart back to normal temperature by circulating warmed defibrinated blood through the coronary vessels.[9] Recovery has also been obtained by passing immediately (within 15 seconds) a very rapid alternating current of not too great intensity."[10] Porter likewise called attention to the observations of MacWilliam[11] that the hearts of fowls and smaller mammals (mouse, rat, cat, rabbit, hedgehog) usually recover from fibrillation spontaneously, whereas it is usually fatal in dogs, goats, and sheep. Hearts of monkeys also frequently recover, and there are occasional reports of recovery in man.

Probably taking a cue from these observations, Garrey surmised that recovery from fibrillation is related to the mass of the myocardium, and in 1914[12] demonstrated that fibrillation stops spontaneously in small sections of tissue taken from fibrillating ventricles or auricles, presumably because the pathways then become too short for re-entry of impulses during a nonrefractory phase.

Personal interest in finding ways and means for avoiding and abrogating ventricular fibrillation in experimental work became particularly acute during cardiodynamic investigations after 1912. With the development of the optical method of recording it was frequently necessary to stab a ventricle with a cannula of an optical manometer or with an instrument for producing valvular lesions. In using such technic, one became impressed with the great resistance of the heart to injury or severe manipulation. Occasionally, however, a quick stab, a slight adjustment of a trocar, or an apparently trifling insult resulted in unexpected fibrillation. This occurred in the hearts of young and old dogs alike, in hearts in good as well as poor dynamic and nutritive states. It gradually became evident that the experiments reported by Kronecker and Schmey[13] were being repeated, with the difference that fibrillation took place without regard to the area punctured. Between 1912 and 1920, various measures and remedies were tried with the hope of avoiding such disasters in experimental work. Anesthetics were changed, dogs were cooled to 30 C. before experiments were started, cardiac nerves were stimulated or sectioned, and many drugs such as digitalis, epinephrine, quinidine, adenylic acid and potassium were administered in the hope that they might have prophylactic or curative powers. All were without obvious benefit.

Initiation of Ventricular Fibrillation. A clue as to the cause of such fibrillation was obtained in 1925 during an investigation of the reactions of the ventricles to surface stimuli.[14] It was discovered that strong shocks applied during the last 0.06 second of systole usually evoke a premature contraction during the early portion of diastole. However, all too frequently they induced ventricular fibrillation which terminated the experiment. This and similar observations made in other laboratories[15, 16, 17] strongly indicated that the end of systole constitutes a "vulnerable period."[18] Such a discovery, important in itself, was not an answer to the question as to how a stimulus falling during a supposedly refractory phase can stimulate at all, and what the physiologic processes are which lead to fibrillation. For a time the best explanation seemed to be that different fractions pass out of their refractory state at different times. Consequently, a strong stimulus delivered during the vulnerable period would find some muscular elements responsive and excite neighboring ones as they, in turn, recover their excitable state.[17] Unfortunately, further observations[19] failed to demonstrate any reduction of fibrillation threshold for premature ventricular beats in which greater asynchronicity in termination of fractionate contractions must occur. Wégria and his associates[19] therefore concluded that sensitivity to fibrillation must depend on some inherent characteristic of heart muscle during the vulnerable period. This concept was temporarily put on the shelf when Moe and his associates[20] demonstrated that a strong stimulus creates a focal area of polarization which lasts into early diastole and could therefore be a source of excitation and a means of inducing local block. However, the recent demonstration of Hoffman and his associates[21] that vulnerability to fibrillation by stimuli occurs synchronously with a pronounced dip

in ventricular excitability would seem to require reconsideration of the possibility that a functional characteristic of cardiac muscle may be concerned.

Basic Studies on Defibrillation

During the second decade of the present century it had become painfully evident that the mortality from accidental electrocution was keeping pace with the rapid extension of electrification and use of electric appliances in our homes, farms, and industries. Consequently, electric industries began to extend their support of researches previously aimed to reduce hazards of electric shock to those concerned with resuscitation from respiratory paralysis and ventricular fibrillation. One of these studies was organized at the College of Physicians and Surgeons, Columbia University, under the direction of Dr. H. B. Williams; another, with which I am more intimately acquainted, was arranged under the chairmanship of Dr. William B. Howell in 1927. Dr. Howell felt that greatest progress could probably be made within the shortest time if the problem were attacked simultaneously in two different laboratories by two investigators. Dr. Hooker and I felt complimented in being chosen as the responsible investigators. Fortunately, both of us had been conditioned by previous experience to undertake the project expeditiously but critically, independently as to plan of procedure, but cooperatively as to objective. It was our understanding that promising discoveries in either laboratory should be tested in the other, so that they could be confirmed or repudiated before publication aroused unwarranted hopes. Personally, participation in this project was not impelled by any expectation that a contribution toward human resuscitation would emerge. However, it seemed conceivable that some procedure might evolve which would at least be valuable for revival of animals under laboratory conditions, thus enabling one to continue experiments that had hitherto proved inexpedient owing to their termination by ventricular fibrillation.

The plan of attack was carefully considered. Since the chance existed that some miracle drug might be able to abolish fibrillation it was felt that screening experiments should not be ignored, but it was agreed that an experimental approach based on previous physiologic experience was apt to prove more rewarding. This turned out to be the case. Our initial attempts were guided by two proven facts: (1) Ventricular fibrillation is a reversible process. (2) Fibrillation can be abolished in isolated perfused hearts by solutions containing an excess of potassium, and normal coordinated beats automatically redevelop when this is followed by perfusion with a normal oxygenated saline solution, such as Locke's or Tyrode solution. It therefore seemed logical to approach the defibrillation problem of hearts in situ by use of a similar procedure. The technical aspects presented the challenge of devising ways and means for accomplishing this. A solution containing excess potassium must be percolated through every fragment of the myocardium when the circulation was at a standstill and the excess potassium must be washed out or neutralized biologically by a solution containing an excess of calcium after arrest of fibrillation had been accomplished. Only so could resumption of a coordinated beat be expected.

The eventual accomplishments of our independent attempts need only be summarized briefly: Hooker,[22] following an earlier procedure of Crile, demonstrated that fibrillation can be abolished in the dog's heart by promptly infusing an oxygenated saline solution containing 0.5 per cent potassium chloride into the cardiac end of a carotid artery, and that effective coordinated beats can then be reestablished by equally prompt carotid infusion of a similar solution containing .024 per cent calcium chloride plus minute concentrations of epinephrine. Hooker had little success in reviving animals by intracardiac injections of potassium and calcium. By contrast, our experience with the successive intra-arterial infusions of potassium and calcium solutions was not very encouraging in dogs.[23] On the other hand, we were successful in arresting fibrillation by injecting a few cubic centimeters of 5 per cent potassium chloride directly into each ventricle and in reviving a normal beat

by subsequent injection of 5 per cent calcium chloride which was distributed through the ventricular walls by massage. Fortunately our studies disclosed the reasons why each of us had been unsuccessful with a procedure that the other found valuable. They served the useful purpose of defining more clearly some of the technical minutiae that must be observed if revival is to succeed by any method:

1. Coordinated contractions cannot redevelop unless fibrillation has ceased completely in every fraction of the myocardium. Since deep-seated fibrillary movements cannot be detected visually, attempts to encourage coordinated beats are often made prematurely. Such aids to recovery must not be applied until all electrocardiographic oscillations have disappeared.

2. The only hope of perfusing adequate quantities of fluid through the coronary vessels by intra-arterial infusions is to administer them under high pressure. Otherwise, most of the fluid runs off by the many tributaries of the aorta other than the coronary vessels.[23]

3. Adequate pacemakers must survive in order to initiate impulses which have sufficient excitatory value to inaugurate contraction.

4. Not too many pacemakers—preferably only one—should dominate the re-excitation of the defibrillated ventricles, for if too many act, they tend to compete for control of the heart beat and often cause reversion to fibrillation.

5. The muscle fractions excited by impulses generated by viable pacemakers must be capable of responding with vigorous contractions; the induction of weak coordinated beats serves no hemodynamic purpose and fails to maintain an adequate coronary and cerebral blood flow.

Defibrillation by Use of Countershock. Another approach to the problem of ventricular defibrillation was based on suggestions in the earlier literature[10, 24, 25, 26] that very strong electric currents may not induce fibrillation but may even stop the process when present and restore coordinated beats. However, all reports seemed to indicate that high voltages are required to achieve defibrillation. Directed studies of the problem were begun in 1932 under the physiologic guidance of Hooker at Johns Hopkins University and of H. B. Williams and B. A. King at Columbia University. In 1933 Hooker, Kouwenhoven, and Langworthy[27] reported success in defibrillating the dog's ventricles and in restoring normal beats by passage of a 60 cycle alternating current of about 1 ampere for 0.1 to 5 seconds through the exposed hearts by means of padded electrodes. They even resuscitated small dogs (about 4 to 5 kilos) from fibrillation by sending currents from 6 to 8 amperes through the chest. The contemporaneous studies of Ferris and colleagues[28] further demonstrated that hearts of animals more nearly comparable in weight to man can be defibrillated by use of large chest electrodes, but this required 2000 to 3000 volts, yielding currents of 27 to 30 amperes.

These investigators[28] cautiously pointed out that, "to be successful, countershock must be administered promptly after the fibrillating shock, probably within a few minutes." At the time, the probability was small that an electrocuted individual could be rushed to an apparatus capable of supplying high amperage and an electrocardiographic diagnosis of fibrillation established within such time limits. In short, the race with time appeared to be the limiting factor in the practical utilization of an important experimental advance. Consequently, as phrased by the present writer,[29] "the chance of success is much greater in the case of patients already on the operating table, particularly when the chest has been opened." These considerations, together with our success in saving large numbers of experimental animals by applying the ordinarily available 110 volt electric current directly to the heart, focused our attention on the necessity of making two important improvements. It was highly important (1) to devise means by which the effectiveness of countershock could be extended for more than two or three minutes after onset of fibrillation and (2) to improve upon the 40 or 50 per cent of failure to defibrillate which still existed. A study of failures revealed that this could be due to several causes: (a) dormancy of rhythmic pacemakers, the heart responding to artificial stimuli such as a slight tap; (b) inability of the myocardium

to respond to a rhythmic pacemaker with contractions strong enough to eject blood under pressure into the aorta; (c) failure of the countershock to abolish fibrillation, particularly in deeper portions of the ventricular walls and septum; the heart appeared quiescent but still caused small electrocardiographic oscillations. Occasionally the presence of such obscure fibrillation can be detected by firm palpation.

It soon became obvious that the first two of these deterrents of successful defibrillation were contingent on the absence of coronary blood flow during fibrillation. Recognizing the cause, it was easy to demonstrate that viable pacemakers and vigorous contractile responses followed defibrillation when aortic pressure was raised and a coronary flow was thereby reestablished *during fibrillation* by cardiac massage.[30] It should be pointed out that the term "cardiac massage" is probably poorly chosen, because an implied kneading and squeezing of the heart muscle is deleterious and must be avoided. Blood is not propelled through the myocardium by squeezing action but by creation of an effective aortic pressure. So-called cardiac massage consists of grasping the heart in the hand and gently but quickly expressing its contents about 40 times per minute while artificial respiration is maintained.* In this way arterial pressure is elevated and the coronary vessels are perfused with oxygenated blood. The pacemakers recover and the muscle machinery is able to respond with vigorous contractions after fibrillation has been stopped by countershock. Failure is often due to difficulty in inhibiting oneself from too early an application of countershock currents. Whenever fibrillation has existed for some time, massage must be continued for a longer time, and slight compression of the ascending arch of the aorta helps to divert a larger part of each systolic discharge through the coronaries.

It sometimes happens in the case of large dogs (15 to 18 Kg.) that fibrillation cannot be abolished in deeper structures, probably because currents of effective strength do not pass through these parts. Since this probably occurs frequently in attempts to defibrillate human hearts, it is desirable to recognize the expedients that have been found helpful: (1) Currents of 220 volts may be used, and indeed would appear advisable for resuscitation of human hearts.* (2) The resistance through the heart can be reduced appreciably by having electrodes as large as the ventricular size will permit and by compressing the heart with the electrodes during the flow of current.[31] (3) A number of shocks may be given in sequence at two-second intervals, a procedure designated as serial defibrillation.[29, 31, 32]

The Search for Defibrillatory, Antifibrillatory, and Adjuvant Drugs

A distinction between defibrillatory, antifibrillatory, and adjuvant drugs is of basic importance. Drugs cannot, at present, be relied upon to cause abrogation of ventricular fibrillation and resumption of regular beats in the dog's heart. In this sense no *defibrillatory drugs* have so far been discovered. A few reports of such actions have been made but not confirmed. Less certainty exists as to whether there are drugs which render the heart less sensitive to fibrillatory agents. These should be called *antifibrillatory drugs*. Many claims for the efficacy of drugs in raising the fibrillation threshold are based on the use of wholly inadequate criteria.[34] Conclusions reached on the basis of experiments on cats are hazardous, since spontaneous recovery generally occurs. So far, the best method available, but by no means a perfect one, for determining changes in the fibrillation threshold consists in determining the minimal strength of a brief direct current shock which, applied precisely during the vulnerable period of ventricular systole, produces fibrillation. By this method it has been found that the fibrillation threshold is

* For description of a mechanical appliance for filling and emptying the ventricles see Beck and Rand.[1] For a recent study of the optimal rate of cardiac compression, see Lape and Maison.[33a]

* Lape and Maison[33a] have just reported that defibrillation can be equally well accomplished by D.C., using somewhat higher voltage, and by a single strong condenser discharge (128 mf. capacity charged to 1500 volts). Whether adequate protection against accidents from such voltages in the operating room can be devised remains to be explored.

raised by procaine, quinidine, and papaverine,[33, 34, 35] is unaltered by digitalis and ouabain[36] and is lowered by ischemia.[37] However, no drug has yet been found which renders the ventricles resistant to fibrillatory agents. It should also be clear that drugs which raise the fibrillation threshold do not necessarily facilitate defibrillation by use of countershock. Procaine or procaine amide injected by syringe into the right ventricular cavity show the greatest promise, but their effectiveness remains in dispute and their depressant effects on respiration and arterial pressure after the ventricles have been defibrillated must not be overlooked.[33a]

Antifibrillatory potency has often been imputed to drugs which alter basic properties of cardiac muscle that are supposedly deranged during fibrillation.[38, 39] Thus Di Palma and Schultz[39] state that the ideal antifibrillatory drug "should lengthen the relative refractory period without producing a supernormal state. It should prevent or eradicate local blocks and restore or maintain the normal propensity of the myocardium to act as a whole. . . . It should not unduly depress contractility of the myocardium or slow conduction. . . . In actuality, most antifibrillatory drugs possess deleterious properties as well as beneficial ones, and it is this unfortunate combination of qualities which has resulted in unsatisfactory therapeutic results."

There is even greater difficulty in discovering drugs that favor recovery from fibrillation. As analyzed above, resuscitation not merely involves the arrest of fibrillation but also requires survival of a pacemaker and the capacity of the myocardium to respond with vigorous contractions. The probability is small that any drug can replace oxygen in promoting survival or revival of excitability and contractility. Nor is any agent known which, after reoxygenation of the myocardium by massage, has the properties which at the same time favor defibrillation but maintain rhythmicity and contractility after defibrillation has been accomplished.

Progress in discovery of drugs useful in the prevention of and recovery from fibrillation can be anticipated only if we keep in mind the processes we expect to alter by them, and when we acquire a better understanding of the basic nature of ventricular fibrillation. The original concept of Garrey[12] that fibrillation is caused by waves of excitation which zigzag their way through the myocardium without definite course but eventually re-enter excitable tissue has much experimental evidence in its favor. It was unfortunate that the process was not called *irregular re-entrant excitation* rather than misnamed *circus movement*. It is perhaps not generally understood that this view differs materially from Lewis' concept[40] of a single mother-ring circling repeatedly around essentially the same path and throwing off impulses as it revolves, much as a pinwheel shoots off sparks. This concept is more properly called the "circus movement theory."* Abundant evidence, topped by the more recent studies of Scherf[41, 42] and of Prinzmetal and his colleagues,[43] seem to have shown clearly that the Lewis concept does not explain auricular fibrillation. Their hypothesis that a single focus is responsible for the origin and maintenance of auricular fibrillation is admittedly consonant with many of their experimental observations. The fact that drugs which lengthen the refractory period and/or conduction time do not neutralize fibrillation, whereas drugs that abrogate heterotopic rhythms do so, constitutes circumstantial evidence opposed to the circus movement theory.[44] It was tempting to interpret our own demonstration[20] that ventricular fibrillation is initiated by a series of accelerating impulses from a stimulated area as favoring the focal concept. However, further investigation by Harris and his associates[45, 46] strongly suggested that another mechanism takes over. Anodal stimulation as well as coronary occlusion induce an initial train of discrete, separated, accelerating electric deflections in punctate leads by contiguous electrodes. But these are superseded by irregularly spaced, rounded, continuous deflections, when the real fibrillating condition develops. However, the observation that leads from separated

* For an attempt to express the different concepts of "circus movements" pictorially see Bijlsma and v. Dongen.[38]

epicardial points display fibrillary waves differing in rate and contour[47] is just as consistent with an irregular re-entrant phenomenon as with a multifocal origin, such as has been suggested by various investigators.[47, 48]

Obviously, the problem of the basic nature of fibrillation remains open for further investigation, and our search for antifibrillatory and resuscitating drugs will remain impeded until ultimate decisions are reached.

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REFERENCES

[1] BECK, C. S., AND RAND, H. J., III: Cardiac arrest during anesthesia and surgery. J.A.M.A. **141:** 1230, 1949.

[2] CUSHNY, A. R.: On the action of substances of the digitalis series on the circulation of mammals. J. Exper. Med. **2:** 233, 1897.

[3] —, AND EDMUNDS, C. W.: Paroxysmal irregularities of the heart and auricular fibrillation. Am. J. M. Sc. **133:** 66, 1907.

[4] WIGGERS, C. J.: The mechanism and nature of ventricular fibrillation. Am. Heart J. **20:** 399, 1940.

[5] HOFFA, M., AND LUDWIG, C.: Einige neue Versuche über Herzbewegung. Ztschr. rat. Med. **9:** 107, 1850.

[6] ERICHSEN, J. E.: On the influence of the coronary circulation on the action of the heart. London M. Gazette **2:** 561, 1842.

[7] HERING, H. E.: Demonstration der Aufhebung des Flimmerns durch Injektion von KCl Lösungen. Deutsche med. Wchnschr. **33:** 1567, 1907.

[8] PORTER, W. T.: In Howell, W. H., ed.: American Textbook of Physiology, ed. 2 (revised). Philadelphia, W. B. Saunders, 1901. Vol. 1, pp. 183, 184.

[9] —: The recovery of the heart from fibrillary contractions. Am. J. Physiol. **1:** 71, 1898.

[10] PREVOST, J. L., AND BATTELLI, F.: Sur quelque effets des décharges électrique sur le coeur des mammifères. J. Physiol. et path. gen. **2:** 40, 1900.

[11] MACWILLIAM, J. A.: The mechanism and control of fibrillation in the mammalian heart. Proc. Roy. Soc., London, s. B **90:** 302, 1918.

[12] GARREY, W. T.: The nature of fibrillary contractions of the heart. Am. J. Physiol. **33:** 397, 1914.

[13] KRONECKER, H., AND SCHMEY, F.: Das Coordinationscentrum der Herzkammerbewegungen. Sitzungsber. d. Preuss. Akad. Wissenschaft zu Berlin **1:** 87, 1884.

[14] WIGGERS, C. J.: The muscular reactions of the mammalian ventricles to artificial surface stimuli. Am. J. Physiol. **73:** 346, 1925.

[15] MINES, G. R.: On circulatory excitations in heart muscle and their possible relation to tachycardia and fibrillation. Tr. Roy. Soc. Canada, Series 3 **8:** 43, 1914.

[16] DE BOER, S.: Die Physiologie u. Pharmakologie des Flimmerns. Ergebn. Physiol. **21:** 1, 1923.

[17] KING, B.: The effect of electric shock on heart action with special reference to varying susceptibility in different parts of the cardiac cycle. Thesis. New York, Aberdeen Press, 1934.

[18] WIGGERS, C. J.: Fibrilacion ventricular y resuscitacion. Bol. Acad. nac. med. Buenos Aires. P. 567, 1938.

[19] WÉGRIA, R., MOE, G. K., AND WIGGERS, C. J.: Comparison of the vulnerable periods and fibrillation thresholds of normal and idioventricular beats. Am. J. Physiol. **133:** 651, 1941.

[20] MOE, G. K., HARRIS, A. S., AND WIGGERS, C. J.: Analysis of the initiation of fibrillation by electrographic studies. Am. J. Physiol. **134:** 473, 1941.

[21] HOFFMAN, B. F., GORIN, E. F., WAX, F. S., SIEBENS, A. A., AND BROOKS, C. McC.: Vulnerability to fibrillation and the ventricular excitability curve. Am. J. Physiol. **167:** 88, 1951.

[22] HOOKER, D. R.: On the recovery of the heart in electric shock. Am. J. Physiol. **91:** 305, 1930.

[23] WIGGERS, C. J.: Studies of ventricular fibrillation caused by electric shock. I. Revival of the heart from ventricular fibrillation by successive use of potassium and calcium salts. Am. J. Physiol. **92:** 223, 1930.

[24] ABIDGAARD, C. P.: Tentamina electrica in animalibus instituta. Societatis medical havniensis collectanea **2:** 1775, 1775.

[25] BATTELLI, F.: Le rétablissement des fonctions du coeur et du système nerveux central après l'anémie totale. J. physiol. et path. gén. **2:** 443, 1900.

[26] D'HALLUIN, M.: Moyen de combattre les trémulations fibrillaires engendrées par le massage du coeur. Zentralbl. Physiol. **18:** 837, 1904.

[27] HOOKER, D. R., KOUWENHOVEN, W. B., AND LANGWORTHY, O. R.: Effects of alternating electrical currents on the heart. Am. J. Physiol. **103:** 444, 1933.

[28] FERRIS, L. P., KING, B. G., SPENCE, P. W., AND WILLIAMS, H. B.: Effect of electric shock on the heart. Electrical Engineering, May, 1936.

KING, B. G.: The effect of electric shock on heart action with special reference to varying susceptibility in different parts of the cardiac cycle. Thesis. New York, Aberdeen Press, 1934.

[29] WIGGERS, C. J.: The physiological basis for cardiac resuscitation from ventricular fibrillation. Method for serial defibrillation. Am. Heart J. **20:** 413, 1940.

[30] —: Cardiac massage followed by countershock in revival of mammalian ventricles from fibrillation due to coronary occlusion. Am. J. Physiol. **116:** P161, 1936.

[31] GUYTON, A. C., AND SATTERFIELD, J.: Factors concerned in electric defibrillation of the heart, particularly through the unopened chest. Am. J. Physiol. **167:** 81, 1951.

[32] LEEDS, S. E., MACKAY, E. S., AND MOOSLIN, K.: Production of ventricular fibrillation and defibrillation in dogs by means of accurately measured shocks across the exposed heart. Am. J. Physiol. **165:** 179, 1951.

[33] BECK, C. S., AND MAUTZ, F. R.: The control of the heart beat by the surgeon. Ann. Surg. **106:** 525, 1937.

[33a] LAPE, H. E., and Maison, G. L.: Cardiac resuscitation and survival: Influence of rate of manual compression, type of countershock and of epinephrine. Am. J. Physiol. **172:** 417, 1953.

[34] WIGGERS, C. J., AND WÉGRIA, R.: Quantitative measurement of fibrillation thresholds of the mammalian ventricles with observations on the effect of procaine. Am. J. Physiol. **131:** 296, 1940.

[35] WÉGRIA, R., AND NICKERSON, N. D.: The effect of papaverine, epinephrine, and quinidine on the fibrillation threshold of the mammalian ventricle. J. Pharmacol. & Exper. Therap. **75:** 50, 1942.

[36] —, GEYER, J. H., AND BROWN, B. S.: The fibrillation threshold after administration of digitalis and ouabain. J. Pharmacol. & Exper. Therap. **71:** 336, 1941.

[37] WIGGERS, C. J., WÉGRIA, R., AND PIÑERA, B.: The effect of myocardial ischemia on the fibrillation threshold. Am. J. Physiol. **131:** 309, 1940.

[38] BIJLSMA, U. G., AND VAN DONGEN, K.: Experimentalle Therapie des Flatterns und Flimmerns des Herzens. Ergebn. Physiol. **41:** 1, 1939.

[39] DI PALMA, J. R., AND SCHULTZ, J. E.: Antifibrillatory drugs. Medicine **29:** 123, 1950.

[40] LEWIS, T.: The Mechanism and Graphic Registration of the Heart Beat. London, Shaw and Sons, 1925.

[41] SCHERF, D.: Studies on auricular tachycardia caused by aconitine administration. Proc. Soc. Exper. Biol. & Med. **64:** 233, 1947.

[42] —, ROMANO, F. J., AND TERRANOVA, R.: Experimental studies on auricular flutter and fibrillation. Am. Heart J. **36:** 241, 1948.

[43] PRINZMETAL, M., AND ASSOCIATES: The Auricular Arrhythmias, ed. 8. Springfield, Ill., Charles C Thomas, 1952.

[44] VAN DONGEN, K., AND TAAL, A.: Remarks on the mechanism of heart fibrillation. Arch. internat. pharmacodyn. **81:** 129, 1950.

[45] HARRIS, A. S., AND GUEVARA ROJAS, A.: The initiation of ventricular fibrillation due to coronary occlusion. Exper. Med. & Surg. **1:** 105, 1943.

[46] —, AND RANDALL, W. C.: Mechanisms underlying electrocardiographic changes observed in anoxia. Am. J. Physiol. **142:** 452, 1944.

[47] KISCH, B.: Electrographische Untersuchungen am flimmerden Säugetierventricle. Ztschr. ges. exper. Med. **24:** 106, 1921.

[48] GROEDEL, F. M., KISCH, B., and Borchardt, P. R.: The exocardial and endocardial electrogram of the ventricles. Exper. Med. & Surg. **5:** 411, 1947.