The links between basic and clinical cardiac electrophysiology

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FORTY OR 50 years ago, the terms "clinical" and "basic" cardiac electrophysiology described two sides of the same coin. The clinical electrophysiologist was an electrocardiographer; the basic electrophysiologist used electrographic and electrocardiographic techniques to study the hearts of animals or isolated tissues obtained therefrom. Clinical and basic electrophysiologists shared a common language and a common interest in the causes and treatment of cardiac arrhythmias, seeking the answers to questions such as: Why does the heart beat? How and where does the impulse conduct? What are the modulators of cardiac rhythm? What are the causes of dysrhythmic beats? Moreover, these questions were asked not only at the outset of the modern era of electrophysiology but are asked today as well. In the following pages I shall emphasize how the links between basic and clinical research have helped us attempt to answer some of these questions, and I shall consider some of the problems that have occurred along the way and some of the prospects for future collaboration.

The modern era in basic and clinical electrophysiology. During the years after World War II, two events occurred that set the stage for the present relationship between basic and clinical investigation. The first was in a related field, neurophysiology, and culminated in the studies of Hodgkin and Huxley, in which the ionic determinants of the action potential of a single cell, the giant axon of the squid, were described.1-4 The second event was the description, by Ling and Gerard in 1949, of glass capillary microelectrodes having sufficiently small tip diameters to permit impalement without injury of single muscle cells.5

Since these discoveries in the 1940s, electrophysiologists have had the means to investigate the cellular and subcellular basis for the control of cardiac rhythm. Their studies have incorporated many of the ideas and techniques of the biophysicist, the electrocardiographer, and the neurophysiologist. The subsequent explosion of information can be understood in light of the following: in 1960, Hoffman and Cranefield coauthored a 323 page book, a critical summary of the body of information concerning electrophysiology to that date.6 It was and remains a classic, encyclopedic in its scope and yet completely accessible to the careful reader. Although other fine volumes have been written since then, none has so completely captured this ever-expanding field. Recent volumes that may be comparable in the completeness of information provided have been multiauthored, reflecting the increased specialization of individuals and diversity of electrophysiology (see refs. 7 and 8).

How have clinical and basic disciplines interacted? Those who have worked in the interface between basic and clinical electrophysiology have found this a remarkably fertile area for investigation. The common interest in and need for understanding electricity as it relates to biological systems has permitted investigators to phrase questions raised clinically in a fashion that permits their exploration in the research laboratory, and to carry the answers obtained to the clinic. Nonetheless, the same drive to learn and to apply knowledge that has been a major strength of the field has provided an important limitation; that is, we are not able to apply knowledge from one area to the other with complete freedom. Such application first requires the interpretation of knowledge. Interpretation is needed because, despite their similarities, neither the goals nor the techn-
niques of basic and clinical research have been entirely interchangeable. As we shall see, the process of interpretation from one arena to another, coupled with the use of deductive reasoning, has led at times to conclusions about the mechanisms of clinically occurring arrhythmias that have not been entirely accurate.

To illustrate these comments, let us recall that until recently, reentry and automaticity were considered by the general community of clinical investigators as the sole mechanisms for extrasystoles and tachyarrhythmias in patients (e.g., ref. 9), and let us ask to what extent was this codification of arrhythmias the result of firm scientific evidence as opposed to flawed interpretation. Reentry was (and remains) recognized as the major cause of most disabling and potentially lethal tachyarrhythmias. A standard text of cardiac arrhythmias published in 1971 stated, “Re-entry [is] a mechanism postulated to explain the production and maintenance of premature beats and other arrhythmias. An area of depressed excitability is present in the myocardium, which is capable of being activated after most of the myocardium has become refractory. Then, when the rest of the heart emerges from the refractory state, this now active focus propagates the impulse throughout the myocardium. This explains ventricular premature beats with fixed coupling and other arrhythmias”.

Another standard text enlarged on the meaning of fixed coupling, “The phenomenon of reentry can be invoked whenever ectopic premature systoles occur at a fixed time interval after dominant beats. . . . This is identified by the constancy of the P-P or R-R intervals between the preceding dominant and premature systoles; a relationship called fixed coupling.”

Note that mention of “fixed coupling” is central to the definitions quoted above. Why was fixed coupling viewed by many cardiologists as, literally, pathognomonic of reentry? To answer this question we must consider arguments and experiments relating to reentry itself in a variety of settings. The literature here has its origins in the 19th century and is extensively reviewed in the text of Scherf and Schott, which traces the contributions of Lewis, Munk, Marchand, de Boer, Wenckebach and Winterberg, Mack and Langendorf, and others.

Over the years, based on the above work and that which we shall now consider, a set of “rules” for the identification of reentrant arrhythmias gained general acceptance. It was agreed that circus movement reentry required (1) unidirectional block resulting from an anatomic or pathologic defect in one or more regions of the heart, (2) slow passage of the impulse over an alternative route, (3) delayed excitation of the tissue just distal to the blocked site, and (4) reexcitation of the tissue proximal to the site of block (see figure 1 and ref. 20). The path length and timing required for a reentrant impulse to complete its circuit and generate a single or multiple premature depolarizations were such that one might expect recurrent episodes of reentry over a single pathway to reproduce accurately the coupling seen between any one inciting beat and the reentrant impulse it induced—hence the concept of fixed coupling.

The means by which these “rules” for reentry were developed are of interest as examples of how basic investigation influenced clinical thought. In 1887, McWilliam first suggested that ventricular fibrillation was the result of an impulse propagating abnormally in the heart “from one fiber to another over which the contraction wave had already passed.” He likened this to a peristaltic contraction, a view very different from the previous theory, that fibrillation was the result of impulse initiation by multiple foci in a hyperexcitable muscle. A generation later, Mayer continued to explore the possibilities raised by McWilliam by studying the medusa, whose subumbrella tissue he cut into a ring. Stimulation at one site led to propagation of contraction around the ring bidirectionally from the site of stimulation until the two pulsatile waves met and effectively extinguished one another (figure 2, A). He then discovered that if stimulation were reapplied and tissue on one side of the stimulus were compressed, the wave of contraction traveled only in one direction (moving from the compression site), circling the tissue (figure 2, B). If compression were removed before the encircling contraction arrived at that site, propagation

![Figure 1](image-url)

**FIGURE 1.** A. Schematic of the terminal portion of the Purkinje system, showing two fibers entering the ventricular myocardium. Normal activation is indicated by the arrows. B. Effects of interposing a depressed segment (crosshatched) in which there is unidirectional block. Antegrade propagation is blocked near 1. Normal activation proceeds through limb A, traverses the myocardium, and reenters the depressed segment at 2, propagating slowly through this site until it gains access to the proximal conducting system after refractoriness has terminated. The concurrence of the pathway, the site of unidirectional block, and conduction sufficiently slow that refractoriness can terminate are all required if reentry is to occur in this model. (Modified after Schmitt and Erlanger.)

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proceeded back to the site of initial stimulation and
continued to conduct around the ring (figure 2, C). It
was Mayer who first suggested the importance of the
path length, the velocity of propagation, and the need
for tissue to rest (later understood as refractoriness) if
this circling propagation were to occur and persist.

These observations were applied to the vertebrate
heart by Mines who considered in light of atrial fibrillation by Garrey. It was Mines who first
defined the need for unidirectional block as a predisposing factor for reentry. 

He also emphasized the idea of propagation
of an impulse around a circuit, retrogradely across the site
of block so that it returns to its site of origin (figure 2,
D). He defined the relationship between the velocity of
conduction and the duration of refractoriness and stressed the likelihood that such reentry might be import-
ant in some clinical arrhythmias.

Mines also found that extrastimuli could abruptly
terminate propagation through the circuit, an obser-
vation that was later refined both experimentally and
clinically so that programmed extrastimuli could be
used to initiate or terminate reentrant rhythms in a
reproducible fashion. Finally, Mines anticipated the
problems that would be faced in studies of the human
and other complex hearts by emphasizing the difficult-
ties inherent in distinguishing reentrant impulses from
focal impulse initiation propagating around a loop
(figure 2, D and E). Simply stated, if an automatic focus
is adjacent to a site of conduction block, propagation
will proceed around a ring but will not quite return to
its site of origin. The net effect will mimic reentry.
Mines suggested the only way to distinguish the two
mechanisms definitively was to section the ring. An
automatic focus would continue to fire here, while a
reentrant rhythm would be extinguished.

These principles concerning reentry were applied to
the heart by Lewis, Rosenblueth et al., 
Kimura et al., Hayden et al., and Moe. Subsequently, during the microelectrode era, Cranefield and Hoffman and associates identified calcium-
dependent action potentials in depressed tissues. This
was important because it was the first observation, in
the Purkinje system, of a potential that could propagate
sufficiently slowly to permit an impulse to reenter prox-
imal areas of the conduction system after their refrac-
tory periods had terminated (thereby completing the
reentrant loop) (figure 1). More recently, Allessie et al.
modified the concept of reentry by demonstrating that a fixed anatomic obstacle may not be
necessary for reentry but that in some instances
(described by their “leading circle” model), the path
length may be defined entirely by the velocity of prop-
agation and the duration of refractoriness. Of impor-
tance in this model was that an anatomic obstacle was
not required for reentry; rather, it could occur in struc-
turally uniform tissues. In fact, the center of the tissue
(in this case, rabbit atrium) was rendered refractory due
to its repetitive invasion by impulses propagating to it
from all sides of the reentrant circuit. Finally, Spach et
al. identified anisotropic conduction, a phenomenon
in which slow propagation occurred across fibers
whose normal cell-to-cell coupling had been inter-
rupted experimentally. This indicated that even in the
presence of a normal transmembrane potential, con-
duction could be sufficiently attenuated to permit the
conditions for reentry. These observations, coupled
with the earlier work referred to, demonstrated that
reentry could occur through an anatomically or a func-
tionally defined pathway and defined the electrophysi-

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ologic characteristics required to permit arrhythmogenesis.

How was this information interpreted and applied to clinical arrhythmias? Of interest, historically, is the publication of de Boer, in 1926,17 postulating that in the presence of an anomalous pathway connecting the atria to the ventricles, a circus movement might evolve which is responsible for supraventricular tachycardias of the type we now refer to generically as involving "preexcitation." De Boer's hypothesis, supported by the experimental work of Butterworth and Poindexter41 and the clinical observations of Wolff42 of Harnischfeger,43 and of Langendorf et al.,44 suggested to clinical investigators in the 1960s that the etiology of arrhythmias such as the Wolff-Parkinson-White syndrome might be reentrant. Durrer et al.45 used electrical stimulation and the previously mentioned "rules" for identification of reentry to study four patients, focusing on the role of premature beats in initiating and terminating supraventricular tachycardia. In one patient, consistent initiation and termination of the arrhythmia led the authors to deduce that circus movement involving a bundle of Kent was the likely cause.

Concurrent and subsequent studies of other supraventricular arrhythmias46-50 lent support to the idea of reentry as the cause of these arrhythmias as well. However, let us consider the scientific basis for some of the arguments put forward. Hunt et al.47 stated, "In humans, recent investigations [i.e., refs. 45 and 48] have utilized atrial pacing to terminate arrhythmias in patients with the Wolff-Parkinson-White syndrome. They proposed a reentry mechanism as the basis for these arrhythmias, and felt that their termination by atrial pacing supported this concept." The authors then proceeded to describe two patients, in one of whom there was no evidence of the Wolff-Parkinson-White syndrome. Yet, relating this patient's electrocardiographic characteristics and response to pacing to those in patients with Wolff-Parkinson-White syndrome, they simply made the assumption that—as for the Wolff-Parkinson-White syndrome—reentry was the cause. This is a good example of the use of interpretation and deduction, in that a conclusion was reached based on similarities with another setting. The reasoning was appropriate and the conclusions defensible. The only problem is that, on the basis of the evidence presented, one cannot know whether the argument was correct. Another example is the case of paroxysmal atrial tachycardia described by Barold et al.49 "The circumscribed period in which the [arrhythmia] could be repeatedly initiated by a single electrical stimulus and its mode of termination in the same manner suggest the possibility that a circus movement may have been responsible..." This argument was entirely correct; it stated a possibility, not a certainty, and it depended on the response of the arrhythmia to premature stimulation permitting the diagnosis of reentry to the exclusion of all other mechanisms. At the time the authors wrote this, such a conclusion reflected the "state of the art." As shall be reviewed later, we now know this not to be the case.

Investigators then studied ventricular tachycardias (e.g., ref. 51) using the same methods for electrical stimulation previously applied to the atrium. In considering the diagnosis of their patient's arrhythmias, Wellens et al.51 stated, "The initiation of a tachycardia by a single premature beat is much easier to understand if one holds a reentry mechanism responsible." In light of the above information, and the responses of most of the ventricular tachycardias studied to premature stimulation, the conclusion reached was that the most likely cause of arrhythmia was reentry.

Nowhere in the above-mentioned manuscripts or in numerous other examples are there obvious flaws in logic. Each group of authors considered the arrhythmias studied in light of an understanding of basic investigation and based their conclusions on the interpretation of basic and of prior clinical investigation. As was done, the diagnosis of arrhythmia as a clinical mechanism moved from the "drawing board" (e.g., de Boer17) to the very likely clinical setting of preexcitation, to tachycardias in the atrium and then in the ventricle, where both the pathway of the arrhythmia and the site of block were more difficult to demonstrate.

Despite the inherent logic and the care and diligence in the marshaling of proofs, the major flaw apparent in the assignment of reentry as the cause of certain of these arrhythmias is the inferential nature of many of the arguments. Whereas in studies of patients with Wolff-Parkinson-White syndrome, surgical interruption of the pathway does terminate the arrhythmia—satisfying Mines' criterion24—similar proofs are lacking for most other arrhythmias. In fact, as emphasized above, in many of the studies performed, reentry was not so much proved as surmised.

In contrast to the system of logic that supported a reentrant mechanism, another body of evidence developed in the 19th century and enlarged on during the first half of the 20th indicated that "focal impulse formation in an ectopic centre"12 might provide an alternative explanation for some tachycardias and some examples of fixed coupling. Such focal impulse initiation might be automatic (as recognized by Mines in his early studies24) or it might be triggered.52,53 The occurrence
in excitable tissues of the afterpotentials or oscillations that cause triggered activity has been recognized for some time.\textsuperscript{54, 55} Scherf believed that "negative afterpotsentials" were the cause of many extrasystoles.\textsuperscript{12} Goldenberg and Rothberger\textsuperscript{56} showed that negative afterpotentials could induce rhythmic discharges in Purkinje fibers treated with veratrine. These investigators also noted resemblance of these discharges to the phenomenology of some paroxysmal tachycardias. However, it remained for Segers and for Bozler to define the phenomenon more fully. Segers\textsuperscript{57} used monophasic recordings to describe "self-sustained beating" resulting from Ba\textsuperscript{2+}, Ca\textsuperscript{2+}, digitalis, epinephrine, aconitine, and veratrine that induced arrhythmias distinct from automaticity. Bozler\textsuperscript{58} described afterpotentials that could be enhanced by epinephrine and give rise to "afterdischarges," or triggered activity, in the turtle heart. Work on oscillatory activity diminished after the early 1940s, although mention of it continued to surface intermittently (e.g., ref. 59). In fact, until the 1970s, when work resumed in earnest,\textsuperscript{60-65} afterpotentials were considered more a curiosity than the cause of specific arrhythmias.

To sum up, information gathered largely before the microelectrode era suggested both focal and reentrant etiologies for extrasystoles and for tachycardias. The mechanism behind the focal origin was somewhat uncertain, although the phenomenology of both automatic and oscillatory activity as potential causes of arrhythmogenic foci was recognized. The mechanism for the reentrant activity was better understood, since experiments on nonmammalian species as well as on the mammalian heart had described the phenomenology of unidirectional block and slow conduction. The clinical interpretation of this information was summarized by Wellens in 1978: "Although this opinion is not shared by all basic electrophysiologists, initiation and termination of tachycardia by premature stimuli given well-defined, reproducible timing intervals has been advanced as pointing to a reentry mechanism. Termination of tachycardia by 'overdrive' pacing would support the latter mechanism. Inability to demonstrate these phenomena has been accepted as suggestive of abnormal automaticity."\textsuperscript{66} It was stated, as well, that the ability of these criteria to discriminate between mechanisms can be limited because factors such as the basic pacing rate and site of stimulation might give misleading results. Hence, the state of the art, well into the present decade, invoked two clinical descriptors of arrhythmias and a clear-cut set of rules for their differentiation. Little or no room was left for other mechanisms for arrhythmias, even though other mechanisms had been described earlier and arguments presented about their applicability.

To understand just how far from actuality the arguments presented about the role of reentry in the etiology of some clinical tachyarrhythmias and fixed coupling may be (not "are"), let us consider (1) parasystole and (2) triggered activity resulting from afterdepolarizations. In so doing, we shall see that such mechanisms are, if not in fact then at least in theory, equally plausible as reentry as a cause of some instances of fixed coupling and that they are a reasonable cause of certain tachycardias as well. Because of the possibility that my opinions may be misinterpreted, let me stress that I am not stating reentry is now to be deemphasized as a cause of arrhythmias; rather I am stating that an important (but perhaps rather small) subset of arrhythmias that is not reentrant can mimic reentry in its electrocardiographic and electrophysiologic expression.

Parasystole. In 1903, Wenckebach\textsuperscript{12, 66} described as "pararhythmia" certain arrhythmias in which basic pacemaker function persisted but was complicated by the emergence of extrasystoles. Subsequently, it was recognized that "pararhythmia" could be typified by two types of behavior: one in which the coupling between the parasystolic beats and the basic rhythm varied in a manner consistent with two pacemakers firing independently of one another; and a second in which the relationship of the basic and parasystolic rhythm changed to one of fixed coupling.\textsuperscript{67}

In the ensuing years, parasystole acquired rather clear descriptors. A standard electrocardiographic definition of parasystolic rhythm read, "This pacemaker fires at regular intervals which are not correlated with the activity of the usual pacemaker. The beats of the ectopic pacemaker occur regularly and manifest no relation to those of the dominant rhythm because of entrance block."\textsuperscript{10} Major aids in the diagnosis of parasystole were the assumptions that intervals between ectopic impulses must be equal to or multiples of the basic ectopic pacemaker rate and that fusion could occur between the dominant and the ectopic pacemaker impulses. The question of fixed coupling in this setting was generally ignored; indeed, the latter was usually interpreted as signifying reentry (see above).

Hence, parasystole was interpreted as an automatic rhythm that was clearly differentiated from reentry. Moreover, the occurrence of fixed coupling signified reentry to most cardiologists, and this would be considered anathema to the clinical diagnosis of parasystole. There were exceptions to the standard view of parasystole, however. Scherf and his associates (see
ref. 12) were convinced that parasystole could express itself as a rhythm showing fixed coupling. Summing up their views on the relationship of either parasystole or reentry to the phenomenon of fixed coupling, Scherf and Schott had stated, "We believe parasystole to be due to automatic ectopic impulse formation, coexisting with another rhythm but not dependent on an initiating beat. Instances of proved parasystole with ectopic beats having accurate coupling can be understood as resulting from the rates of and/or the ratio between the two rhythms; in certain cases by subthreshold stimuli of an electric pacemaker becoming suprathreshold only during the supernormal phase of the preceding beat. The mechanism underlying the origin in the same center of extrasystoles with accurate coupling and of parasystolic ectopic beats has not yet been satisfactorily clarified."

Despite the understanding by some investigators that an automatic rhythm, parasystole, might incorporate fixed coupling in its clinical expression, the mechanism for this was not understood. Moreover, the contribution of an automatic mechanism, parasystole, to a rhythm deemed reentrant, fixed coupling, was not generally accepted. In 1976, Jalife and Moe published the first in a series of papers that were to provide much of the information about mechanism that was needed to explain fixed coupling as part of the spectrum of parasystole. The authors cited four previous works as seminal to their own experiments: the observations that electrotonus can influence electrical activity, including pacemaking frequency, distal to a site of block; that current pulses of low amplitude and long duration could accelerate automatic rhythms of isolated pacemaker tissues; and that subthreshold depolarizing stimuli delivered early in diastole of a pacemaker cycle could delay the appearance of the next spontaneous beat. Other information essential to the work of Jalife, Moe, and associates was that a parasystolic pacemaker required entry block to "protect" it from the effects of the dominant cardiac pacemaker and that propagation of an impulse from the parasystolic site might be modulated by exit block. Jalife and Moe then performed experiments using a three-chambered bath in which the central segment was perfused with sucrose, thereby providing a site of depressed conduction between the two outer compartments (figure 3, A). The segment of fiber bundle in the first compartment incorporated pacemaker cells that initiated impulses spontaneously; the segment in the third compartment was driven or beat spontaneously. The Jalife-Moe experiments showed that the electrotonic effects of spontaneous or driven impulses in chamber three occurring during the first half of the diastolic cycle delayed the next spontaneous discharge in chamber one; those occurring during the second half of diastole accelerated the next discharge. Moreover, a fixed and reproducible mathematical relationship between the electrotonic events and the shift in pacemaker activity could be identified (figure 3, B). Depending on the extent of block between the dominant and the ectopic pacemaker, as well as the frequency of impulse initiation by the dominant pacemaker with respect to the cycle length of the ectopic pacemaker, the rate of impulse initiation of the latter could be conditioned by the former so that a variety of patterns, including fixed coupling, resulted. Hence, a parasystolic pacemaker could be expected at times to fire independently of a dominant pacemaker and at other times to show dependence, expressed as fixed coupling.

This experiment became the basis for the theory of "modulated parasystole." In exploring this, Jalife, Moe, and their collaborators developed a mathematical model for parasystole and applied this not only to isolated tissues but to the electrocardiograms of patients with ventricular and atrial arrhythmias. One of the most unusual and insightful publications in this series was an evaluation of the electrocardiogram of the late Richard Langendorf, which demonstrated...
sinus extrasystoles having P waves identical to the normal sinus impulse, no compensatory pauses, and a duration of the postextrasystolic cycle nearly approximating the basic sinus PP interval. Patterns of trigeminy, quadrigeminy, and pentageminy occurred at times. The investigators thought the arrhythmias might result from parasystole, although the "classic" criteria for parasystole were not followed; that is, the interectopic intervals were not precise multiples of a common denominator and fusion beats were not identifiable. The investigators prepared a computer model for sinus node parasystole based on their earlier experimental and modeling experience. The model accurately reflected all characteristics of the electrocardiographic record, and the authors concluded that "the fact that our model of unidirectional entrainment/resetting does have a clinical counterpart in the case presented. . . suggests that the [modulated parasystole] hypothesis points in the right direction."76

In summary, evidence long predating the modern era suggested that the automatic rhythm, parasystole, could express a pattern of fixed coupling thought by most investigators to be typical of reentry. Before microelectrode technology was brought to bear, the arguments for reentry as a cause for fixed coupling had a more weighty experimental basis than those for automatic foci, leading to conclusions about "mechanism" that were drawn in good faith and yet based on incomplete information. The microelectrode studies offered proof that parasystole could induce some arrhythmias that incorporated fixed coupling in their pattern. Hence, in this example of basic and clinical electrophysiology complementing one another, the setting and the question were provided clinically. The answer came from studies in the microelectrode laboratory and was then reapplied to the clinic. The criticism mentioned previously with respect to reentry resurfaces here, in that there is still some element of interpretation, the need to surmise. But the evidence and logic have been impressively strengthened.

**Afterdepolarizations and triggered activity.** If our information about mechanism ended here, we could still attempt to analyze all arrhythmias in terms of reentry or automaticity, and we probably would be wrong. I state this because beginning in the 1970s,60–65 the phenomenology of afterdepolarizations was explored to an extent that made it no longer possible to ignore the role of these and other oscillatory phenomena in arrhythmogenesis. As was the case for parasystole, the exploration of oscillatory activity as a cause of arrhythmias had a long history; before the microelectrode era, Scherf,12 Segers,60 Bozler,58 and others (see above) all had performed experiments suggesting a role for oscillations in membrane potential in the initiation of cardiac arrhythmias.

The phenomenology of afterdepolarizations has been most completely categorized by Cranefield,52, 53 who has also actively explored their possible role in arrhythmogenesis. Afterdepolarizations are oscillations in membrane potential occurring before (early) or after (delayed) full repolarization of the transmembrane potential. Such oscillations are obligatorily induced by action potentials (they cannot arise de novo), and if they attain threshold potential they induce rhythms referred to as "triggered."

**Early afterdepolarizations.** Early afterdepolarizations

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**FIGURE 4.** Early afterdepolarizations and triggered activity. Panels A through D show a cesium-superfused Purkinje fiber driven at ever-increasing cycle lengths. In panel B, an early afterdepolarization is clearly seen as a "hump" during terminal repolarization, and in the next-to-last beat a triggered action potential occurs. In C there is bigeminy, and in D brief bursts of tachyarrhythmia, with the action potentials showing fixed coupling. (Reprinted from ref. 77 with permission.)
are cycle length dependent in that their amplitude increases as drive cycle length is increased, resulting ultimately in single or multiple premature beats and/or runs of tachycardia (figure 4).77 Not only is a relatively consistent relationship between drive cycle length and afterdepolarization amplitude seen with early afterdepolarizations, but they can give rise to rhythms that are clearly bigeminal, trigeminal, etc., in which the coupling is “fixed,” as is seen with reentry (or parasystole). Moreover, cycle length–dependent tachycardias may be initiated when the rate of their dominant cardiac pacemaker is sufficiently low to permit their emergence. This phenomenon can mimic reentry in its cycle length dependency and in its coupling. Yet, some early afterdepolarization–induced rhythms, especially those that arise at relatively high membrane potentials, respond to pacing procedures by being overdrive suppressed. The tendency to more frequent occurrence at slow pacemaker rates and the manifestation of overdrive suppression can lead to confusion of early afterdepolarization–induced rhythms with those that are automatic.77

No clinically occurring arrhythmia has been convincingly attributed to early afterdepolarizations. However, experimental animal and isolated tissue studies have shown similarities between arrhythmias resembling torsades de pointes and the early afterdepolarization. Brachmann et al.78 used cesium injection into intact animals to explore this relationship. Cesium induced a long QT interval as well as a pleomorphic tachycardia having some resemblance to torsades de pointes. Studies of isolated tissues have shown that cesium prolongs repolarization and induces early afterdepolarizations (especially in the setting of low [K+]o, thereby providing a possible explanation for the torsades-like arrhythmia seen in the intact animal.77, 78 Isolated tissue studies have shown that quinidine also induces early afterdepolarizations and triggered activity in the setting of low [K+]o.78 However, attempts to induce torsades in the normal, intact heart using quinidine or quinidine in the setting of hypokalemia have been relatively unsuccessful.

To date, the experiments on early afterdepolarizations and their relationship to torsades have shown that arrhythmias occur more readily after a long diastolic cycle or cycles, tend not to be overdrive suppressible, and are potentiated by common interventions (e.g., low [K+]o, cesium, quinidine). However, these associations are as yet insufficient to implicate early afterdepolarizations as either the sole cause of or as an important cause of these arrhythmias in human subjects. Indeed, experimental models of conduction abnormalities have shown that myocardial infarction80 or a combination of ischemia, reperfusion, and quinidine81 can induce arrhythmias resembling torsades de pointes. This diversity of mechanisms inducing the same arrhythmia highlights the complexity of torsades and the likelihood that its electrocardiographic manifestation is a “final common pathway” that can result from more than one mechanism.

**Delayed afterdepolarizations.** Delayed afterdepolarizations differ from the above in that they increase in amplitude and tend to attain threshold more readily as heart rate increases.60–65 Hence, delayed afterdepolarizations can also induce fixed coupling and tachycardias but do so more readily at rapid than at slow stimulus rates. A major effort has been made to test the association between delayed afterdepolarization–induced triggered activity and clinical arrhythmias as well as to differentiate triggered from reentrant activity.82–84 A convenient electrophysiologic means for discriminating such triggered activity from reentry is to interpose a series of driven beats using as wide a range of drive rates as possible followed by cessation of drive. Whereas reentrant rhythms might be expected to show a prolongation of the coupling interval of the first ectopic beat that follows the cessation of drive, the first postspacing interval for a triggered beat invariably shortens. Overdrive pacing over a wide range of drive cycle lengths demonstrates a linear relationship, i.e., shortening of the first postspacing interval of the

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**FIGURE 5.** The vertical axis shows the coupling interval for triggered action potentials in a digitalis toxic Purkinje fiber, expressed as a function of pacing cycle length. Note the linear relationship, with the coupling interval decreasing as pacing cycle length decreases. See text for description.
arrhythmia after each progressively faster drive train (figure 5).

A great deal of information about triggered activity has been derived from studies in which digitalis was administered to experimental animals. After toxic doses of digitalis, repetitive ventricular responses can be induced by single extrastimuli or short bursts of cardiac pacing.85, 86 The coupling interval of the first triggered beat tends to decrease as the cycle length of the paced beats is decreased.87, 88 reproducing the relationship seen for triggered action potentials in isolated tissue.61, 63 A subset of arrhythmias in the 24 to 96 hr period after coronary ligation in the dog also seems to be triggered.89, 90 This is of interest because the predominant arrhythmia in the 24 hr infarct appears to be automatic,90–92 the triggered rhythm may be induced by either the automatic rhythm or by pacing. Catecholamine injection into the canine coronary sinus can induce an atrial tachycardia whose coupling interval characteristics mimic coupled action potentials in isolated coronary sinus preparations having triggered arrhythmias.93, 94 Hence, in the atria and ventricles of intact animals, several disparate interventions can cause triggered activity. The mechanism common to the diverse triggered arrhythmias appears to be calcium loading of the cell, which in turn induces an oscillatory transmembrane current carried by sodium and referred to as $i_n^t$ (the transient inward current).95, 96

In the clinical setting, two approaches have been used to identify triggered rhythms. One depends on electrocardiographic analysis to identify whether the phenomenology of an arrhythmia is consistent with triggered activity (e.g., ref. 82), and other involves invasive electrophysiologic testing (e.g., ref. 97). Most, if not all, of the clinical studies to date have relied on interpretation of data obtained in microelectrode and intact animal experiments, thus they are subject to the same criticisms of interpretation mentioned earlier with respect to reentry. Perhaps the most promising group of patients studied with a view toward identifying delayed afterdepolarization–induced triggered activity as a cause of arrhythmias is that with exercise-related ventricular tachycardia and no demonstrable coronary artery or cardiac disease.98–105 These tachycardias are inducible with catecholamine infusion and can be initiated and terminated by pacing. They characteristically follow an acceleration of sinus rate, and the coupling interval of the first arrhythmic beat decreases with the preceding drive (or sinus) cycle. The tachycardias appear sensitive to β-blockade, verapamil, and adenosine, all of which have been shown to suppress triggered activity.

In sum, triggered activity has been well defined at the cellular level and reasonably documented in experimental animals. To what extent it contributes to clinical arrhythmias is not yet certain, yet it is clear that the days when we could dismiss all clinical arrhythmias as simply “reentrant” or “automatic” are over.

The future. In reviewing this small subset of clinical and basic electrophysiologic research, I have attempted to highlight the intense interaction that has existed between basic and clinical disciplines in defining arrhythmogenic mechanisms. It is clear that clinical observations have led to studies of mechanisms in the basic research laboratory and that ideas from the latter have been applied to patients. That these ideas have not necessarily been applied in balanced fashion and that interpretation often has involved both science and prejudice is also apparent. Nonetheless, given that we do not yet know what is “right” or “real” in many settings, it is likely that interpretation and prejudice will continue, for at least a while, to play an important role in many decisions.

What will help us—as well as create new problems—will be new means for considering mechanisms and for applying them to the clinic. That such means are needed is apparent, considering that there is much about mechanism, prevention, and treatment that we still do not know. From what areas can we expect new information? In part, we shall continue to use standard electrophysiologic methods, which recently have generated exciting new ideas concerning the characteristics of reentrant and automatic rhythms. The studies of reentry106, 107 have identified strict criteria, relating to the cycle lengths and morphologies of arrhythmic P waves and/or QRS complexes after periods of pacing, that appear to identify reentrant rhythms more accurately than criteria used in the past. Unfortunately, failure to meet the criteria does not indicate that a rhythm is not reentrant. The studies of automaticity have demonstrated the occurrence of automatic rhythms not only in specialized conducting fibers, but also in muscle when it is depolarized to low membrane potentials.108, 109 They have also shown that this type of automaticity results from a different pacemaker mechanism than that which occurs in a normally polarized fiber, that it is less readily overdrive suppressed (with the magnitude of overdrive suppression decreasing as the membrane is depolarized), and that at very low membrane potentials it may increase in rate after periods of rapid pacing, thereby mimicking a triggered rhythm.110 This further highlights the complexity presented to us as we attempt to discriminate among various arrhythmogenic mechanisms.
Although the traditional investigative tools I have just described will continue to expand our understanding, there are new technologies and interdisciplinary interactions that promise to widen our horizons even further. Perhaps the most explosive growth in electrophysiologic investigation recently has been in biophysics. The advent of techniques to disaggregate and study the current-voltage relationships of single cardiac myocytes has now permitted the quantification of ionic determinants of the transmembrane potential in a fashion that was impossible with multicellular preparations. Moreover, the ability to remove "patches" of membrane from the cell and study individual channel species now promises to provide quantitative information about the ionic control of the transmembrane potential in normal and pathologic states and about the action of drugs.

These techniques and standard electrophysiologic methods are being used not only alone but also with biochemistry and molecular biology to advance our understanding of normal physiology and pathophysiology. For example, we are learning about the links between receptor stimulation, second messengers, and regulatory proteins and their modulation of cardiac rhythms and underlying ionic currents (e.g., refs. 15-18). This type of information—from studies in normal and pathologic environments—will provide a new dimension not only in our understanding of cardiac arrhythmogenesis but also in our understanding of neural and humoral modulation. In other biochemical studies we have learned about the lysophosphoglycerides that are released at the time of ischemic injury and that have profound arrhythmogenic effects on cardiac tissues. Moreover, we have appreciated that these same substances alter the fluidity of the cell membrane. Hence, they not only induce arrhythmias but, by changing the environment, may alter the binding of antiarrhythmic drugs. Finally, molecular biological techniques are being used to clone receptors and channels. In the near future, we shall have as good an understanding of the three-dimensional anatomy of these structures as we now have of the intact heart itself, information that will be of benefit in designing therapies for cardiac arrhythmias.

The potential impact of the new technologies on basic and clinical electrophysiology is such that the limits of reality and fantasy become blurred. It is important that we see these advances not only as isolated laboratory phenomena but as identifiers of pathophysiology that truly can be related to the function of the heart in situ. With this in mind, it is not unrealistic to dream of learning the changes that occur in the structure and state of membrane channels during their normal function and as pathology supervenes. It is not unrealistic to expect that the interaction of those events with neural, biochemical, and metabolic information can be synthesized so that first we can understand and then apply such information to prevention and therapy. The time is at hand to marry molecular biological technology with other available tools, not only to synthesize a channel or a receptor but to visualize its three-dimensional structure, perhaps with the aid of techniques such as x-ray crystallography. Once this is done, we can begin to consider the structure-activity relationships of cellular subunits and to tailor molecules that uniquely interact with them, providing new vistas in therapy.

The progress that is now possible and the public and institutional perception of such progress are of great concern because the continued study of the heart and of isolated tissues are not viewed by some as having the glamour and seemingly infinite possibilities of the new technologies. However, we will not be able to realize the fullest application of these new technologies if we do not continue to develop clinical and basic investigators who understand and study pathophysiology at the level of the organism and the organ. The importance of this statement resides not only in the need for synthesis and application of information as we explore ever more diverse universes of thought but also because each of the new technologies brings with it its own set of artifacts and opportunities for misinterpretation that must be considered as we attempt to relate the information we obtain to the heart itself. The problem we now face was put succinctly in a statement attributed to Chandler McC. Brooks: "[Studies in the single cell] tell us what a cell can do, not what it does do." In other words, the quantitative information we expect to obtain with some of the new technology may tell us more about the limits of a cell's ability to perform in an artificial environment than its usual role in the physiologic and pathophysiologic settings of the healthy and diseased heart. Another problem is that referred to earlier: at the time the electrocardiogram was developed, the clinical and basic investigator inhabited the same universe. They used largely the same tools, spoke the same language (and often were the same person). However, the disciplines and techniques we now contemplate are so diverse that clinical and basic investigators no longer speak a common language. Moreover, as training becomes more time-consuming, specialized, and expensive, we are seeing some clinical investigators who are unskilled, unschooled, and at times uninterested in research at the most basic level.
and some basic investigators whose realm of interest is defined by the anatomy and physiology of the channel rather than of the heart to whose function the channel contributes.

Conclusions. Where does this leave us? Certainly, some important doubts and questions about mechanism raised in the premicroelectrode era have been settled. We have seen that much more than logical and cogent interpretations are needed if we are to understand mechanism. We have recognized that the search for information relating to mechanism is still in its incipient stages, at this point promising more than delivering information that will be of use clinically.

Having accepted this and having reached out for links with new disciplines and areas of technology, we find ourselves well positioned to continue the search for answers to those questions that I listed in the first paragraph of this perspective. We are poised to continue a voyage of discovery that will involve new ideas, new structures, new languages, and ever more fundamental answers to our questions. If we face this future with a willingness to learn and to communicate across fields of investigative expertise, then the least of our gains will be knowledge and understanding and the greatest will be limited solely by our collective imagination.

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