In an era that finds us continually bombarded with numbers and images about threats, both real and imagined, a threat as old as the Bible is that of cardiac arrhythmia. The year of Wenckebach's observation, 1914, was the same year in which George Ralph Mines published his initial experiments on reentry, observations on "circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation" that were seminal to the field. That year was little more than a decade after Einthoven's description of the ECG, which rapidly became and has since remained the primary tool facilitating both our understanding and our diagnosis of arrhythmias during these 100 years since its invention.

The decades after the first therapeutic application of quinidine saw the testing and addition to arrhythmia therapy of drugs such as procaine, procainamide, ajmaline, and diphenylhydantoin. By the end of the 1960s, with propranolol and lidocaine available, there seemed to be great promise in the evolution of meaningful drug treatment. This was not only the product of work in drug development, but also of research using microelectrodes to record from cells and studies using animal models that informed us about the mechanisms of drug action (permitting their classification) and the mechanisms responsible for arrhythmias. Lidocaine and β-blockers had come onto the scene, and disopyramide, flecainide, and the calcium channel blockers were soon to follow; it seemed like the bad old days of quinidine and procaine amide were to give way to a new beginning.

The dousing of our optimism came quickly. Use of the then-new Holter monitoring technique demonstrated that we knew far less about the expression of arrhythmias then we had thought. Replacement of the 2-minute rhythm strip by 4-hour, then 6-hour, and finally 24 hour or longer periods of monitoring showed us that arrhythmias could be quantified and considered in terms of their reproducibility and that drug effects could be measured in far more convincing fashion than we had previously thought.6,7 We also learned that much of what we had interpreted as antiarrhythmic efficacy in fact reflected placebo effect and/or the inherent variation in arrhythmia expression over time.

Next came the Cardiac Arrhythmia Suppression Trial (CAST), which had 2 outcomes. First, it showed us the dark side of administering antiarrhythmic drugs (in this case flecainide, encainide, and moricizine) to patient populations not truly in need of them. Second, it reinforced a mindset that strove to develop drugs mimicking the repolarization-prolonging effects of amiodarone, which was reported as an antiarrhythmic agent in 1969.9 This intent to prolong repolarization, (the class III effect of Singh and Vaughan Williams) led to the clinical testing of the uniquely I\textsubscript{Kr}-blocking derivative of sotalol, d-sotalol. The resultant Survival With Oral d-Sotalol (SWORD) trial, in which mortality in the d-sotalol-treatment group was excessive, not only mirrored the CAST experience for a different patient population but further dampened the enthusiasm for new antiarrhythmic drug development. Nonetheless, some apparently useful drugs (eg, dofetilide, ibutilide, and azimilide) have evolved from the effort to prolong repolarization and, in some instances, have been approved for patient care.

In part, the limited development of new drugs was the result of industry's post-CAST and SWORD lack of enthusiasm coupled with a lack of imagination in industrial and academic basic science. So constrained was our vision regarding targets for antiarrhythmic development that the old adage "if the only tool you have is a hammer, then everything looks like a nail" could have been used to characterize the field. There was recognition of the need for new targets, and though investigators called for them and wrote of them, they seemed not to come.

Hence, there evolved a major disconnect between need for novel and safe antiarrhythmic drug therapy and satisfaction of this need. Recently, this need has been emphasized by the Communicable Disease Center, which tells us of 420 000 sudden deaths per year in the United States alone that are
presumably the result of arrhythmia. It is seen in the statistics showing that atrial fibrillation afflicts 5% or more of the population over 65 years of age. It is highlighted by the fact that myocardial infarction and its associated arrhythmias, remain a scourge, while knowledge of the multiple incarnations of cardiomyopathy increasingly assails us.

What many of these arrhythmic settings have in common is an element of myocardial hypertrophy. Such hypertrophy may be global, as in systemic hypertension; it may be regional, as in septic hypertrophy; or it may be subtler, as in the localized hypertrophy that characterizes peri-infarct zones. Arrhythmias occur in all of these conditions. To deal with them, we have on hand a panoply of drugs that is as applicable to our current knowledge of arrhythmias as the blunderbuss is to our current knowledge of firearms.

Think of the above scenario in light of what we are beginning to understand. Arrhythmias are not the entities we once considered them to be, not a happening we can understand purely in light of animal electricity. They derive from a complex interaction of molecules that either directly impact electrical activity (by synthesizing the channels and pumps that transfer ions and charge) or indirectly impact electrical activity by influencing and modulating the activity of these molecules. We now understand that atrial fibrillation is not a single arrhythmia, despite the fact that it often has a typical pattern electrocardiographically. The same can be said for ventricular tachycardia. This statement is readily understood if we recognize that torsades de pointes resulting from congenital long-QT syndrome may derive from any one of a number of lesions in different channel proteins (eg, SCN5A, HERG, KVLQT1, etc), each of which is, in effect, a different disease. This syndrome has also taught us that it is not always enough to have a molecular lesion (ie, an anomaly of the substrate), but that a trigger may be necessary to bring about clinical expression. This is seen in the effect of sympathetic stimulation via beta-adrenergic pathways to tip the balance in favor of torsades de pointes in KVLQT1-associated long-QT syndrome.

As we hunt for targets, most of these likely as old as Job, albeit new to us, and as we explore the diversity within the human heart, we need to pull together the threads of disease, hypertrophy, and arrhythmia and further conceptualize them in light of substrate and trigger. In engaging in such thinking, one can appreciate the value of the recent work on calmodulin kinase IV (CaMKIV) and the clarity of understanding which results in many cases of hypertrophy such targets will be equally applicable and therefore attractive. Even if applicability turns out to be limited to hypertrophy-associated arrhythmias, however, the value of the direction taken will still be immense, both for the identification and the exploration of new therapies.

A final thought derives from the continued debate over the value of mouse models in the study of human arrhythmias. Clearly, the mouse has an ECG that is repugnant to those of us who enjoy looking at T waves; indeed the mouse QRS-T complex is as truncated as some of the modified murine genes that are studied. Moreover, the ion channels determining repolarization differ, and even the mechanisms for arrhythmias may differ in mouse as compared with man. Nonetheless, the quality of thought going into work on these models and the clarity of understanding which results in many cases clearly augur well for the long-term upgrading of our therapeutic armamentarium, a point well-made in the current issue of the Circulation.

References
