Special Article

A Short, Biased History of Triggered Activity

Michael R. Rosen

Department of Pharmacology, Center for Molecular Therapeutics & Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, NY, USA

This manuscript is one man's view of the early days of triggered activity. It is a biased view, representing my personal recollections tempered by revisiting the literature. I have prepared the manuscript in this fashion to satisfy the charge of the editors to recall a part of history during which I lived and to which, in some small way, I contributed. It is possible and indeed likely that another individual writing on this topic would remember differently, which of course contributes to the intrigue of history.

Address:
Michael R. Rosen

Gustavus A. Pfeiffer Professor of Pharmacology Professor of Pediatrics Director, Center for Molecular Therapeutics Columbia University 630 West 168 Street PH7West-321 New York, NY, 10032 USA
e-mail:
mrr1@columbia.edu

Medical students tell me that three mechanisms can contribute to tachyarrhythmias: reentry, automaticity and triggered activity. The students accept this as a given; it is part of their rote learning. I find this amusing, because forty years ago arrhythmias were either reentrant or automatic, and nothing more ... and this had been part of my rote learning. At the present time in my career I espouse the tripartite dogma of arrhythmogenic mechanisms, but I am less sure than ever that we have it all right: clearly our knowledge continues to evolve and the only thing that would surprise and disappoint me would be the failure of its further evolution.

Discovering afterdepolarizations and triggered activity

I completed my clinical cardiology training in 1970 and began a postdoctoral fellowship in electrophysiology, studying microelectrode techniques with Brian Hoffman. My interests were in arrhythmias, antiarrhythmic drugs and digitalis. I understood the mechanisms for arrhythmias were well-established: indeed a recent graduate of the Hoffman lab had questioned my desire to study them, as "everything that could be learned had been learned." Concurrent re-

view articles reinforced that notion, detailing the roles of automaticity and reentry, the use of catheter recordings of His bundle, atrial and ventricular electrograms, and programmed pacing techniques to distinguish between the two mechanisms.[1]

Digitalis was the tool for my studies in the Hoffman lab, and Heinz Gelband and I began a series of experiments which, we thought, would teach us more about how digitalis' effect on automaticity contributed to ectopic impulse initiation.[2-4] We isolated Purkinje fiber bundles and superfused them with arterial blood from a donor dog (Figure 1).[5] Ouabain was administered intravenously to the donor in a dose sufficient to cause ventricular arrhythmias after a period of 25-40 min (Figure 2A). In these experiments we observed unusual waveforms that we described as "slow, graded depolarizations of varying magnitude (low-amplitude potentials) during phase 4 of the transmembrane potential recorded from isolated canine Purkinje fibers exposed to toxic ouabain concentrations. The appearance of the low amplitude potentials in the records of transmembrane potentials was more or less simultaneous with the onset of ouabain-induced junctional or ventricular arrhythmias in the donor (Figure 2B)."
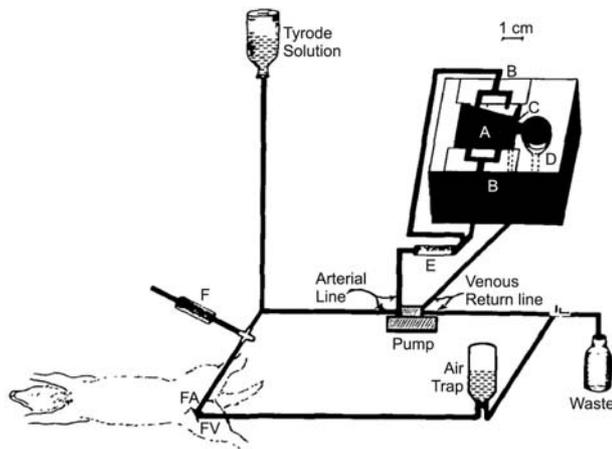
Between January and August of 1973

Figure 1. Schematic diagram of blood perfusion system: (A) perfusion chamber; (B) entry ports for blood or Tyrode's solution; (C) exit port; (D) overflow compartment; (E) glass heat exchanger; (F) Statham pressure gauge; (FA) femoral artery; (FV) femoral vein. See text for complete description (reprinted from reference 5, by permission).
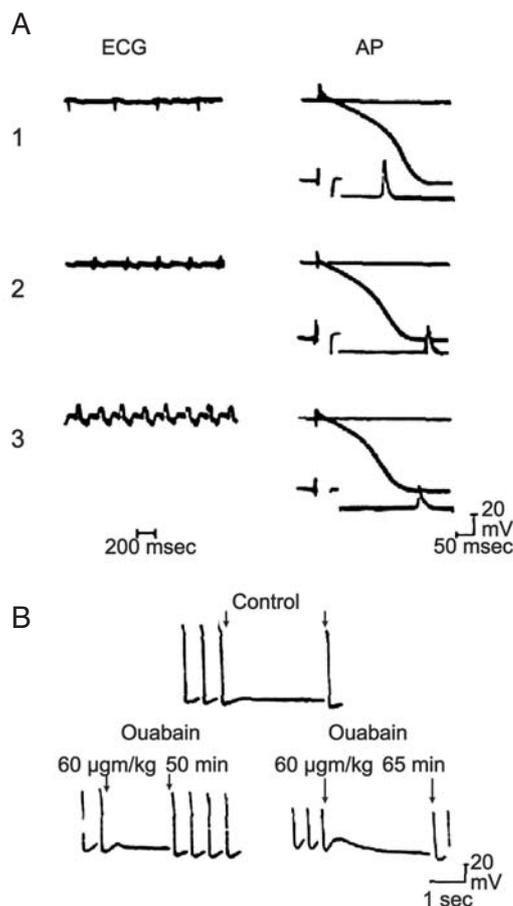

Figure 2. A: Effect of toxic ouabain concentration on ECG and Purkinje fiber action potential: temperature, 36-37° C; cycle length, 500 ms. (1) Control. ECG shows sinus rhythm, rate 140 beats/min, action potential (AP) amplitude 118 mV, resting membrane potential (RMP) -96 mV, Vmax 457 v/s, action potential duration (APD) 310 ms. (2) Forty minutes after injection of ouabain, 60 μg/kg. ECG shows an ectopic tachycardia, AP amplitude 110 mV, RMP -90 mV, Vmax 314 v/s, APD 280 ms. (3) Sixty minutes after ouabain injection. ECG shows ventricular tachycardia, AP amplitude 100 mV, RMP -83 mv, Vmax 252 v/s, APD 265 ms.

B: Ouabain-induced low amplitude potentials. Temperature 36° C, donor plasma potassium 4.6 mEq/L. Cycle length 500 ms. Control. AP amplitude 110 mV. Drive discontinued at first arrow, reinstituted at second arrow. Fifty minutes after ouabain, 60 μg/kg, at onset of ventricular tachycardia. AP amplitude 90 mV. The slope of phase 4 depolarization has increased and, on discontinuation of the drive, there is a low amplitude potential. Sixty-five minutes after ouabain, ventricular tachycardia persists. AP amplitude 58 mV prior to discontinuation of drive and 63 mV at its reinstitution. Slope of phase 4 has increased further. Magnitude of low amplitude potential 14 mV (reprinted from reference 2, permission).

we published three papers on digitalis, two of them on blood-perfused preparations in which the primary intent was as much to test the stability of the blood perfusion experiment as to learn about digitalis,[2,4] and one on Tyrode's superfused preparations.[3] We documented the occurrence of the low amplitude potentials (Figure 3), distinguished them from automaticity, and noted circumstances under which they could be brought to threshold. We speculated that these waveforms might be responsible for the repetitive ventricular responses that Bernard Lown had described in the setting of digitalis toxicity.[6,7]

Given the self-involvement of youth, I never suspected that others might be discovering the same phenomenon at the same time we were. And yet in Utica, New York, in Gordon Moe's lab, Greg Ferrier, Keitaro

Hashimoto and colleagues were doing just that, resulting in three publications in June of that year on what they called transient depolarizations.[8-10] Much of what each group reported was complementary to the other's work. But while we focused on the effects of the low amplitude potentials on impulse initiation and conduction, the Utica group emphasized an observation that was to become key in discriminating the arrhythmias induced by transient depolarizations from other arrhythmogenic events: that is, as pacing rate increased so did the amplitude of the transient depolarization (Figure 3). At a critical cycle length threshold was reached and bursts of arrhythmia occurred. Clearly this was consistent with the repetitive ventricular response of Lown.[6,7]

And so we had two labs, one mechanism and two names for it. Given what became a friendly rivalry between the Hoffman and Moe laboratories neither side was going to concede on terminology. Ferrier suggested moving to an earlier descriptor of the waveform, oscillatory afterpotential (see below),[11] but the suggestion finally adopted by us and the field at large was that of Paul Cranefield.[12] He and Andy Wit had been studying the waveforms in mitral valve and coronary sinus,[13,14] and Cranefield also had a long interest in oscillatory activity.[15] It was he who proposed the terminology of early and delayed afterdepolarizations and the concept of triggered activity as an ectopic form of arrhythmic activity distinct from automaticity (which was suppressed by overdrive pacing) and reentry. We all came to recognize that delayed afterdepolarizations can only be identified definitively when they are subthreshold and that when they are large enough they can bring the membrane potential to the threshold potential for a triggered (nondriven) impulse, which in turn may be followed by one or more afterdepolarizations. The impulse was termed "triggered" because it required a preceding action potential as its initiator and did not arise de novo.[12,16]

Discovering the mechanism

The remainder of the decade of the 70s was busy with experiments trying to assess the behavior and the mechanisms responsible for afterdepolarizations, as well as their potential applicability to the clinic. With regard to mechanism, work in the Moe lab and our lab suggested potential contributions from calcium[8] and sodium,[17] respectively. But the exploration of mechanism at the level of ion currents moved far beyond the two laboratories, and will be summarized in the following paragraphs.
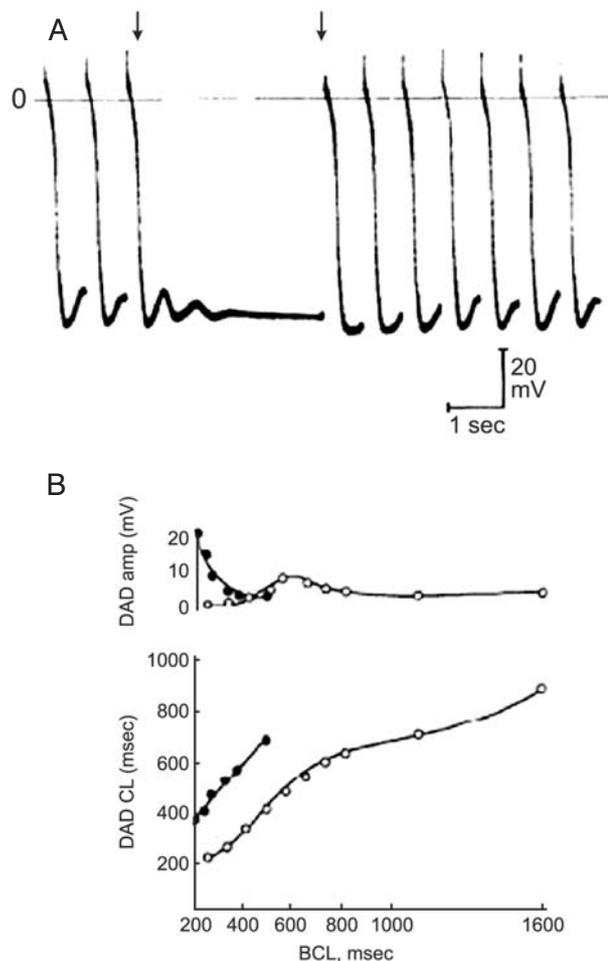

Figure 3. A: Occurrence of low amplitude potentials in sequence. Purkinje fiber impalement following 32-min ouabain perfusion. Cycle length 630 ms, temperature 37°C, perfusate $[K+]_0$ 4.0 mmol/L, AP amplitude -92 mV, maximum diastolic potential (MDP) -74 mV. On discontinuation of the drive (filled arrow) three low amplitude potentials occur in succession, respectively 12, 7, and 2 mV in magnitude. This is followed by slight hyperpolarization. The interval between low amplitude potentials approximates the drive cycle length. After reinstitution of the drive (clear arrow) several cycles are required before phase 4 returns to its former slope. Note the phase shift that occurs between the peak of the low-amplitude potentials and phase 0 of the action potentials. (Reprinted from reference 3, by permission).
B: Relationship of the amplitude (amp) and cycle length (CL) of the first two delayed afterdepolarizations (DAD) in a sequence to the basic drive cycle length (BCL) for a Purkinje fiber in a different experiment from A. Unfilled circles, first delayed afterdepolarization; filled circles. second delayed afterdepolarlzation. See text for discussion (reprinted from reference 44, by permission).

Delayed afterdepolarizations occur when there is a large increase in intracellular calcium resulting from abnormalities in sarcoplasmic reticulum sequestration, or release of calcium, or a combination of the two. The increased cytosolic calcium was proposed to

alter sarcolemmal permeability, activating a nonspecific membrane channel permitting an inward current carried mainly by sodium, resulting in the delayed afterdepolarization.[18] Alternative proposals were that the current results from electrogenic Na/Ca exchange leading to the net transfer of sodium ion, carrying positive charge into the cell and generating an inward current.[19,20] The mechanism remains under investigation.

A widely recognized cause of delayed afterdepolarizations (and the one that led to the research in our own and the Utica labs) is cardiac glycoside toxicity.[2-4,8-10] Digitalis inhibits the Na^+-K^+ pump leading to an increased $[Na]_I$, which increases intracellular Ca^{2+} via the Na^+-Ca^{2+} exchanger.[21] Catecholamines provide another cause of delayed afterdepolarizations,[14,22,23] possibly by enhancing calcium entry.[24] Catecholamine- and/or pacing-induced delayed or early afterdepolarizations and triggered activity have been described in atrial fibers of the mitral valve[13] and coronary sinus,[14] in other regions of the atria[25] and pulmonary veins,[26] ventricular muscle, and Purkinje fibers.[22,23] Delayed afterdepolarizations have also been identified in the upper pectinate muscles bordering the *crista terminalis* in rabbit heart,[27] hypertrophied ventricular myocardium,[28] human atrial myocardium,[29] and Purkinje fibers surviving on the subendocardial surface of canine myocardial infarcts.[30,31]

Delayed afterdepolarizations have been studied in voltage-clamp experiments, where they were attributed to a transient inward current activated by repolarization after a depolarizing voltage clamp pulse.[32,33-37] The current also increases in amplitude with increasing duration of the voltage clamp pulses or increasing pulse frequency. Such changes in the clamp pulse may lead to an increase in $[Ca]_I$.[38] The amplitude of the transient inward current is maximal at -50 to -70 mV and decreases at lower and higher membrane potentials. This is very different from the pacemaker currents initiating automaticity, for which the inward current I_f increases with hyperpolarization.[39]

The link between a depolarizing pulse (whether caused by a voltage clamp or by an action potential) and transient inward current may involve sarcoplasmic reticulum calcium release and reuptake. In normal settings, release is initiated by the depolarization phase of the action potential and reuptake is complete by the end of the action potential. Under conditions of sarcoplasmic reticulum calcium overload, there may not be complete calcium uptake and/or there may be secondary calcium release after repolarization.[40] In addition, the occurrence of propagating

Ca waves in myocytes and resultant induction of delayed afterdepolarizations have been demonstrated.[41]

Delayed afterdepolarizations are not all the same

Translating the voltage clamp results to spontaneously occurring or paced action potentials demonstrates that any of the following will increase delayed afterdepolarization amplitude and induce triggered activity: increased amplitude and/or duration of the action potential plateau;[42] increased frequency at which action potentials are induced; decreased resting membrane potential in muscle or Purkinje fibers from the normal level around -80 mV to less than -70 mV.[43]

When delayed afterdepolarizations do not reach threshold, there is no triggered activity.[44] For two afterdepolarizations in sequence, the relationship is shown in Figure 3. In cardiac fibers manifesting a single afterdepolarization after each action potential, the afterdepolarization amplitude increases as drive rate increases (in contrast to early afterdepolarizations, which have the opposite relationship). In any setting, at a critical drive rate the afterdepolarization may attain an amplitude sufficient to reach threshold and triggered activity is seen. A premature impulse may further increase the amplitude of the afterdepolarization of the action potential following the short cycle, and the likelihood of a premature impulse initiating triggered activity increases at more rapid drive rates. There are differences in the characteristics of triggered activity caused by delayed afterdepolarizations, depending upon the cause. The initial sequence of catecholamine-induced triggered beats in atrial fibers often shows a gradual decrease in cycle length followed by a relatively constant cycle length.[14,45] This decrease in cycle length may be paralleled by a decreasing maximum diastolic potential, in part due to K^+ accumulation outside the cell during rapid activity secondary to restricted diffusion in the extracellular space.[46,47] The decreased maximum diastolic potential contributes to the gradual rate acceleration of the triggered activity. In contrast, during triggered activity in digitalis-toxic Purkinje fibers the maximum triggered rate occurs after a few impulses rather than a gradual acceleration.[48]

The rates of triggered rhythms in the coronary sinus usually slow gradually before the rhythms terminate. This gradual slowing is accompanied by a progressively increasing maximum diastolic potential and there is usually a delayed afterdepolarization following the last triggered impulse.[14,45] This spontaneous ter-

mination is caused, at least in part, by an increased rate of electrogenic sodium extrusion.[45] Sodium pump activity is enhanced by the increased intracellular Na^+ concentration, which results in turn from the increased Na^+ influx during the period of triggered activity. The increased outward sodium pump current increases the maximum diastolic potential, reducing the rate of triggered activity. If the increase in sodium pump current is sufficient, the triggered activity terminates.[45]

Digitalis-induced triggered activity is not usually associated with gradual slowing and hyperpolarization. Rather there is often a speeding of rate, with a decrease in action potential amplitude and depolarization. Because the Na^+ pump is inhibited by digitalis, termination may be caused by Na^+ or Ca^+ accumulation in the cell secondary to the rapid rate. A decreased Na^+ or Ca^{++} transmembrane concentration gradient might diminish the afterdepolarization and the action potential amplitude and lead to cessation of activity.

Seeking a basis for clinical applicability

Programmed electrical stimulation is one means by which mechanisms of clinical arrhythmias are studied, and the effects of stimulation sequences on triggered activity caused by delayed afterdepolarizations in isolated tissues have been critical in attempts to identify triggered rhythms in intact animals and human subjects.[49,50] The benchmark characteristic of delayed afterdepolarization-induced triggered activity is its increasing frequency of occurrence as drive rates increase. Once triggered activity occurs it can be terminated by premature stimulation, sometimes with a single premature stimulus.[13] Alternatively, premature impulses may reset the triggered rhythm, analogous to what is seen with automatic rhythms. The effectiveness of premature impulses to terminate triggered rhythms increases if they are preceded by periods of rapid drive.[51]

Triggered activity can also be terminated by overdrive pacing, depending on the rate and duration of the pacing period.[51] Following short periods of overdrive at rates moderately faster than the rate of a triggered rhythm, the subsequent triggered rate may increase, perhaps because of the decrease in maximum diastolic potential. This post-overdrive acceleration is similar to that which can occur during abnormal automaticity. The rate then slows, and maximum diastolic potential increases until pre-overdrive values are reached.

Translating laboratory findings to the clinic

In attempting to test the clinical applicability of delayed afterdepolarizations in the 1970s, we were intrigued by the cycle-length dependence of delayed afterdepolarizations and the extent to which clinical pacing protocols might be devised to identify triggered activity. Bob Reder and I came up with some "rules" for clinical arrhythmias induced by delayed afterdepolarizations[48] and these were further refined by Nancy Johnson (see below).[52]

Despite these advances, we couldn't seem to find an arrhythmia we could attribute to delayed afterdepolarization-induced triggered activity. The answer to this problem came from Charles Fisch. He and Suzanne Knoebel had been studying accelerated atrioventricular junctional escape rhythms[53] (Figure 4A) but had not been able to find a mechanism for their behavior. We started a collaboration in which a key person was the statistician Gene Lovelace.[44] We established a set of definitions (see Figure 4B). The "rules" applied were as follows:[44]

Rule 1. There should be a consistent and definable relation between the occurrence of an afterdepolarization-induced beat and the duration of the preceding cycle or cycles, so that the shorter the preceding cycle length, the more likely an afterdepolarization-induced impulse.

Rule 2. There should be a consistent and definable relation between the dominant cycle length and the duration of the manifest escape interval, and between the manifest escape interval and the cycle length of the arrhythmia.

Rule 3. The R-R interval for an early ectopic beat (for example, an atrial or ventricular premature depolarization that occurs at an interval of less than approximately 75 percent of the dominant cycle) that interrupts the sinus cycle and initiates the accelerated junctional escape mechanism may be variable and have no consistent relation to the preceding dominant R-R interval.

Rule 4. There may be a tendency for the true junctional rhythm to accelerate over one or several cycles.

Using these rules to test the relationships between cycle lengths of the accelerated atrioventricular junctional escape rhythms and those of preceding driven or spontaneous rhythms, we found all criteria for delayed afterdepolarization-induced triggered activity were satisfied.[44]
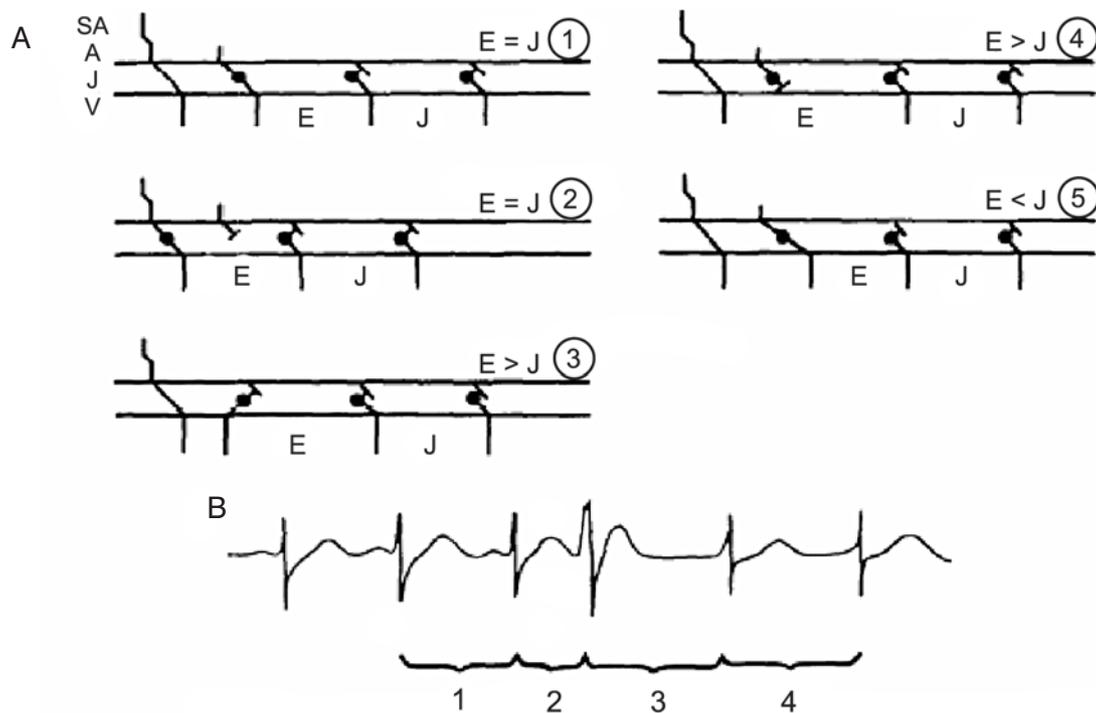
Figure 4. A: Lewis diagram demonstrating the various mechanisms permitting accelerated junctional escape (A – atrium; E – manifest escape; J – junction or interjunctional cycle; SA – sinoatrial node; V – ventricle). 1. Conducted atrial premature depolarization with escape and true interjunctional interval being equal (E=J). 2. Atrial premature depolarization blocked above the junctional site with the manifest escape and true interjunctional intervals being equal (E=J). 3. Ventricular premature depolarization activating the ventricles before reaching the junctional site, resulting in a manifest escape interval longer than the true interjunctional cycle length (E>J). 4. Atrial premature depolarization penetrating to the level of the junctional focus, discharging, but failing to reach the ventricle, resulting in an escape interval longer than the true junctional interval (E>J). 5. Conducted atrial premature depolarization with delay of conduction below the accelerated junctional focus with a resultant manifest escape interval shorter than the true interjunctional interval (E<J).
B: electrocardiographic intervals measured: (1) dominant R-R; (2) ectopic R-R; (3) manifest escape interval; (4) true junctional interval (reprinted from reference 44, by permission).

Much has also been written about the applicability of delayed afterdepolarization-induced triggered activity to other clinical arrhythmias. It is clear that triggering is not the major mechanism for most ischemic arrhythmias, which remain most firmly associated with reentry. However, in settings where there is Ca^{++} overload there is invariably the propensity for triggering, and single triggered beats or sequences thereof may provide the initiating factor for reentry.[54]

One other important factor to mention before leaving this subject is the contribution of Waldo and associates to the description of transient entrainment.[55-57] The application of their criteria to the study of clinical arrhythmias has further enabled the distinction between triggered and reentrant rhythms.

Discovering that we had rediscovered triggered activity

One of my favorite sayings, attributed to Carl Wiggers, is: "To enjoy the thrill of discovery don't go to the li-

brary." And while our library work clearly was not as careful as it should have been at the time of our earliest experiments, we did go to the library and we did learn as we moved forward following our "discovery" of delayed afterdepolarizations and triggered activity. In so doing, we came to realize that more than anything we were rediscovering a wave-form and a behavior that had previously been described in no less detail and with no less effort using other techniques.

The story probably starts with David Scherf who, while he never described delayed afterdepolarizations or triggered activity, spoke of focal impulse initiation[58] that clearly differed from that which we associate with automaticity in the sinoatrial node or the specialized conducting system. The first definitive depictions of delayed afterdepolarizations occurred nearly concurrently in two laboratories on two different continents. Bozler[59] in the US and Segers[60] in France, using extracellular recording techniques, described these oscillations and discussed their possible meaning. Fig-

ure 5 provides an example of Bozler's recordings. He called the wave-forms oscillatory afterpotentials, the term Greg Ferrier suggested adopting[11] after the Moe and Hoffman labs had come up with their conflicting "modern" terminologies. Cranefield's suggestion of "delayed afterdepolarizations"[12] was not a refutation of Bozler's terminology, but a refinement. Using the Bozler descriptor would have lumped early and delayed afterdepolarizations as a single phenomenon: with Cranefield's approach they were given separate identities, which facilitated discussion and thought regarding mechanism.

The work of Bozler and Segers was largely forgotten after the 1940s. In the 1960s, microelectrode recordings by Mario Vassalle clearly showed digitalis-induced delayed afterdepolarizations.[61] These were interpreted as a form of automaticity. Then, in the late 1960s, Steve Wittenberg and Perry Hogan in Fran Klocke's lab in Buffalo produced two papers in which digitalis clearly induced both delayed afterdepolarizations and triggered rhythms in a canine model, both *in situ* and *in vitro*: these were interpreted as digitalis-induced enhanced automaticity.[62] Similarly, Temte and Davis[63] had produced Ca overload in Purkinje fibers and demonstrated afterdepolarizations, and Davis later found the same phenomenon with digitalis.[64] For some years after the Cranefield definition came to hold sway, some authors continued to use terms like "triggered automaticity."[65,66] While most of us derided this terminology, these individuals may not have been so wrong in their interpretation, as will be explored in the next section.

Where to next: what is left unanswered?

I started this article by saying that the only thing that would surprise me would be the failure of the further evolution of our knowledge. We have gotten to a point where I think we will again have to consider, in a mechanistic sense, the differences between delayed af-terdepolarization-induced triggered activity and automaticity. Paul Cranefield many years ago opined that impulse initiation in the sinus node might originate as triggered.[67] However, the behavior of most triggered versus automatic rhythms and the understanding of their mechanism seemed to argue against this. Yet, recent data may bring the two closer together again. The Lakatta lab's description of a calcium clock and the contribution of the Na/Ca exchanger to automaticity puts us in a situation where a Ca-based mechanism is critical to sinoatrial node function as well as to the generation of triggered activity.[68,69] Does this mean the two are the same? I would suggest—cautiously—that they are not: the sinus node has a multiplicity of contributors to its impulse initiation, starting with the inward pacemaker current I_f, and incorporating inward T- and L-type Ca currents as well as the repolarizing K currents, plus the Na/Ca exchanger.[39,68-70] For triggered activity, all that is needed and appears to be present is Ca overload, leading to alterations described above at the level of the sarcoplasmic reticulum and the current I_{ti}.

It may be that a Ca clock and the Na/Ca exchanger are at the core of impulse initiation, with expression of automaticity versus triggered activity depending on the "sorting out" of ion channels in cells of interest and the pathophysiology of any clinical situation. Alternatively, the clock may be the supporting cast, modulating the activity of the other channels and pathophysiology as primary drivers. Whatever the case may be, triggered activity is here to stay: unraveling its mysteries versus those of other forms of impulse initiation is just one of the provocative challenges awaiting us.

References

1. Wellens HJJ. Value and limitations of programmed electrical stimulation of the heart in the study and treatment of tachycardias. Circulation. 1978; 57: 845-853.
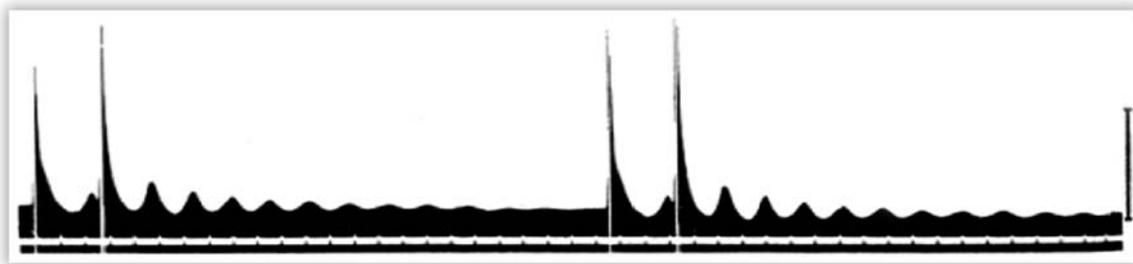2. Rosen MR, Gelband H, Hoffman BF. Correlation between effects of ouabain on the canine ECG and transmembrane

Figure 5. Oscillatory afterpotentials induced by applying equal parts of Ringer's and $CaCl_2$ to turtle right auricle and recorded with monophasic techniques. The action potentials occurred spontaneously and gave rise to trains of oscillations. Time marks are 0.2 s and vertical calibration is 0.5 mV. (Experiment by Emile Bozler in 1943, reprinted from reference 59).

potentials of isolated Purkinje fibers. Circulation. 1973; 47: 65-71.

3. Rosen M, Gelband H, Merker C, Hoffman BF. Mechanisms of digitalis toxicity: Effects of ouabain on phase four of Purkinje fiber transmembrane potentials. Circulation. 1973; 47: 681-689.

4. Rosen M, Gelband H. Effects of ouabain on canine Purkinje fibers in situ and perfused with blood. J Pharmacol Exp Ther. 1973; 186: 336-372.

5. Rosen M, Gelband H, Hoffman BF. Effects of blood perfusion on electrophysiologic properties of isolated canine Purkinje fibers. Circ Res. 1972; 30: 575-588.

6. Lown B. Electrical stimulation to estimate the degree of digitalization. Am J Cardiol. 1968; 22: 251-259.

7. Lown B, Cannon RL, Rossi MA. Electrical stimulation and digitalis drugs: Repetitive response in diastole. Proc Soc Exp Biol Med. 1967; 126: 628-701.

8. Ferrier GR, Moe GI. Effect of calcium on acetylstrophanthidin induced transient depolarizations in canine Purkinje tissue. Circ Res. 1973; 33: 508-515.

9. Ferrier GR, Saunders JH, Mendez C. A cellular mechanism for the generation of ventricular arrhythmias by acetylstrophanthidin. Circ Res. 1973; 32: 600-689.

10. Hashimoto K, Moe GK. Transient depolarizations induced by acetylstrophanthidin in specialized tissue of dog atrium and ventricle. Circ Res. 1973; 32: 618-624.

11. Ferrier GR. Digitalis arrhythmias: role of oscillatory afterpotentials. Prog Cardiovasc Dis. 1977; 19: 459-474.

12. Cranefield PF. Action potentials, afterpotentials, and arrhythmias. Circ Res. 1977; 41: 415-423.

13. Wit AL, Cranefield PF. Triggered activity in cardiac muscle fibers of the simian mitral valve. Circ Res. 1976; 38: 85-98.

14. Wit AL, Cranefield PF. Triggered and automatic activity in the canine coronary sinus. Circ Res. 1977; 41: 435-445.

15. Cranefield PF, Aronson RW. Cardiac Arrhythmias: The Role of Triggered Activity and Other Mechanisms. Mount Kisco, New York: Futura; 1988.

16. Cranefield PF. The Conduction of the Cardiac Impulse: The Slow Response and Cardiac Arrhythmias. Mount Kisco, New York: Futura; 1975.

17. Rosen MR, Danilo P. Effects of tetrodotoxin, lidocaine, verapamil and AHR-2666 on ouabain-induced delayed afterpolarizations in canine Purkinje fibers. Circ Res. 1980; 46: 117-124.

18. Colquhoun D, Neher E, Reuter H, Stevens CF. Inward current channels activated by intracellular Ca in cultured cardiac cells. Nature. 1981; 294: 752-754.

19. Karagueuzian HS, Katzung BG. Voltage-clamp studies of transient inward current and mechanical oscillations induced by ouabain in ferret papillary muscle. J Physiol (London). 1982; 327: 255-271.

20. Arlock P, Katzung BG. Effects of sodium substitutes on transient inward current and tension in guinea-pig and ferret papillary muscle. J Physiol (London). 1985; 360: 105-120.

21. Akera T, Brody TM. The role of Na+, K+ ATPase in the inotropic action of digitalis. Pharmacol Rev. 1977; 29: 187-220.

22. Nathan D, Beeler GW Jr. Electrophysiologic correlates of the inotropic effects of isoproterenol in canine myocardium. J Mol Cell Cardiol. 1975; 7: 1-15.

23. Dangman KH, Danilo P Jr, Hordof AJ, Mary-Rabine L, Reder RF, Rosen MR. Electrophysiologic characteristics of human ventricular and Purkinje fibers. Circulation. 1982; 65: 362-368.

24. Reuter H. Localization of beta adrenergic receptors and effects of noradrenaline and cyclic nucleotides on action potentials, ionic currents and tension in mammalian cardiac muscle. J Physiol (London). 1974; 242: 429-451.

25. Wit AL, Cranefield PF, Gadsby DC. Triggered activity. In: Zipes DP, Bailey JC, Elharrar V, editors. The Slow Inward Current and Cardiac Arrhythmias. The Hague: Nijhoff. 1980; p. 437-454.

26. Patterson E, Jackman WM, Beckman KJ, et al. Spontaneous pulmonary vein firing in man: relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. J Cardiovasc Electrophysiol. 2007; 18: 1067-1075.

27. Saito T, Otoguro M, Matsubara T. Electrophysiological studies on the mechanism of electrically induced sustained rhythmic activity in the rabbit right atrium. Circ Res. 1978; 42: 199-206.

28. Aronson RS. Afterpotentials and triggered activity in hypertrophied myocardium from rats with renal hypertension. Circ Res. 1981; 48: 720-727.

29. Mary-Rabine L, Hordof AJ, Danilo P Jr, Malm JR, Rosen MR. Mechanisms for impulse initiation in isolated human atrial fibers. Circ Res. 1980; 47: 267-277.

30. El-Sherif N, Gough WB, Zeiler RH, Mehra R. Triggered ventricular rhythm in 1-day-old myocardial infarction in the dog. Circ Res. 1983; 52: 566-579.

31. LeMarec H, Spinelli W, Rosen MR. Effects of doxorubicin on ventricular tachycardia in conscious dogs. Circulation. 1986; 74: 881-889.

32. Eisner DA, Lederer WJ. Inotropic and arrhythmogenic effects of potassium-depleted solutions on mammalian cardiac muscle. J Physiol (London). 1979; 294: 255-277.

33. Kass RS, Tsien RW, Weingart R. Ionic basis of transient inward current induced by strophanthidin in cardiac Purkinje fibres. J Physiol (London). 1978; 281: 209-226.

34. Kass RS, Lederer WJ, Tsien RW, Weingart R. Role of calcium ions in transient inward currents and aftercontractions induced by strophanthidin in cardiac Purkinje fibres. J Physiol (London). 1978; 281: 187-208.

35. Vassalle M, Mugelli A. An oscillatory current in sheep cardiac Purkinje fibers. Circ Res. 1981; 48: 618-631.

36. Karagueuzian HS, Katzung BG. Voltage-clamp studies of transient inward current and mechanical oscillations induced by ouabain in ferret papillary muscle. J Physiol (London). 1982; 327: 255-271.

37. Tseng G-N, Wit AL. Characteristics of a transient inward current causing catecholamine induced triggered atrial tachycardia. Circulation. 1984; 70 (Suppl. II): 221.

38. Reuter H. The dependence of slow inward current in Purkinje fibres on the extracellular calcium-concentration. J Physiol (London). 1967; 192: 479-492.

39. DiFrancesco D. A new interpretation of the pacemaker current in calf Purkinje fibers. J Physiol (London). 1981; 314: 359-376.

40. Tsien RW, Kass RS, Weingart R. Cellular and subcellular mechanisms of cardiac pacemaker oscillations. J Exp Biol. 1979; 81: 205-215.

41. Ter Keurs HEDJ, Boyden PA. Ca2+ and arrhythmias. In: Spooner PM, Rosen MR, editors. Foundations of Cardiac Arrhythmias. New York: Marcel Dekker, Inc; 2001. p. 300.

42. Henning B, Wit AL. The time course of action potential repolarization affects delayed afterdepolarization amplitude in atrial fibers of the canine coronary sinus. Circ Res. 1984; 55: 110-115.

43. Ferrier GR. Effects of transmembrane potential on afterpotentials induced by acetylstrophanthidin in canine ventricular tissues. J Pharmacol Exp Ther. 1980; 215: 332-341.

44. Rosen MR, Fisch C, Hoffman BF, Danilo P, Lovelace DE, Knoebel SB. Can accelerated atrioventricular junctional escape rhythms be explained by delayed afterdepolarizations? Am J Cardiol. 1980; 45: 1272-1284.

45. Wit AL, Cranefield PF, Gadsby DC. Electrogenic sodium extrusion can stop triggered activity in the canine coronary sinus. Circ Res. 1981; 49: 1029-1042.

46. Kline RP, Siegal MS, Kupersmith J, Wit AL. Effects of strophanthidin on changes in extracellular potassium during triggered activity in the arrhythmic canine coronary sinus. Circulation. 1982; 66 (Suppl 2): 356.

47. Kline RP, Morad M. Potassium efflux in heart muscle during activity: Extracellular accumulation and its implications. J Physiol. 1978; 280: 537-538.

48. Rosen MR, Reder RF. Does triggered activity have a role in the genesis of cardiac arrhythmias? Ann Intern Med. 1981; 94: 794-801.

49. Malfatto G, Rosen TS, Rosen MR. The response to overdrive pacing of triggered atrial and ventricular arrhythmias in the canine heart. Circulation. 1988; 77: 1139-1148.

50. Sung RJ, Shapiro WA, Shen EN, Morady F, Davis J. Effects of verapamil on ventricular tachycardias possibly caused by reentry, automaticity, and triggered activity. J Clin Invest. 1983; 72: 350-360.

51. Moak JP, Rosen MR. Induction and termination of triggered activity by pacing in isolated canine Purkinje fibers. Circulation. 1984; 69: 149-162.

52. Johnson N, Rosen M. The distinction between triggered activity and other cardiac arrhythmias. In: Brugada P, Wellens HJJ, editors. Cardiac Arrhythmias: Where to Go from Here? Mount Kisco, NY: Futura; 1987. p. 129-145.

53. Knoebel SB, Fisch C. Accelerated junctional escape. A clinical and electrocardiographic study. Circulation. 1974; 50: 151-158.

54. Wit AL, Rosen MR. Afterdepolarizations and triggered activity. In: Fozzard H, Haber E, Jennings R, Katz A, Morgan H, editors. New York: Raven Press; 1986. p. 1449-1491.

55. Waldo AL, Henthorn RW, Plumb VJ, Maclean WA. Demonstration of the mechanism of transient entrainment and interruption of ventricular tachycardias with rapid atrial pacing. J Am Coll Cardiol. 1984; 3: 422-430.

56. Waldo AL, Maclean WA, Karp RB, Kouchoukos NT, James TN. Entrainment and interruption of atrial flutter with atrial pacing. Circulation. 1977; 56: 737-745.

57. Waldo AL, Plumb VJ, Arciniegas JG, et al. Transient entrainment and interruption of the atrioventricular bypass pathway type of paroxysmal atrial tachycardia. Circulation. 1983; 67: 73-83.

58. Scherf D, Schott A. Extrasystoles and Allied Arrhythmias. Heinemann, Chicago; 1973.

59. Bozler E. The initiation of impulses in cardiac muscle. Am J Physiol. 1943; 138: 273-282.

60. Segers M. Le battement auto-entretenu du coeur. Arch Int Pharmacodyn. 1947; 75: 144-156.

61. Wittenberg SM, Streuli F, Klocke FJ. Acceleration of ventricular pacemakers by transient increases in heart rate in dogs during ouabain administration. Circ Res. 1970; 26: 705-716.

62. Hogan PM, Wittenberg SM, Klocke FJ. Relationship of stimulation frequency to automaticity in the canine Purkinje fiber during ouabain administration. Circ Res. 1973; 32: 377-383.

63. Temte JV, Davis LD. Effect of calcium concentration on the transmembrane potentials of Purkinje fibers. Circ Res. 1967; 20: 32-44.

64. Davis LD. Effects of changes in cycle length on diastolic depolarization produced by ouabain in canine Purkinje fibers. Circ Res. 1973; 32: 206-214.

65. Anderson GJ, Swartz J. Triggered automaticity in canine myocardial infarction. Int J Cardiol. 1983; 2: 445-447.

66. Goren C, Santucci BA, Bucheleres HG, Denes P. Chronic recurrent ectopic junctional tachycardia resembling triggered automaticity in mitral valve prolapse syndrome. Am Heart J. 1981; 101: 504-507.

67. Cranefield PF. Does spontaneous activity arise from phase 4 depolarization or from triggering? In: Bonke FIM, editor. The Sinus Node: Structure, Function and Clinical Relevance. The Hague: Martinus Nijhoff; 1978. p. 347-356.

68. Lakatta EG, Vinogradova TM, Maltsev VA. The missing link in the mystery of normal automaticity of cardiac pacemaker cells. Ann NY Acad Sci. 2008; 1123: 41-57.

69. Maltsev VA, Lakatta EG. Dynamic interactions of an intracellular Ca^{2+} clock and membrane ion channel clock underlie robust initiation and regulation of cardiac pacemaker function. Cardiovasc Res. 2008; 77: 274-284.

70. Biel M, Schneider A, Wahl C. Cardiac HCN channels: structure, function and modulation. Trends Cardiovasc Med. 2002; 12: 206-212.