DRUG TREATMENT FOR DISORDERS OF CARDIAC RHYTHM: PAST, PRESENT, AND FUTURE

MEDICAL GRAND ROUNDS

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INTRODUCTION

Cardiac arrhythmias appear to have troubled man at least as long as there are written records. Ancient manuscripts attest to sudden unexpected death, then as now probably most commonly a result of ventricular fibrillation. Early writings also allude to irregularities of the pulse. The history of cardiac arrhythmias as we know them, however, really date only to Einthoven's development of the electrocardiogram (1) and pioneering basic electrophysiological experiments, both in the early part of this century. The next three decades saw an explosion of writings describing and naming irregularities of cardiac rhythm. A number of basic electrophysiological experiments which established putative mechanisms for the newly described arrhythmias were reported in parallel with the electrocardiographic reports. It was an exciting time for basic and clinical electrophysiologists. Specific drug treatment for these rhythm disturbances lagged much behind. Treatment with cardiac glycosides to slow the ventricular response to supraventricular rhythm disturbances had preceded development of the electrocardiogram, of course, but gained a more rational basis with the new knowledge gained with electrocardiography. Aside from occasional use of atropine-like cholinergic drugs and cardiac glycosides, drug therapy of cardiac arrhythmias was, for over 30 years, the use of quinidine. Wenckebach is responsible for beginning the systematic use of cinchona alkaloids in 1912.(2) Six years later it was found that the most potent of the cinchona alkaloids was quinidine, the dextrorotatory isomer of quinine. (3) The observation that local anesthetics had anti-arrhythmic properties, in 1936, provided the next big advance, and set the stage for the use of the amide derivative of the local anesthetic procaine. Use of lidocaine, another local anesthetic, and the anti-convulsant phenytoin as anti-arrhythmic agents came close on the heels of the use of procainamide. A review of drug treatment of cardiac arrhythmias ten years ago would have been chiefly a review of those four drugs, quinidine, procainamide, lidocaine, and phenytoin. The last decade has seen considerable activity in the development of new drugs for the treatment of arrhythmias and parallel advances in the understanding of the mechanisms for the rhythm disturbances. Much of the drug development and testing has gone on outside the United States. The outlook for new anti-arrhythmic drug development looks brighter now than ever before. Thanks to the work of basic and clinical electrophysiologists over the last decade and a half, our knowledge of the causes of arrhythmias is burgeoning again, reminiscent of the early part of the century. It is again an exciting time for cardiac electrophysiologists. Now the American internist is beset with a bewildering barrage of strange new drug names as some of these agents have found their way into clinical investigation and emergency humane use in this country. Some may be approved for clinical use in the United States in the near future.

Development of new drugs and better understanding of the mechanisms of arrhythmias have stimulated a search for better classifications of anti-arrhythmic agents based upon their electrophysiological properties.

A sound approach to drug therapy of arrhythmias requires an understanding of the electrical cause of the rhythm disturbance. An understanding of the putative mechanisms of arrhythmogenesis requires a reasonable understanding of the normal electrophysiology of the heart. Consequently, I have three goals in this review: (1) a brief, superficial review of normal cardiac electrophysiology and current concepts of arrhythmogenesis; (2) a consideration of the classification of anti-arrhythmic drugs; and (3) a brief review of the uses and some of the characteristics of 19 drugs, all but 8 of them - quinidine, disopyramide, procainamide, lidocaine, phenytoin, bretylium, verapamil, and the beta-adrenergic blocking drugs (here taken as a single agent for this purpose) - still in investigational stage in this country.

In the brief overview of normal cardiac electrophysiology to follow, focus on the ways that cardiac disorders may change the electrophysiological properties of heart cells favoring development of two abnormalities: abnormal impulse formation and conduction delay. Conduction delay is essential for the development of re-entry of an impulse in such a way that a continuous circulating wavefront of electrical activity ensues. Abnormal impulse formation and re-entry are the fundamental electrical causes of cardiac arrhythmias.

NORMAL CARDIAC ELECTROPHYSIOLOGY

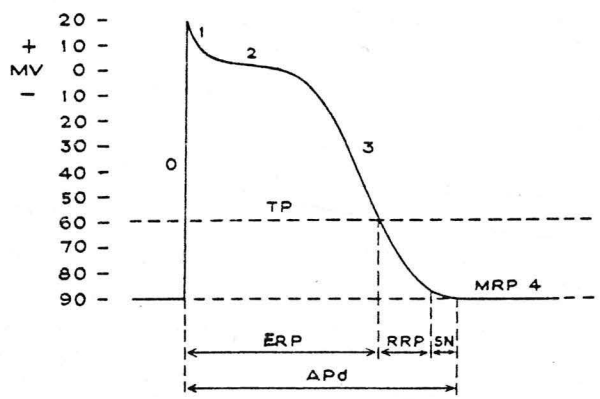
BASIC CONCEPTS

The ionic basis for the cardiac action potential is considerably more complicated than the corresponding mechanisms in skeletal muscle. In the heart - in contrast to skeletal muscle - the action potential lasts longer, consists of several phases, and varies in its characteristics from one region to another. (Figures 1 and 2). The action potential of the Purkinje fibers, for example, consists of five phases and lasts over 300 milliseconds. The upstroke of the cardiac action potential (phase 0) is extremely rapid and corresponds to the similarly rapid depolarization in skeletal muscle and nerve fibers. In most regions of the heart, however, two phases follow depolarization that have no counterparts in skeletal muscle and nerve. A short phase of repolarization (phase 1) is followed by a long plateau (phase 2) which in great part accounts for the long duration of the cardiac action potential. Repolarization (phase 3) and the resting potential (phase 4) of the cardiac action potential are fairly similar to their counterparts in skeletal muscle and nerve.

The inability of the myocardium to be re-excited immediately after depolarization is called refractoriness. The period during which excitability is reduced is called the refractory period. In describing cardiac excitability, the term effective refractory period is preferable to the term absolute refractory period. Electrical stimuli delivered to the heart later during the effective refractory period can, if they are strong enough, elicit a local response, that is, a transient depolarization that is not propagated. The relative refractory period is one in which only an abnormally strong stimulus can

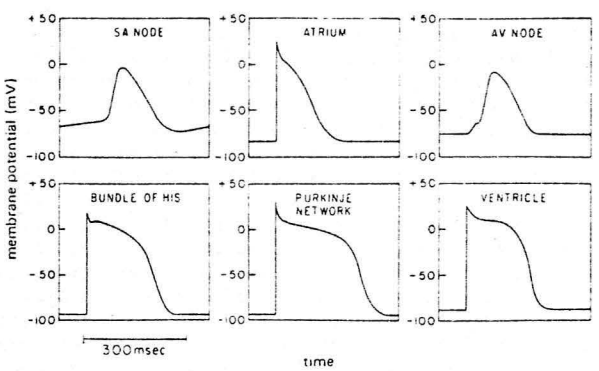
FIGURE 1

DIAGRAM OF THE ACTION POTENTIAL OF A VENTRICULAR MUSCLE CELL



MRP = membrane resting potential; 0 = depolarization; 1, 2, 3 = phases of repolarization; 4 = diastolic phase = MRP, APd = duration of action potential; TP = threshold potential; ERP = effective refractory period; RRP = relative refractory period; SN = supernormal period.

FIGURE 2



Action potential configurations in different regions of the mammalian heart.

initiate a propagated action potential. Not only is a stronger than normal stimulus necessary to elicit a response, but an abnormally slow-rising and low-amplitude response follows the stimulus after prolonged latency. This long latency, partly due to decremental conduction, is of considerable importance in arrhythmias associated with re-entry, an issue that will be discussed in greater detail later. The supernormal period that follows the relative refractory period is one in which stimuli that are slightly smaller than the usual diastolic threshold stimulus elicit a propagated response. The interval between depolarization and recovery of normal, resting excitability, the full-recovery time, encompasses the effective and relative refractory periods and the supernormal period.

There are both similarities and differences in the ionic bases for the cardiac action potential compared to the action potentials of skeletal muscle and nerve. The differences reflect highly specialized ionic channels of the sarcolemma of the heart, a semipermeable membrane. The conductances of different ions change sequentially during the cardiac action potential. At rest, the sarcolemma is highly permeable to potassium but relatively impermeable to sodium, chloride, and calcium; and consequently the conductance of potassium is high and the conductance of sodium, chloride, and calcium are low. The remarkable capacity of the cardiac sarcolemma to undergo sequential changes in ion conductance accounts for the complex characteristics of the cardiac action potential and for many features of the normal and abnormal electrocardiogram. (Figure 3, Table 1).

For clarity, several terms that are used in describing the action potential are defined or discussed below:

Membrane potential (E_m), a potential difference, represents the voltage difference between the interior and exterior of the cell. By convention, the resting potential is defined as the charge inside the cell compared to the outside, in which case the resting potential is negative. An increase in resting potential therefore represents a more negative charge inside the cell and a decrease in resting potential represents a less negative charge in the interior of the cell.

Depolarization represents a decrease in the electronegativity of the cell interior. The amplitude of the action potential is the extent to which the negativity of the cell decreases from its resting level.

Repolarization describes the return of membrane potential to a more negative level following depolarization, that is, recovery of the cell to the normal resting potential.

Hyperpolarization represents an increase in resting potential to more negative values.

An inward current represents that flux of charge that results if positive ions move into the cell. An efflux of negative ions also gives rise to an inward current.

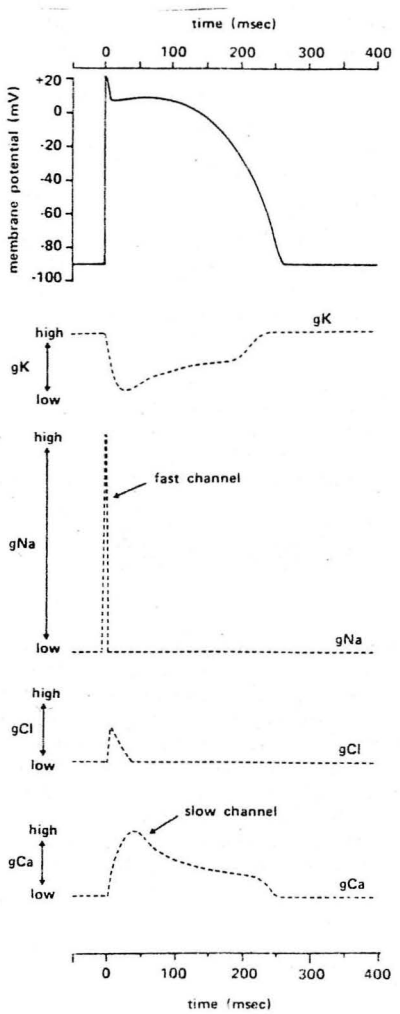
An outward current results either from an influx of negatively charged ions into the cell or an efflux of positively charged ions.

Membrane resistance is defined by the relationship between membrane potential and current flow in accord with Ohms law: $R=E/I$,

TABLE 1
ION MOVEMENTS RESPONSIBLE FOR CARDIAC ACTION POTENTIAL

Ion	Movement	Current	Phase of Action Potential
Na^+	In	Inward	0 (depolarization)
Cl^-	In	Outward	1 (early repolarization)
K^+	Out	Outward	
Ca^{2+}	In	Inward	2 (plateau)
K^+	Out	Outward	
K^+	Out	Outward	3 (repolarization)

FIGURE 3



Changes in ionic conductances during the action potential in a Purkinje fiber. Note the typical action potential (top) and reading from top to bottom, the accompanying changes in conductance for potassium (gK), sodium (gNa), chloride (gCl), and calcium (gCa). An increase in gNa or gCa augments inward current flow, whereas increasing gK or gCl augments outward current flow.

where R is resistance, E is potential, and I is current flow.

Membrane conductance (g) is the reciprocal of membrane resistance, so $(g) = 1/R = I/E$. Conductance provides an index of the ability of the membrane to allow ion movement from one side to the other. Conductance describes the current which flows in only one direction at any time.

Membrane permeability (P) is a measure of the ability of a membrane to allow flux of a substance from one side to the other. Permeability and conductance reflect similar properties of the membrane, but they do not describe the same thing. For uncharged molecules flux is determined by concentration of the molecule and permeability; for charged molecules the relationship is more complex as ion fluxes are modified when there is a membrane potential. Permeability describes ion fluxes in both directions across the membrane at any time.

The propagated wave of depolarization that initiates contraction of the heart is carried from cell to cell by regenerative action potentials. While several regions of the heart have specialized conduction properties, all impulses are transmitted by myocyte to myocyte communication. Cardiac nerves do not participate in the propagation of the wave of depolarization throughout the heart.

When membrane potential becomes depolarized beyond a threshold, a propagated action potential is initiated. If depolarization fails to reach the threshold an action potential is not initiated, the membrane recovers, and no wave of depolarization is propagated. On the other hand, when depolarization exceeds the threshold, membrane depolarization continues even though the initiating stimulus is extinguished. Thus once threshold is reached, the remainder of depolarization becomes independent of the stimulus that initiated depolarization.

The characteristics of the resting and action potentials differ from one region of the heart to another. Nevertheless, for the sake of simplicity, there are enough between-region similarities to consider them in two groups: first, the Purkinje fibers, and atrial and ventricular working myocardial cells; and second, the cells of the sino-atrial and atrio-ventricular nodes.

RESTING AND ACTION POTENTIALS OF PURKINJE CELLS AND WORKING ATRIAL AND VENTRICULAR MYOCARDIAL CELLS

Resting Potential

The resting potential of Purkinje cells and working atrial and ventricular myocardial cells is determined predominantly by the potassium ion concentration gradient. (Figure 3). At rest the sarcolemma is relatively permeable to potassium ions but relatively impermeable to sodium, chloride, and calcium. Potassium flux out of the cells down the concentration gradient causes a net negative charge inside the cell, usually -80 to -90 mV, approximating the equilibrium potential for potassium (about -95mV). Conditions or cardiac disorders that change the potassium concentration inside or outside the cell may alter the resting potential and contribute to the genesis of arrhythmias.

As considered below, a small amount of sodium enters the cell and a small amount of potassium leaves the cell with each action potential. Long-term maintenance of the sodium and potassium gradients depend upon a sarcolemmal Mg-ATPase to pump sodium out and potassium in. Pumped ion movements are probably not exactly equal, more sodium is pumped in than potassium is pumped out. This creates a small net outward current which may make a significant contribution to membrane potential changes under some conditions. Alterations in the sodium pump, e.g. in some disease states, may contribute to arrhythmias as a result of the inability of the cell to maintain normal sodium and potassium gradients.

Phase 0

As noted earlier, the resting and action potentials of these cells have a characteristic configuration with respect to time that, for convenience, have been divided into four phases. During phase 0, the period of initial, rapid membrane depolarization, the potential inside the cell becomes positive (about +20 mV) because the excited membrane temporarily becomes more permeable to sodium than to potassium and the membrane potential transiently approaches the equilibrium potencial for sodium (about +45 mV).

The changes in sodium permeability result from the opening and closing of special channels in the membrane through which sodium ions pass with ease. (Figure 4). Current concepts hold that the movements of two "gates" control the opening and closing of each channel. One gate moves rapidly (a fraction of a msec) to open the channel when the membrane is suddenly depolarized by a stimulus. The other gate moves less rapidly (a few msec) on depolarization and its function is to close the channel again. Both the steady-state location of the gates and the speed with which they move in and out of position depend on the level of membrane potential. Thus the term time-and voltage-dependent conductance.

Once opened, the gates remain in position until the membrane potential is changed again. Full return of the gates to their resting position requires full repolarization of the membrane to the resting potential. If repolarization is incomplete, some of the inactivation gates remain closed and the maximum number of sodium channels that can be opened by subsequent depolarizations is reduced.

The rapid depolarization of phase 0 is caused by a large current of sodium ions flowing into the cell down the sodium gradient. But to achieve this requires that first the sodium channels be opened effectively. This requires that a sufficiently large area of membrane is depolarized rapidly enough to the threshold potential (about -75 mV). Local circuit currents flowing just in front of a propagating action potential serve this purpose. At threshold potential further membrane depolarization begets more depolarization and the depolarization becomes self-regenerative. The speed of this regenerative depolarization (the upstroke of the action potential) depends on the intensity of the inward sodium current which in turn depends on the magnitude of the sodium electrochemical gradient and the fraction of available or

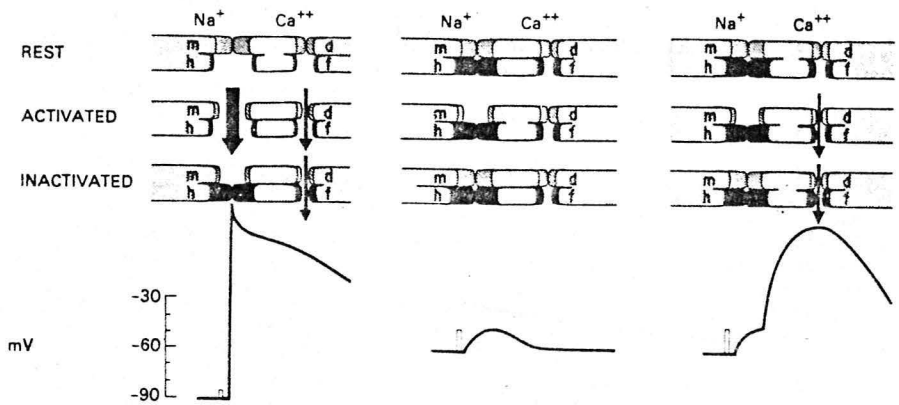


FIGURE 4:
Schematic representation of membrane channels for inward current at the resting potential and during activation and inactivation. The left panel illustrates the sequence of events in a fiber with a normal resting potential of -90 mV. The inactivation gates of the Na+ channel (h) and the slow Ca++/Na+ channel (f) are both open at rest. During activation (when the cell is stimulated) the m gates of the Na+ channel open and the resulting inward current of Na ions depolarizes the cell, giving rise to the upstroke of the action potential depicted below. The h gates then close the channel, thereby inactivating the Na+ conductance. During the upstroke of the action potential the membrane potential exceeds the more positive threshold potential of the slow channel: the activation (d) gates of this channel then open and Ca++ and Na+ flow into the cell, giving rise to the plateau phase of the action potential. The f gates which inactivate the Ca++/Na+ channel close much more slowly than the h gates which inactivate the Na+ channel. The middle panel shows the behavior of the channels when the resting potential is reduced to below -60 mV. The majority of the inactivation gates of the Na+ channel remain closed as long as the membrane remains depolarized; when the cell is stimulated, the resulting inward Na+ current is too small to cause an action potential. The inactivation (f) gates of the slow channel, however, are not closed and, as shown in the right panel, excitation of the cell which is sufficient to open the slow channel, permitting the flow of slow inward current, may cause a slow response action potential to occur.

noninactivated sodium channels. The maximum rate of this depolarization is very much faster in Purkinje fibers and working atrial and ventricular myocytes than in cells of the sino-atrial and atrio-ventricular nodes. (Figure 2). Action potentials with such rapid rates of depolarization are called fast responses and they propagate rapidly throughout the heart.

The voltage-dependence of the sodium channels, noted above, is seen when one attempts to stimulate a cardiac muscle cell immediately after phase 0. (Figure 5). No significant response is elicited. This failure to respond with a second action potential, called refractoriness, is due in part to the persistent depolarization during phase 2, the plateau phase. The voltage-dependence of recovery of the sodium channel is reflected in several important phenomena where partial depolarization of the myocyte just before stimulation reduces the fast inward current. Such partial depolarization can exist when cardiac disease reduces the membrane potential of the resting state. In the partially depolarized state, a depolarizing stimulus produces a more slowly rising phase 0 with reduced amplitude because the sodium channels remain partially deactivated. These slowing rising action potentials are produced not only by activation of the myocardium at a resting potential less negative than normal but also by premature stimulation of the myocardium before full recovery from a prior action potential. They are perhaps best called depressed fast responses to distinguish them from the somewhat similar slow responses which are discussed later. The small rate of rise of depressed fast responses causes them to propagate slowly and may form the basis of conduction abnormalities (delay, decrement, or block) which may contribute to the genesis of arrhythmias.

Phase 1

Phase 1 is the brief period of rapid repolarization that follows the upstroke of the cardiac action potential. (Figure 1). Several membrane changes occur to explain this phase. There is a fall in sodium conductance. There is a tranisent, voltage-dependent increase in chloride conductance. The roughly four-fold greater outside concentration allows chloride to flow into the cell until the membrane potential approaches zero. It also appears that a considerable portion of the outward current is also carried by outward movement of potassium. (Figure 3, Table 1).

Phase 2

Phase 2, the plateau of the cardiac action potential, is the most distinctive part of depolarization and repolarization of the heart and is responsible for the prolonged nature of the action potential. (Figure 1). During phase 2 there is only a small net outward current; the inward current carried by the inward movement of calcium and, to a lesser degree, sodium is approximately balanced by the outward current carried by potassium movement out of the cell. (Figure 3, Table 1).

The inward movement of calcium during phase 2 owes to the incomplete inactivation of the "slow calcium" channel. The activation

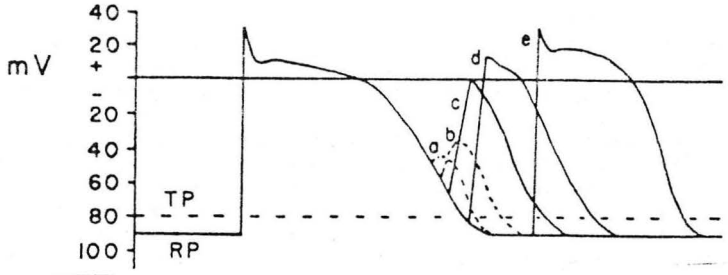


FIGURE 5. Diagrammatic representation of a normal action potential and the responses elicited by stimuli applied at various stages of repolarization. The amplitude and upstroke velocity of the responses elicited during repolarization are related to the level of the membrane potential from which they arise. The earliest responses (a and b) arise from such low levels of membrane potential that they are too small to propagate (graded or local responses). Response c represents the earliest propagated action potential but it propagates slowly because of its low upstroke velocity and low amplitude. Response d is elicited just before complete repolarization, and its rate of rise and amplitude are greater that those of c because it arises from a higher membrane potential; however, it still propagates more slowly than normal. Response e is elicited after complete repolarization and, therefore, has a normal rate of depolarization and amplitude and so propagates rapidly.

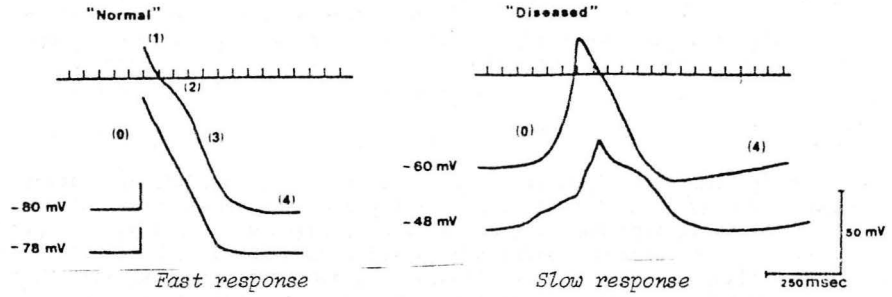


FIGURE 6: Transmembrane potentials simultaneously recorded from two endocardial sites in speciments of "normal" (fast response) and "diseased" (slow response) right atrial appendage, during stimulation at a cycle length of 500 msec and during spontaneous beating, respectively. In each instance, records from one of the two sites are displaced downward for ease of visualization. Values for maximum diastolic potential in millivolts are shown for each cell. Arabic numerals 0 to 4 designate usual phases into which the transmembrane action potential is divided. Time marks are 50 msec apart. Time and voltage calibrations are indicated in the lower right-hand corner.

gates of this channel are opened during phase 0 along with, but more slowly than, those of the "fast channel." The inactivation gates of the slow calcium channel close much more slowly than those of the fast channel. (Figure 4).

The slow calcium channel may be important in the genesis of potentially arrhythmogenic slowly rising action potentials, called slow responses. (Figure 6). Membrane excitation may occur during partial depolarization of the membrane or before complete repolarization at a time when the fast (sodium) channel is closed and cannot be opened but the gates of the slow calcium channel are available for activation. (Figure 4). Such excitation of the cell may then open the slow channel permitting the flow of a slow inward current which may cause a slowly rising action potential, a slow response. Slow responses may contribute to the genesis of arrhythmias in a manner similar to depressed fast responses as discussed above.

Phase 3

Phase 3, the time of rapid repolarization, occurs when membrane permeability to potassium returns at the end of the plateau phase to high levels characteristic of the resting cell. (Figure 1). Opening of the potassium channels along with closure of the slow calcium channels, allows a return to a state of high potassium conductance thus generating a repolarizing outward current. (Figure 3, Table 1). The gating mechanisms for potassium efflux during phase 3 are complex and not well understood. Like the inward flow of sodium during phase 0, potassium efflux during phase 3 is regenerative, but appears to be more voltage-than time-dependent.

The potassium ion-selective channels bring the membrane potential back to resting level and re-establish the normally high conductance for potassium which typifies the resting myocardium.

Phase 4

Phase 4 is the resting state of the cells which is described above. There is no spontaneous depolarization during diastole of normal working atrial and ventricular myocytes, that is, they do not have pacemaker potential. As will be described below, pacemaker potential or automaticity is a property that is characteristic of certain cells in the specialized conduction system of the heart, especially in the sino-atrial node, near the distal part of the atrio-ventricular node, and in the His-Purkinje system. In the normal heart, the sino-atrial node is the predominant pacemaker because it has the fastest rate of spontaneous diastolic depolarization. Lower automatic pacemakers may take over as the heart's pacemaker, generally at rather slow rates, when upper pacemakers fail or are blocked.

Spontaneous diastolic depolarization results from the gradual decline in an outward component of membrane current. This declining current has been most extensively studied in Purkinje cells and is apparently carried by a potassium current that is voltage-but not time-dependent.

Abnormal diastolic depolarization can be induced, however, in Purkinje cells and in working atrial and ventricular myocytes. As the resting membrane potential is reduced - conditions that may be present in face of heart disease - the rate of diastolic depolarization and hence the rate of automatic firing increases, a phenomenon that could contribute to the genesis of arrhythmias.

Delayed Afterdepolarizations and Triggered Sustained Rhythmic Activity

In addition to automaticity, there is a second mechanism by which impulses may be rhythmically initiated in normal cardiac cells. This mechanism is dependent upon delayed afterpotentials and the nondriven impulses that result are called triggered activity. Delayed afterpotentials are transient depolarizations that occur after termination of an action potential and arise as a result of that action potential. (Figure 7). Delayed afterpotentials may follow the action potentials when the membrane potential is lowered by cardiac disease. Delayed afterpotentials may be subthreshold, but under certain conditions, they may exceed threshold potential. When this occurs, a nondriven action potential arises from the afterdepolarization. In some tissues catecholamines increase the amplitude of afterpotentials causing them to reach threshold potential. The amplitude of the afterpotentials is also sensitive to the rate at which the action potentials are elicited; an increase in the rate raises the amplitude. Furthermore, if a premature action potential is elicited during stimulation at a normal rate, the afterdepolarization following the premature action potential has greater amplitude than that following the regular action potential. At sufficiently high rates of regular stimulation or with a sufficiently early premature beat, the afterdepolarization may itself lead to another afterdepolarization that causes a third afterdepolarization and so on for the duration of what is called triggered sustained rhythmic activity.

The ionic basis of the afterpotentials and the factors that influence them are unknown. The amplitude of afterdepolarizations can be reduced by slow calcium channel blocking drugs and these drugs can also prevent the appearance of triggered activity. It is not known, however, whether the slow calcium channel is involved directly in the initiation of afterdepolarizations.

RESTING AND ACTION POTENTIALS IN THE SINO-ATRIAL AND ATRIO-VENTRICULAR NODES

There are several important differences in the electrical properties of the cells of the sino-atrial (SA) and atrio-ventricular (AV) nodes as compared with Purkinje cells and working atrial and ventricular myocardial cells. Cells of the SA node are usually continuously active, never at rest. Strictly speaking, then, phase 4 is not a resting potential. The maximum diastolic potential of the SA and AV nodes is about 20 mV less negative than the other cardiac cells. The ionic movements responsible for phase 4 in the SA and AV nodes are

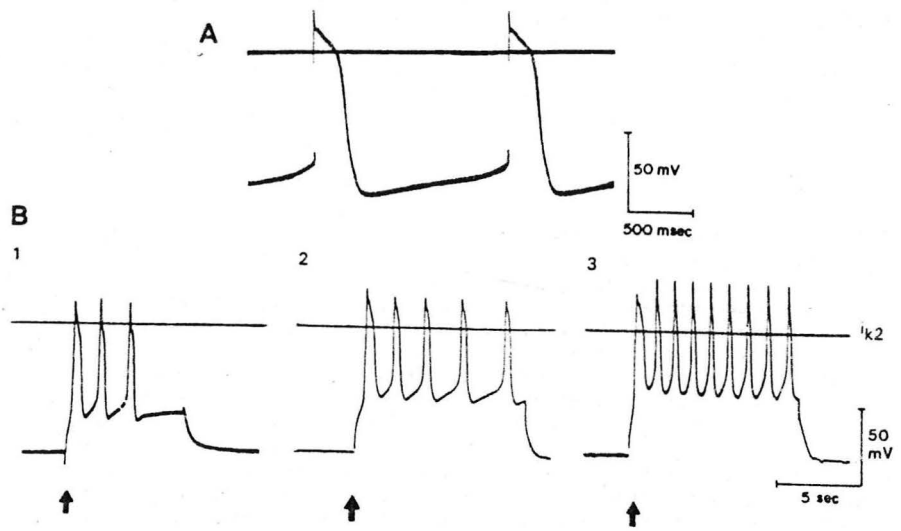


FIGURE 7. Spontaneous diastolic depolarization and automaticity in canine Purkinje fibers. A shows automatic firing of a Purkinje fiber with a maximum diastolic potential of -85 mV. The diastolic depolarization results from the decay of the pacemaker current. B shows the automaticity which can occur when membrane potential is decreased. In part 1, when the fiber is depolarized (at the arrow) from a resting potential of -60 mV to -45 mV by injecting a long-lasting current pulse through a microelectrode, three nondriven action potentials occur. In part 2, a larger-amplitude current pulse reduces the membrane potential to -40 mV, resulting in a sustained rhythmic activity. In part 3, a still larger current pulse reduces the membrane potential to -30 mV and sustained rhythmic activity then occurs at a higher rate. Such rhythmic activity occurring at membrane potentials less negative than -60 mV probably depends on different pacemaker currents that the rhythmic activity shown in A.

not well worked out. These cells are small and difficult to study by micropuncture techniques.

Phase 0 is markedly different in cells of the SA and AV nodes than in other cardiac cells. The amplitude of the action potential is smaller (60-80 mV) and the upstroke is much less rapid. The smaller inward current is carried by calcium and sodium that flows predominantly through the slow calcium channel. These slow responses conduct only slowly through the nodes. Furthermore the refractory period of the nodes is quite long. The markedly slow conduction and long refractory periods of the nodes may contribute, under certain conditions, to the development of reentrant arrhythmias.

THE GENESIS OF ARRHYTHMIAS

As noted above, abnormal impulse formation and reentry account for cardiac arrhythmias. Enhanced automaticity of lower pacemakers may come about as a result of (1) an increase in the rate of spontaneous diastolic depolarization; (2) a shift of the threshold potential to a more negative value; or (3) a decrease in the maximum diastolic potential, the latter approaching threshold and the fiber becoming more excitable. (Figure 8). When the rate of spontaneous depolarization of a cell exceeds the firing rate of the normal firing of the sino-atrial node and that depolarization propagates to other parts of the heart, a premature extra-depolarization or a sustained arrhythmia ensues. To date delayed afterpotentials and triggered sustained rhythmic activity have been demonstrated only experimentally. Demonstration of this mechanism as the cause of arrhythmias in man has not yet been forthcoming.

How the phenomenon of reentry can cause arrhythmias is not as immediately apparent as abnormal impulse formation and bears a few comments. The basic idea of reentry is an old one. In a classical experiment published in 1908, Mayer (5) demonstrated the generation of a circular wave of depolarization in a ring of tissue from the jelly-fish when he imposed a transient one-way conduction block in the ring of tissue. (Figure 9a). This idea was extended to heart tissue six years later (6) by Mines and became the scientific backbone for the concept now commonly known as macro-reentry. (Figure 9b). The physics of reentrant circuits like this can explain only a few clinical arrhythmias - the length of the pathway is too long and the need for an anatomical blockade of conduction is too restricting. A giant step forward was taken in the 1960s when Moe proposed the concept now known as micro-reentry. (7) In this postulate, only a microscopic area is necessary for the establishment of a reentrant circuit. We now know that the conditions for micro-reentry do exist in many parts of the heart in the presence of a number of cardiac disorders and that micro-entry probably accounts for a large fraction of clinical arrhythmias. The necessary conditions for the development of a re-entrant circuit are three: (1) there must be unidirectional conduction block at some site in the heart; (2) slow conduction must proceed over an alternate pathway; and (3) reactivation of tissue proximal to the site of block must occur. Many structural or ionic abnormalities may

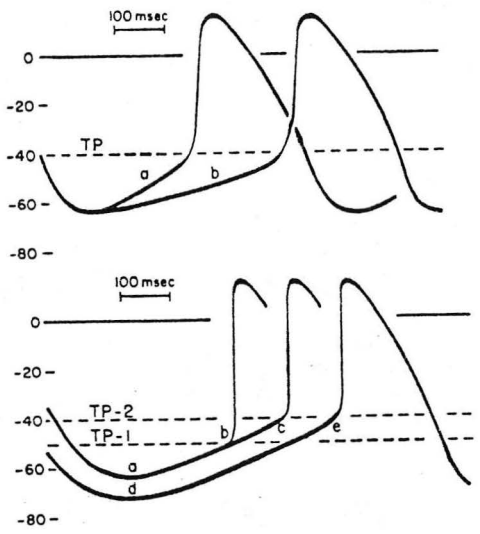


FIGURE 8. Diagram illustrating the principal mechanisms underlying changes in the frequency of discharge of a pacemaker fiber. The upper diagram shows an increase in rate caused by an increase in the slope of diastolic, or pacemaker, depolarization from b to a, and thus a decrease in the time required for the membrane potential to decline to the threshold potential level (TP). The lower diagram shows the increase in rate associated with a shift in the level of the threshold potential from TP-2 to TP-1, and a corresponding decrease in cycle length (compare a to b with a to c); also illustrated is a further increase in rate due to a decrease in the maximum diastolic potential level (compare a to c with d to e).

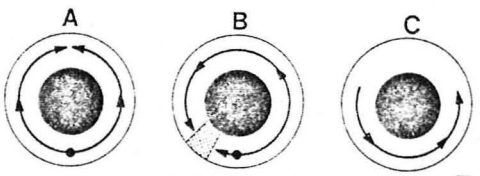


FIGURE 9a. Schematic representation of reentry in a ring of jellyfish subumbrella tissue as it was induced by Mayer in 1908. In A, the ring was stimulated in the area indicated by the black dot, and impulses propagated away from the point of stimulation, in both directions, and collided; no reentry occured. In B, the cross-hatched area was compressed while the ring was stimulated, again at the black dot. The impulse propagated around the ring in only one direction, having been blocked in the other direction by the area of compression; immediately after stimulation the compression was relieved and, in C, the unidirectionally circulating impulse is shown returning to its point of origin and then continuing around the loop.

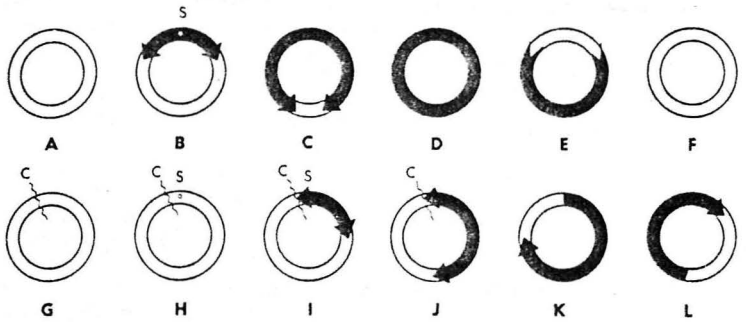


FIGURE 9b. Diagrams of the circus-movement theories based on the classic experiment performed by Mayer and Mines. A, a muscular ring cut from the heart of a ray. B and C, stimulation at *S* results in a simultaneous spread of excitation in both directions (shaded part). D, the two waves meet and excitation involves the whole ring, and so comes to a standstill. E, recovery begins in the area first excited and the process of recovery proceeds simultaneously in both directions until, in F, the whole ring has recovered. In G, a clamp is applied at *C*. H, stimulation has just started at *S* with the clamp in place. I, excitation proceeds up to the clamp and stops. It continues only in the other direction thereafter. J, excitation advances in one direction only to activate more of the ring. K, the clamp *C* is quickly removed before the impulse reaches it and recovery begins at *S*. The excitation wave can then pass through the area at *S*, in L, which again becomes excitable when the activation front reaches it, allowing the excitation wave to circulate again over the ring, with the front of the excitation wave, as it were, trying to catch up with its rear, but not succeeding. This process may continue for hours. However, a certain velocity of the excitation wave, a certain duration of the refractory period in each part of the ring, and a certain length of the muscular ring are necessary for the success of the experiment.

be present in the diseased heart to cause a unidirectional conduction block. In addition, different states of refractoriness of adjacent cells may lead to a unidirectional block. The extremely slow conduction velocity required for micro-reentry can be accounted for by the very slow propagation of the slow responses or depressed fast responses discussed above. Micro-reentry may occur in either branched or unbranched structures as illustrated in figures 10, 11, and 12.

Another, doubless less frequent, mechanism for micro-reentry called summation has been described. It is illustrated in figure 13.

MECHANISMS FOR SPECIFIC ARRHYTHMIAS

A detailed description of the possible mechanisms for specific arrhythmias is beyond the scope of this review. Nevertheless, a simple listing of the current consensus on the mechanism(s) for some arrhythmias is worthwhile for the consideration of drugs for the treatment of arrhythmias which follows. These mechanisms are outlined in table 2.

TABLE 2

POSSIBLE MECHANISMS FOR SPECIFIC ARRHYTHMIAS

- Atrial Premature Depolarizations
  - Micro-reentry (atrial, AV node, SA node)
  - Automatic ectopic foci
  - ??? triggered activity
- Atrial Flutter
  - ? Macro-reentry (single anatomically defined loop)
  - ? Micro-reentry
  - ? Automatic focus
- Atrial Fibrillation
  - ? Macro-reentry (Multiple "daughter" loops)
  - ? Multiple micro-entrant foci
- Supraventricular Tachycardia
  - Micro-reentry
    - Anomalous pathway
    - AV node
    - SA node
    - Atrial
  - Automatic ectopic foci
    - Atria
    - Bundle of His
- Ventricular Premature Depolarizations
  - Automatic ectopic foci
  - Micro-reentry (His-Purkinje system or muscle)
  - ??? triggered activity
- Ventricular Tachycardia
  - Automatic ectopic foci
  - Micro-reentry (His-Purkinje system or muscle)
  - ??? triggered activity
- Ventricular Fibrillation
  - Multiple micro-reentrant foci

More detailed discussion of some of the concepts discussed above can be found elsewhere. (8-11)

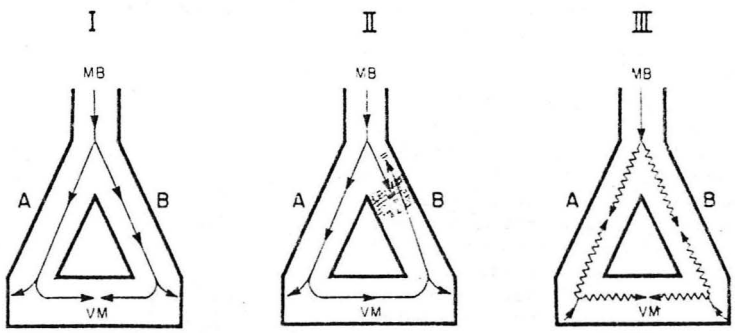


FIGURE 10. Schematic representation of a bundle of Purkinje fibers (MB) in the distal ventricular conducting system which divides into two branches (A and B) before making contact with ventricular muscle (VM) to form a loop. Panel I shows the sequence of activation under normal conditions; the impulse of sinus origin invades the main bundle (MB) leading to the loop and conducts through both branches A and B into ventricular muscle where the impulses collide and die out. Panel II shows the sequence of activation in the presence of an area of unidirectional conduction block. (shaded area in branch B); conduction is blocked in the antrograde direction (from B to VM) but not in the retrograde direction (from VM to B). Conduction velocity is normal in the rest of the loop, since this is not depressed and, therefore, the impulse conducts rapidly around the loop, returning to the main bundle (MB) before it has recovered excitability, and is then blocked in this refractory tissue. Panel III indicates a possible sequence of activation when conduction is slowed throughout the loop, but no region of unidirectional conduction block is present. Thus, the impulse conducts slowly from the main bundle through both branches. However, the ventricular muscle is first activated by impulses conducting rapidly from other regions where conduction is not depressed. Again there is no excitable return pathway via which reentry can take place.

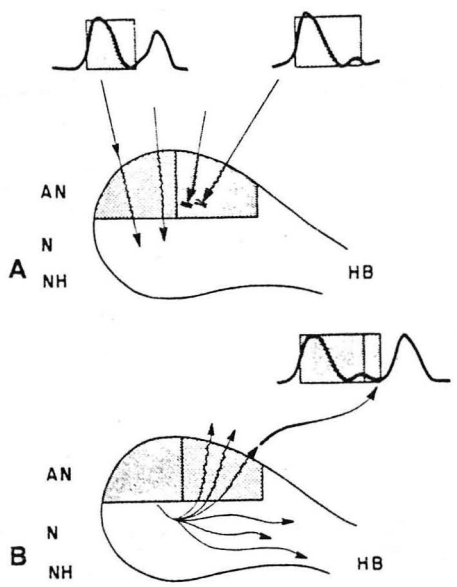


FIGURE 11: Reentry of an atrial impulse in the AV node. Both A and B show diagrammatic representations of the AV node with the upper (AN), middle (N), and lower (NH) node indicated; HB indicated the His bundle. In A, action potentials recorded from two regions of the upper node are illustrated at the top; the action potential at the left has a shorter refractory period than that shown at the right, as indicated by the shaded area. Therefore, when a premature atrial impulse enters the AV node (arrows) it may be able to propagate through the part of the upper node with the shorter refractory period but blocks in the region with the longer refractory period. This is also depicted in the action potential recordings at the top. B shows a possible continuation of these events: the propagating impulse (arrows) can return to excite the area of the node in which anterograde conduction block has occurred and thereby reenter the atrium; action potentials recorded from the return nodal pathway are shown above. The impulse can also conduct into the His bundle.

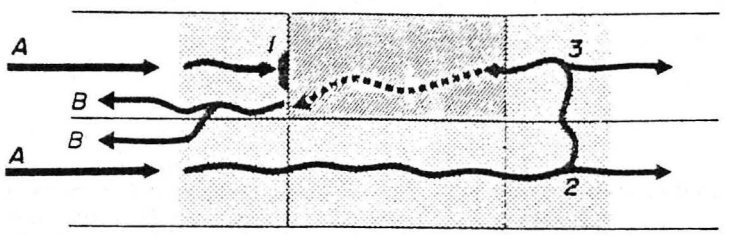


FIGURE 12. Model of reflection. An impulse enters an unbranched Purkinje fiber bundle at A. The stippled section is depressed and the crosshatched section more so. The impulse is blocked from further propagation at site 1: however, it propagates through the remainder of the bundle, arriving at site 2, from which it continues to propagate in a forward direction, as well as activating site 3. From site 3, activation proceeds both forward and backward. The impulse that is propagated forward travels through the depressed segment and ultimately reenters the proximal conducting system at B.

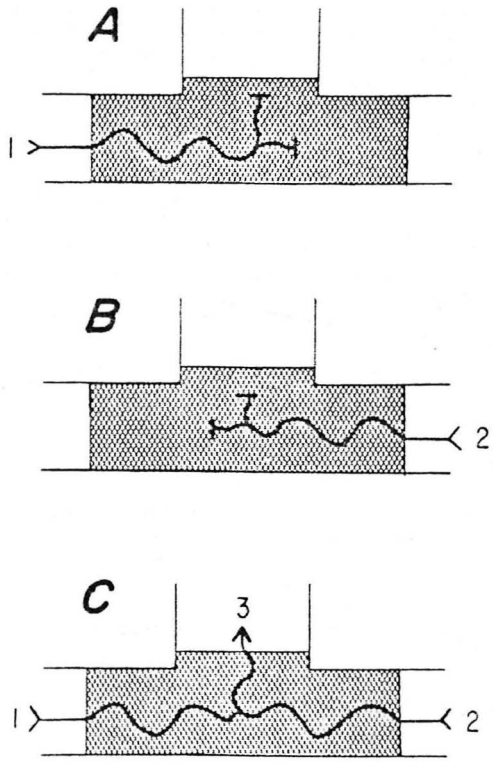


FIGURE 13. Model of summation. A depressed area (stippled) is represented at a branching point of a cardiac fiber. When stimulated at sites 1 or 2 alone, conduction fails to propagate further; however, when sites 1 and 2 are stimulated simultaneously, the impulse summates with the depressed segment and propagates through segment 3.

CLASSIFICATION OF ANTIARRHYTHMIC AGENTS

There has been and there continues to be considerable debate about the best way to classify the antiarrhythmic agents. (12-15) The most commonly used classification scheme is the one proposed by Vaughan Williams and Singh and their co-workers. (12, 16-21) In this classification, drugs are grouped according to their effects on the cardiac action potential. This classification grew from the observations that virtually all known drugs with antiarrhythmic properties have one dominant electrophysiologic action on the myocardial cell. These effects also may be modulated by the drug's subsidiary myocardial effects or by its extracardiac effects so that the net pharmacologic effect on the heart may not be completely predictable based on *in vitro* data. As the classification system now stands, there are four major groups. (Table 3)

TABLE 3

DOMINANT ACTIONS OF ANTIARRHYTHMIC DRUGS

Class	Depression of Phase 0 and Fast Response	Effect on Action Potential Duration	Sympatholytic Effect	Depression of the Slow Response
I	+ + + +	Lengthen +, 0, or shorten +	0-+ (non-competitive)	0
II	0 - +	0 or shorten +	+ + + + (competitive)	0
III	0	Lengthen + + + +	+ (non-competitive)	0
IV	0	Lengthen +	+ (non-competitive)	+ + + +

The dominant activity of the class I agents is to slow the maximum rate of rise of depolarization (phase 0) of the action potential. These effects are caused by direct membrane-stabilizing actions. Most of these agents are also local anesthetics for nerves as well as for myocardial membranes, but their sensitivities may differ markedly in this regard, so that much lower concentrations of drug may produce more comparable electrophysiologic effects in myocardial fibers than in nerves. (22) In clinically relevant concentrations, the decreased maximum rate of depolarization is associated with an increase in the threshold of excitability, a depression in conduction velocity, marked prolongation in the effective refractory period, and inhibition of the spontaneous diastolic depolarization in automatic cells. The effects on pacemaker cells is usually seen at much lower drug concentrations than those that influence conduction velocity or the threshold of excitability. By depressing spontaneous diastolic depolarization, the class I agents may

control arrhythmias that are due to enhanced automaticity or decreased threshold of excitability. By altering the effective refractory period, they may be effective in abolishing reentrant arrhythmias.

Class II agents are those with beta-adrenergic blocking activity that is due to competitive inhibition. The rationale for classifying the beta-blockers into a separate category arises from the observations that hyperactivity of the sympathetic nervous system has been shown to be a major factor in the genesis of some cardiac rhythm disorders. (23) In fact, ablation of the sources of sympathetic transmitter and presynaptic sympathetic blockade as well as competitive inhibition of beta-adrenergic receptors lowers the incidence of certain arrhythmias. (23) Initially, beta-blockers were classified along with the class I agents because of the discovery that they possessed a local anesthetic effect on nerve. (24) Considerable debate subsequently ensued on the relative contributions of the membrane effect and beta-adrenergic antagonism to the antiarrhythmic actions of these drugs. The debate is now substantially resolved in favor of the notion that their action is mediated chiefly or exclusively through beta-adrenergic antagonism. The membrane-active properties of these agents are apparent in the intact organism only in doses far beyond those needed to achieve beta-adrenergic blockade and those doses that are used clinically. (24) The major electrophysiologic effect of the beta-blockers at clinically relevant concentrations is depression of the rate of spontaneous depolarization (phase 4).

The class III agents prolong the action potential duration and thus the effective refractory period. They have little or no other effects on the cardiac action potential. This classification has an interesting history. It has been known for some time that rhythm disorders are common in thyrotoxicosis and uncommon with hypothyroidism. Subsequently, it was found that induction of hyperthyroidism in rabbits shortened the action potential duration and induction of hypothyroidism lengthened the action potential duration without other effects on the action potential. (25) This observation then led to the hypothesis that drugs that had an effect of "pure" prolongation of the action potential duration would be effective antiarrhythmic agents. Prolongation of the action potential duration appears to explain the effects of bretylium and amiodarone.

Class IV drugs are selective blockers of the entry of calcium (and sodium to a lesser degree) through the slow-channel. As noted above, with depression of the fast response, marked reduction in conduction velocity may result from the emergence of the slow response and action potentials with pacemaker potential may arise entirely on the basis of the slow inward current. Consequently, the presence of the slow response may cause arrhythmias on the basis of reentry or enhanced automaticity. Verapamil, the prototype class IV drug, exerts its antiarrhythmic effects through a selective blockade of the atrioventricular node and its effects on calcium transport. Early experiments demonstrated potent antiarrhythmic effects on experimental animals (20) and man (54) at concentrations that did not exhibit any class I, II, or III activity and the new class IV designation was proposed. (20) Subsequent work confirmed the reasonableness of that classification. (27)

The major current difficulty with the classification so far outlined is with the class I agents. There are sufficient differences among the large number of drugs in this class to consider sub-division of the class I drugs. Harrison and his colleagues have suggested sub-division into three sub-groups. (28-29) (Table 4) There has always been a keen

TABLE 4

ACTIONS OF CLASS I ANTIARRHYTHMIC DRUGS

Class	Action on Phase 0 and the Fast Response		Action Potential Duration	Refractoriness
	Normal cells	Abnormal cells		
IA (Quinidine-like) Quinidine Procainamide Disopyramide	Depression	Depression	Prolongs	Prolongs
IB (Lidocaine-like) Lidocaine, Phenytoin, Tocainide, Mexiletine, Aprindine, Ethmozin	0	Depression	Shorten (slightly)	Shorten (slightly)
IC Encainide, Lorcainide, Flecainide	Marked depression	Marked depression	Little effect	Little effect

debate on the degree of differences between the quinidine-like drugs and the lidocaine-like drugs. Indeed, the differences are sufficient enough that quinidine-like properties and lidocaine-like properties are part of the basis of several classification schemes. (15) While quinidine-like drugs depress the rate of phase 0 depolarization in normal and abnormal cells, lidocaine-like drugs depress phase 0 only in cells that are depressed and partially depolarized, e.g. ischemic cells. (15) Furthermore, while quinidine prolongs the action potential duration, lidocaine shortens the action potential duration and refractoriness but prolongs the recovery of excitability relative to the change in repolarization. (30-31) Three of the newest class I drugs, encainide, flecanide, and lorcainide appear to have similar properties and to differ in some important ways from both the quinidine-like and lidocaine-like drugs. These three drugs markedly depress phase 0 but have little effect on either repolarization or the action potential duration. In the scheme proposed by Harrison and his co-workers, these differences provide the basis for the sub-classification. (28-29) Hence, class IA drugs (the quinidine-like drugs) depress phase 0, prolong the action potential duration, and prolong repolarization. The class IB drugs (the lidocaine-like drugs) depress phase 0 in abnormal cells but little or not at all in normal cells, but shorten the action potential duration and refractoriness. The class IC drugs (encainide, flecainide, and lorcainide) markedly depress

phase 0 and have little effect on action potential duration and refractoriness. (Table 4) Those drugs which prolong the action potential duration, the class IA drugs, are likely to be effective for a wider range of arrhythmias because they have two important electrophysiological features of antiarrhythmic drugs.

I will use the Harrison modification of the Singh and Vaughan Williams classification system in the subsequent review of the properties of specific drugs.

PROPERTIES OF CURRENTLY AVAILABLE AND INVESTIGATIONAL ANTIARRHYTHMIC DRUGS

CLASS IA DRUGS

There are three major class IA drugs: quinidine, procainamide, and disopyramide. N-acetyl procainamide (NAPA), is included here because of its relationship to procainamide. The proper classification of NAPA is unclear.

QUINIDINE

Quinidine is, of course, the prototype class IA agent and prototype antiarrhythmic drug for that matter. It is a natural alkaloid found in cinchona bark. Cinchona alkaloids were probably first employed clinically in Paris in 1749 by a French physician, Jean Baptiste de Senac, for atrial fibrillation. (32) Quinidine has been in regular use since the early part of this century and is still probably the most widely used antiarrhythmic agent. It is available in this country as sulfate, gluconate, and polygalacturonate salts for oral use and as the gluconate salt for intramuscular and intravenous use.

CLINICAL PHARMACOLOGY

The pharmacologic properties of quinidine have been studied extensively. (33) At clinically relevant concentrations quinidine depresses phase 4 (spontaneous) depolarization, reduces the maximal rate of rise of phase 0 depolarization, modestly prolongs the action potential duration but markedly prolongs the effective refractory period. These effects are the characteristic direct effects of quinidine and account for its ability to reduce arrhythmias owing to abnormal automaticity and reentry. Quinidine slows conduction and prolongs the refractory period in areas of conduction block and may thereby block a circulating reentrant arrhythmia. The circulating wave front meets a refractory zone and the circus movement is inhibited.

Quinidine also has mild vagolytic and non-competitive antiadrenergic effects. The vagolytic action of the drug may increase the heart rate; the antiadrenergic effect tends to reduce it. In most people there is then no change in heart rate or a slight degree of tachycardia after quinidine administration. In situations of excessive sympathetic activity such as general anesthesia or thyrotoxicosis, quinidine often produces bradycardia. The interaction between the direct and autonomic effects of quinidine are most important in regards to conduction through the atrioventricular node. The direct effect on conduction is depression. In conscious persons, this effect is largely abolished or reversed by

the net effect of the autonomic actions. In contrast, quinidine, like most class I drugs, usually depresses conduction and increases refractoriness in accessory pathways bypassing the atrioventricular node. (34)

Recent work has clarified the relative significance of changes in depolarization and repolarization in the antiarrhythmic effects of quinidine. (35) The increase in the duration of the QRS complex (depolarization) was better correlated with serum quinidine levels than the QT interval (repolarization) in the therapeutic range. Marked QT prolongation was much more commonly found with toxic levels of quinidine.

Quinidine is usually administered orally. It is painful when administered intramuscularly. Intravenous administration (0.2-0.3 mg/kg/min) in hemodynamically stable patients is possible but requires caution and careful monitoring. (36-37) These studies question the popular notion that intravenous quinidine regularly produces severe hypotension. Most human data with oral administration are with the sulfate salt. There is considerable variation in oral absorption. (38-40) Quinidine sulfate is more rapidly absorbed than gluconate. (39) There are scant data dealing with the pharmacokinetics of the sustained release form of quinidine sulfate and with the polygalacturonate salt.

Quinidine is generally administered every six hours. The dose range for the sulfate salt is 800-2400 mg and for the gluconate salt is 990-2970 mg. The gluconate form may be administered every 6 or every 8 hours. (40) The elimination is 6-7 hours in most patients. The considerable inter- and intra-patient variabilities in pharmacokinetics and the narrow therapeutic:toxic ratio dictate the use of monitoring serum drug levels as well as the duration of the QRS and QT intervals on the electrocardiogram. The therapeutic window (with fluorometric assays using double serum extraction) is between 2.3 and 5μg/ml. (41-42) Values with different techniques will differ. An immunoassay is coming into wide use now. Preliminary experiences are that the values with this assay are similar to those obtained with the fluorometric assay of doubly extracted serum.

Quinidine's major route of elimination is the liver, but quinidine clearance appears to be diminished only by severe liver disturbances. (43) Considerable controversy surrounds the effect of renal impairment on quinidine excretion. Some of the confusion may owe to the use of relatively non-specific quinidine assays that include non-active quinidine metabolites that are excreted by the kidneys. Recent work with more specific assays have not shown an important effect of renal function on quinidine levels. (41, 44)

CLINICAL UTILITY

Used alone or in combination with digitalis glycosides or beta-adrenergic blockers, quinidine is of great value in terminating atrial fibrillation and atrial flutter. Prophylactic administration reduces the incidence of reversion to atrial fibrillation after electrical cardioversion. (45) Used alone, it is not very likely to be effective in abolishing or preventing paroxysmal supraventricular tachycardias owing to atrioventricular node reentry because it does not depress AV conduction in a predictable manner, although it may be preventative by virtue of preventing premature atrial or ventricular depolarizations

that could initiate the tachycardia. Quinidine may speed the ventricular response to atrial flutter. This may occur because of a net increase in atrioventricular conduction from direct and autonomic influences of quinidine. The major effect, however, is often a decrease in atrial rate which may allow an AV conduction ratio nearer unity. Consequently, digitalis glycosides or beta-blockers should usually be used with quinidine in the treatment of atrial flutter.

Quinidine is valuable in atrial arrhythmias that are conducted to the ventricles by means of anomalous pathways in the pre-excitation syndromes. (34, 46)

Quinidine is effective in controlling most types of ectopic and reentrant ventricular arrhythmias, but it is less valuable for digitalis induced arrhythmia than lidocaine, phenytoin, or beta-blockers. It should not be used or should be used with great caution in the patient with considerable prolongation of the QT interval. In that context, quinidine may actually precipitate an arrhythmia, the peculiar rhythm disturbance, polymorphic ventricular tachycardia or torsade de pointes. (47)

ADVERSE SIDE-EFFECTS

Quinidine administration is usually free of major hemodynamic side-effects. Long-term oral administration of usual doses is associated with only a slight, clinically unimportant decrease in cardiac contractility. (48) Over-dosage may lead to hypotension resulting from vasodilation or myocardial depression or both. (45) Rarely, quinidine causes marked vasodilation in low doses. For this reason, the first dose is always given in the presence of health care workers.

The reported side-effects from quinidine makes a long list. Some are idiosyncratic; others are a manifestation of hypersensitiy. (49) The commonest problems, by far, are gastrointestinal. Anorexia, nausea, vomiting, colic, and especially diarrhea may limit the use of quinidine in up to 30% of patients. Sustained action preparations may be associated with fewer gastrointestinal side effects. (45)

As with any cinchona alkaloid, cinchoism may occur.

Hypersensitivity reactions are not common but are numerous and include hemolytic anemia, thrombocytopenia, drug fever, and rashes.

The most feared side-effects of quinidine are sudden death and quinidine syncope. The mechanism is probably polymorphic ventricular tachycardia (torsade de pointes) which may deteriorate into ventricular fibrillation or spontaneous ventricular defibrillation. In earlier days, the incidence of these complications may have been as high as 2-4%. The current incidence is probably much lower. Many episodes probably occurred because of quinidine administration to patients with a prolonged QT interval or in toxic doses. This leads to an increase in the temporal dispersion of excitability favoring the development of ventricular fibrillation or polymorphic ventricular tachycardia. In rare cases, however, ventricular fibrillation appears to be idiosyncratic. (47, 50)

PROCAINAMIDE

Procainamide was developed in the wake of discovery of antiarrhythmic effects of procaine. The short action of procaine and its central nervous system (CNS) side effects limited its usefulness. Substitution of an amide for the ester linkage increased the resistance of the drug to plasma hydrolysis and reduced CNS side effects without loss of antiarrhythmic properties. It has similar electrophysiologic properties and therapeutic uses to quinidine and has been second only to that drug in long-term antiarrhythmic therapy.

CLINICAL PHARMACOLOGY

The electrophysiologic properties of procainamide in isolated muscle and in intact animals and man are very much like those of quinidine. (51-53)

In addition to the direct electrophysiologic effects, procainamide, like quinidine, also appears to have a mild vagolytic effect and the net results of procainamide on heart rate and atrioventricular conduction are similarly dependent on other conditions such as the degree of intrinsic sympathetic tone. (51-55)

Procainamide can be administered orally or intravenously with good results. Intramuscular administration is possible but is generally discouraged. Bioavailability of orally administered drug is about 75% (56) but may be variable in the presence of severe heart disease. (57) In normal persons, the elimination half-time is about 3.5 hours but may be considerably prolonged in the face of renal or cardiac failure. (58-59) Metabolism of procainamide occurs in the liver with conversion to N-acetyl procainamide (NAPA); but one-half of the procainamide is recovered unchanged in the urine. (57) The rate of acetylation depends on whether the patient has fast or slow acetylating abilities. (60) A consideration of the pharmacokinetics of procainamide is complicated by the current controversy regarding the efficacy of the N-acetyl derivative as an antiarrhythmic agent. The elimination half-life of NAPA is about twice as long as the parent drug. (61) This is considered in greater detail below in the section on NAPA.

The maintenance dose of oral or intravenous procainamide is usually 2-3 mg/kg/hr (50-75 mg/kg/day) in the absence of renal impairment. Oral or intravenous loading doses may be given when necessary with minimal serious complications but careful blood pressure monitoring is required and the rate of intravenous administration must not exceed 50 mg/min. (62-63) A major disadvantage of long-term oral administration of procainamide is the necessity for dosing every 3 or 4 hours. The recent introduction of a sustained-action oral procainamide may allow administration every 6 hours but only limited pharmacokinetic data are available to confirm this claim. It seems clear that treatment with procainamide is optimal when the dose is determined by serum levels of the drug. The therapeutic window is 4-10μg/ml (64) although many patients can be adequately controlled with levels of 4-8μg/ml. (56, 63) Levels above 16μg/ml are often associated with toxic side effects. (63) Many laboratories now provide serum analysis of NAPA along with procainamide levels and a sum of the two. I recommend considerable caution in using the NAPA or summed levels in making clinical decision until the efficacy of NAPA as an antiarrhythmic agent is more clear.

CLINICAL UTILITY

The spectrum of usefulness of procainamide closely parallels that of quinidine but it has been particularly useful in the suppression of ventricular ectopic activity. (65-66) It is particularly useful for acute administration for potentially life-threatening ventricular rhythm disorders. For that purpose it is the second-line drug after lidocaine. (66) Procainamide is generally a little less effective for supraventricular rhythm disturbances than quinidine.

ADVERSE SIDE-EFFECTS

The hemodynamic side-effects of procainamide are not major and do not seriously limit its use. Contractility is not detectably altered by long-term oral administration of usual doses. (48) Rapid administration of large dosese, however, may cause vasodilation and hypotension (62) and myocardial depression. (67)

At higher doses, gastrointestinal side-effects similar to those seen with quinidine may occur. Generally this is less of a problem with procainamide than with quinidine. Central nervous system side effects (giddiness, depression, hallucinations, etc.) may also limit its use, especially at higher doses. Leukopenia and agranulocytosis have been reported but are rare. (68)

The major limiting side-effect of procainamide is the development of a systemic lupus erythematosis-like syndrome. It may occur weeks or years after initiation of procainamide. Unfortunately it is not uncommon and may occur in as many as 20% of patients. (69) Usually, but not always, the disease regresses with cessation of drug therapy. It is more common in slow acetylators of the drug.

A procainamide-induced drug fever is encountered occasionally.

Procainamide also has the potential to produce ventricular tachycardia, polymorphic ventricular tachycardia (torsade de pointes), and ventricular fibrillation as does quinidine, but appears to do so less commonly.

N-ACETYL PROCAINAMIDE (NAPA)

N-Acetyl procainamide is a metabolite of procainamide that is noted in the serum of patients receiving procainamide.(See above). It has been reported to have antiarrhythmic properties (70) and thus has become the subject of interest as a new antiarrhythmic drug that might have some of the properties of the parent drug but fewer of the side-effects. It is currently undergoing testing in several centers. The electrophysiologic properties of NAPA that are currently available do not justify its inclusion in the class IA group, but I have included it here for the purpose of discussion because of its natural relationship to its parent drug.

CLINICAL PHARMACOLOGY

The electrophysiological properties of NAPA are different from those of the parent drug in several important ways. In anesthetized dogs, NAPA produced less prolongation of conduction times and had a significant effect only on the HV interval. Both drugs increased the QT interval, the Wenckebach cycle length, and the refractory period

of ventricular and atrial tissues in a similar fashion but NAPA was less potent. (71) NAPA produced less increase in the refractory period of the atrioventricular node and the effect was not parallel to that of procainamide. In canine Purkinje fibers NAPA had no significant effect on phase 4 depolarization, resting membrane potential, action potential amplitude, or maximal velocity of phase 0 depolarization. Action potential duration was prolonged in a dose-dependent way and higher concentrations produced a secondary plateau in phase 3. (72)

NAPA can be administered either orally or intravenously. About 85% of an oral dose is systemically available and peak levels occur 45-90 minutes after ingestion. (73) The elimination half-life is about 9 hours. (74) Elimination of NAPA is significantly diminished in patients with renal failure. (75) Effective plasma concentrations are reported to be in the range of 9.4 to 19.5μg/ml with the frequency of side effects increasing with concentration and being more frequent with levels over 10. (76)

Oral dosage of NAPA is 0.5 to 2.5g every 6 to 8 hours. The intravenous dose of NAPA is not yet well established.

CLINICAL UTILITY

Several trials have shown antiarrhythmic activity of NAPA in selected patients. (76-78) In a study of patients with chronic ventricular premature depolarizations, NAPA was effective in only a few. (79) Consequently, the evidence that NAPA is a particularly efficacious antiarrhythmic agent with wide applicability is scant at this time.

ADVERSE SIDE EFFECTS

The adverse side effects of NAPA do appear to be less severe than those of the parent drug. The SLE-like syndrome or positive ANA titers are particularly rare, even in patients who developed them while receiving procainamide. Gastrointestinal and central nervous system side effects like those of procainamide have been reported. (76-78)

DISOPYRAMIDE

Disopyramide was synthesized in 1954, described as an anti-arrhythmic in 1962 (80), reported in a clinical trial in 1963 (81), marked in France in 1969 and in the USA in 1977. Extensive reviews of its properties have been published in recent years. (82-87)

CLINICAL PHARMACOLOGY

The structure of disopyramide does not resemble quinidine or procainamide, but its electrophysiological effects on cardiac muscle are very similar to those drugs.

The direct effects of disopyramide in intact animals and man may be mitigated by the drug's associated anticholinergic properties. The direct depressant action on the sino-atrial and atrio-ventricular nodes may be more than offset by the anticholinergic properties so that an increase in the sinus rate or increase in AV conduction may occur with its administration. The net effect depends upon intrinsic autonomic tone, the state of the conduction system, and other factors so that the net effect on heart rate and AV conduction is often unpredictable.

The agent can be administered orally or intravenously but only the oral form is clinically available in the USA. Following ingestion of the drug, 80-90% is absorbed rapidly achieving peak levels in 2-3 hours. Disopyramide is variably bound to plasma proteins. Protein binding is concentration dependent with lower binding with increasing drug concentration. The variability in protein binding contributes to the rather complicated pharmacokinetics of disopyramide which are not yet well worked out. The reported values for the elimination half-life in normal people range from 4.5 to 8.9 hours. The half-life may be considerably prolonged in patients with cardiac or renal failure.

Approximately half of the drug is excreted in the urine as the unchanged drug and about half as the N-monodealkylated hepatic metabolite. This metabolite has been reported to have only about one-fourth of the antiarrhythmic activity but may have 20 times as much anticholinergic activity as the parent drug.

The therapeutic window has been reported to be 2-4μg/ml but the complicated pharmacokinetics and protein binding characteristics make dogmatic statements about a therapeutic range rather tenuous at this point. Toxic side effects have been reported in some patients with levels of 5μg/ml although many patients do not exhibit toxicity with levels of 7-9μg/ml.

Usual adult doses range from 400-800mg/day in four divided doses. Rare patients have required as much as 1600mg/day. A loading dose of 300mg followed by 150mg at six hour intervals may be used to achieve therapeutic serum levels more quickly for standard sized adults. It should be reduced for persons smaller than 50 kg and for patients with renal failure. The elimination half-life in patients with renal failure has ranged from 8-43 hours.

CLINICAL UTILITY

The usefulness of disopyramide for the control of arrhythmias closely parallels that of quinidine and procainamide. In general it appears to have been slightly more successful in the treatment of ventricular than supraventricular rhythm disturbances but the experience with supraventricular rhythm disturbances is not yet extensive. Its role in supraventricular rhythm disturbances is less certain. As it does not predictably impede AV conduction, supraventricular tachycardias resulting from AV node reentry may not respond. Facilitation of AV conduction may produce an increase in the ventricular response to atrial flutter or fibrillation. Disopyramide does prolong conduction through anomalous pathways and may be useful in controlling the ventricular rate when atrial fibrillation and flutter complicate the preexcitation syndromes. It is currently approved by the FDA only for treatment of ventricular rhythm disturbances, however.

ADVERSE SIDE EFFECTS

The hemodynamic side effects of disopyramide are more notable than those of quinidine and procainamide. While patients with normal ventricular function and no history of heart failure tolerate disopyramide administration without the precipitation of heart failure, administration to patients

with a history of heart failure or with considerable compromise of ventricular function often induces heart failure. Consequently it should not ordinarily be used in such patients at risk for heart failure and should be used only with considerable caution in association with drugs that decrease the contractile state of the heart such as beta-blockers and verapamil.

The commonest side-effects owe to the anticholinergic properties of the drug: dry mouth, worsened symptoms of prostatism, and constipation, etc. Gastrointestinal and central nervous system side effects occur but are relatively rare.

Ventricular tachycardia, polymorphic ventricular tachycardia (torsade de pointes), and ventricular fibrillation may be induced by disopyramide in a similar manner to that described for quinidine, but the incidence appears to be less than that for quinidine.

AJMALINE

Ajmaline is an alkaloid derived from Rauwolfia serpentina that has no sedative, hypnotic, tranquilizing, or hypotensive effects. Like all class I drugs, ajmaline decreases the slope of phase 0 depolarization. It prolongs the relative refractory period. It increases the refractory period of the atria, ventricles, and accessory pathways, and increases the HV interval - this increase may be marked in patients with disturbances of atrioventricular conduction. Ajmaline has been used principally for two purposes. The first is to diagnose patients with Wolff-Parkinson-White syndrome who may have accessary pathways with very short refractory ventricular response should atrial fibrillation develop. The second use is as a provocative test of the AV conduction system in patients suspected of having paroxysmal heart block.

It is currently limited to investigational use.

CLASS IB DRUGS

There are two drugs that are currently FDA approved that are included in this class, lidocaine - the prototype of the group - and phenytoin. The great value of intravenous lidocaine in the treatment of rhythm disorders has stimulated considerable effort to develop lidocaine-like drugs that are suitable for long-term oral administration as well as intravenous use. Consequently, this class has the longest list of drugs that are currently in various stages of clinical investigation in this country. Several are in clinical use in other countries and may be approved for use in the USA in 1983 or 1984. Investigational drugs that will be considered in this section are tocainide, mexiletine, aprindine, and ethmozin.

LIDOCAINE

The local anesthecic lidocaine was synthesized in 1946, initially used as an antiarrhythmic in 1950 and came into clinical use in the USA in the mid-1960s. It has assumed a central role as a first-line drug for the treatment of ventricular arrhythmias. There is now an extensive literature and clinical experience dealing with lidocaine. (88-89)

CLINICAL PHARMACOLOGY

As noted above, the exact mode of action of lidocaine is still being debated, despite the extensive experience with it. In most respects, the action of lidocaine is clearly similar to the type IA drugs. As noted above, the major differences are that (1) lidocaine has minimal effects on phase 0 depolarization in normal cardiac cells but an appreciable effect on phase 0 in abnormal, e.g. ischemic, cells; and (2) slightly shortens the action potential duration and refractoriness. It is clear that lidocaine reduces the rate of spontaneous or epinephrine-induced phase 4 (diastolic) depolarization in latent pacemakers. It is possible that lidocaine diminishes reentrant arrhythmias as a result of a quinidine-like action on phase 0 depolarizations of diseased cells in a reentrant pathway.

Lidocaine is usually administered intravenously. Intramuscular administration is possible. Only 35% of an oral dose is absorbed and most of that is rapidly metabolized by the liver so that long-term

oral use is not feasible. (This property has stimulated vigorous searches for oral lidocaine-like drugs).

Adequate blood levels can be achieved with an intravenous loading dose of 1-2 mg/kg followed by a constant infusion of 1-4 mg/min. An additional small bolus may be required and should precede raising the constant infusion to a higher level. Adequate blood levels are said to be 1.5-6μg/ml but measurement of blood levels are rarely of any practical value because of the urgent nature of its use and the short half-life (about 108 minutes).

Its hepatic metabolism makes lidocaine pharmacokinetics susceptible to pertubations in hepatic blood flow and function so that the dose must be decreased by about one-half in patients with liver disease or a low cardiac output state. Variations in renal function have little effect on lidocaine pharmacokinetics.

CLINICAL UTILITY

Lidocaine is the first-line drug for suppression or prevention of ventricular rhythm disturbances in the setting of heart disease (especially myocardial ischemia), cardiac surgery, and digitalis toxicity. Seventy to ninety percent efficacy for these indications have been reported.

Only a small percentage of supraventricular arrhythmias are reverted by lidocaine, but because the drug depresses conduction in the bypass tracts of patients with pre-excitation it may be used to reduce the ventricular response to atrial fibrillation and flutter in these patients.

The use of prophylactic lidocaine after myocardial infarction to prevent primary ventricular fibrillation (that is, not preceded by ventricular premature beats) has created some controversy. The available evidence suggests that it is efficacious for this purpose. (90) But do the benefits outweigh the risks in a large sophisticated coronary care unit where defibrillation can be performed within 20-30 seconds of onset of the arrhythmia? I doubt it but I think that prophylactic lidocaine after MI in a hospital with less sophisticated support available can be justified.

ADVERSE SIDE EFFECTS

Lidocaine is a relatively safe antiarrhythmic drug. Moderate doses have little effect on cardiac function so that it is safe after myocardial infarction and in the presence of heart failure. It has only minimal depressant effects on the cardiac conduction system and rarely leads to heart block or to severe depression of sinus node impulse formation in therapeutic doses. Toxic doses or administration with other antiarrhythmics may occasionally suppress sinus node or escape pacemaker function. Like quinidine, lidocaine may rarely accelerate the ventricular response to atrial flutter. Paradoxical induction of serious ventricular rhythm disturbances appears to be much less common than with quinidine and like drugs.

The major side effects are neurological. The threshold for these side effects are variable but tends to be low in the elderly. Dizziness, drowsiness, paresthesias, and euphoria occur first and are followed at higher levels by speech disturbances, confusion, nausea, vomiting,

excitement, psychosis. Tremors or even seizures or respiratory arrest and coma have occurred rarely usually at toxic levels. True idiosyncratic or hypersensitivity reactions are rarely encountered.

PHENYTOIN

The anticonvulsant drug phenytoin, a structural analogue of the barbiturates, was introduced for treatment of seizures in 1938 and was found to have antiarrhythmic properties in 1950. It was first used clinically as an antiarrhythmic in 1958. Subsequently a very large clinical and experimental experience has been accumulated. (88, 91) Although it has been widely used for its antiarrhythmic properties it is not specifically approved by the FDA for that purpose.

CLINICAL PHARMACOLOGY

The electrophysiologic properties of phenytoin closely parallel those of lidocaine for the most part. A central or neurodepressant component in the action of phenytoin has also been suggested.

Metabolism is principally hepatic. It may be administered orally or intravenously. Intravenous administration must be slow, not exceeding 50mg/min to avoid cardiac depression and hypotension. With either route of administration a loading regimen of 1000mg the first day and 500mg the next is usually given followed by maintenance doses of 300-400mg/day. Once daily administration is satisfactory. Effective antiarrhythmic serum levels are reported to be 5-25µg/ml.

CLINICAL UTILITY

The clinical utility of phenytoin does not parallel that of lidocaine in spite of the similar electrophysiologic actions. Its only major use is for supraventricular or ventricular arrhythmias induced by digitalis excess. Occasionally it is useful for the management of non-digitalis toxic ventricular rhythm disturbances that have not responded to other drug therapy. When antiarrhythmic drug therapy of digitalis toxic rhythm disturbances are necessary, phenytoin is usually the first-line choice or the second-line choice after lidocaine.

ADVERSE SIDE EFFECTS

The cardiovascular effects of phenytoin owe to its vasodilatory and cardiodepressant properties. These effects are most marked during rapid intravenous administration and are not usually a problem during long-term oral administration of standard doses. Neurological side effects such as dizziness, ataxia, nystagmus, and dysarthria are dose related and are uncommon with doses used for control of arrhythmias. A large number of allergic reactions to phenytoin are known from its wide use as an anticonvulsant agent. They include a systemic lupus erythematosis-like syndrome, pseudolymphoma and several skin disorders. Lymphadenopathy, gingival hyperplasia, and a megaloblastic anemia occur fairly frequently. The nature and frequency of side effects have contributed to the lack of enthusiasm for phenytoin as a long-term antiarrhythmic agent.

TOCAINIDE

Tocainide is a primary amine analog of lidocaine. It was developed to provide lidocaine-like properties with oral administration. It has undergone extensive testing in Europe and the USA and is now in clinical use in parts of Europe. It has been tested in the USA by Astra but has not yet been approved for clinical use. Astra made it widely available for compassionate humane use until a few months ago and a large number of Americans now receive it as part of that protocol. Astra recently entered into a special joint arrangement with Merck Sharp and Dohme for further clinical testing in the USA. It will soon be available again through Merck for compassionate use for new patients. It appears reasonably likely that it will gain FDA approval for clinical use soon and may be clinically available in 1983 or 1984. Its use has been the subject of several extensive reviews. (28, 87, 92-95)

CLINICAL PHARMACOLOGY

Tocainide differs from lidocaine structurally only in lacking two ethyl groups, which protects the drug from first-pass hepatic elimination after oral ingestion. The cardiac electrophysiological data gathered to date suggest that its properties are very similar to those of lidocaine and mexiletine.

It is effective after oral or intravenous administration. Orally administered tocainide is well absorbed with availability approaching 100%. Administration with meals slows the rate of absorption but does not alter the bioavailability. Peak serum levels are achieved 60-90 minutes after ingestion. Tocainide is metabolized by the liver, but 30-50% of a dose is excreted unchanged in the urine. The elimination half-life is 13.5-14.7 hours in patients with heart disease and a little shorter, 11 hours, in normal volunteers. These elimination properties make tocainide suitable for administration two or three times a day. A three-times daily regimen is probably preferable. The dose necessary to maintain therapeutic blood levels when administered every 12 hours may frequently lead to high enough blood levels (10-15µg/ml) soon after ingestion to cause transient side effects. Furthermore, some groups have reported better drug efficacy with administration every 6 hours compared to every 8 hours. Therapeutic plasma concentrations have been reported to be in the range of 6-10µg/ml by one group and 6-12 µg/ml by another group. Different long-term dose regimens have been used. Typically a loading dose of 400-600mg is followed by a daily maintenance dose of 400-1200mg/day. Usually treatment is begun with a daily dose of 1200mg with titration of the dose every 2 days until toxic symptoms appears or control of the rhythm disturbance is achieved. Higher daily doses have been used occasionally, but doses greater than 2400mg/day are usually intolerable.

Intravenous tocainide has not been as extensively tested. When used, it is generally given as a dose of 750mg over 15 minutes.

CLINICAL UTILITY

Statements about the spectrum of tocainide's antiarrhythmic effects are necessarily biased by the fact that it has been tested almost exclusively for ventricular rhythm disturbances. This is not surprising considering its development as a lidocaine analog. It has been tested in a wide array of conditions including prophylactic treatment after myocardial infarction, ventricular rhythm disturbances responsive to other drugs, and ventricular rhythm disturbances refractory to other oral antiarrhythmic drugs. The greatest amount of data is in the last of these categories including the experiences from the American humane use protocol. The considerable differences in the nature of the populations studied and the treatment protocols makes simple summary statements about treatment efficacy difficult at this time. As many of the reported patients were refractory to other drugs before tocainide was used, the true efficacy of tocainide is doubtless higher than these figures would indicate. It appears that tocainide will suppress more than 75% of ventricular premature beats in the majority of patients treated and that it will prevent recurrence of serious ventricular rhythm disturbances in the majority of patients treated.

Our current experience is biased regarding the efficacy of tocainide with respect to the previous response of the patient to lidocaine. Many of the patients who have been given tocainide received it in part because lidocaine had been successful. The Stanford group has studied this issue specifically. As a general rule, the response or lack of response to intravenous lidocaine did predict the response to oral tocainide but there were occasional exceptions, for both tocainide success after lidocaine failure and vice versa.

ADVERSE SIDE EFFECTS

The hemodynamic effects of tocainide are minimal. There is only slight depression of cardiac contractility. Blood pressure often rises slightly owing to a slight increase in systemic vascular resistance. Tocainide, like lidocaine, only rarely causes serious depression of normal impulse formation of the sinus node or worsening of intrinsic conduction system disease.

Gastrointestinal and central nervous system side effects are frequent but are usually minor and well tolerated. They often respond to adjustment in dose. The central nervous system complaints include tremor, dizziness, paresthesias, nervousness, agitation, memory loss, confusion, and convulsions. The common gastrointestinal side effects are nausea, vomiting, anorexia, and abdominal pain. More serious side-effects are rare and include skin rashes, hepatitis, and a systemic lupus erythematosis-like syndrome.

MEXILETINE

Mexiletine has a structure similar to that of lidocaine and tocainide. It, too, was developed with the hope of finding an agent that could be administered orally and have lidocaine-like action. It has been studied extensively in Europe and the USA. It is now in clinical use in parts of Europe. It has been available for some time

in the USA from Boehringer Ingelheim for compassionate use in patients with refractory, life-threatening rhythm disturbances. It is likely that it, like tocainide, will be approved by the FDA in the not-too-distant future. It may be clinically available by 1983 or 1984. There are several extensive reviews of mexiletine that have been published recently. (28, 87-88, 96-98)

CLINICAL PHARMACOLOGY

The basic and clinical cardiac electrophysiological properties of mexiletine are very similar to those of lidocaine and tocainide. Like tocainide, there is minimal first-pass removal by the liver after oral ingestion so that it is suitable for oral administration. It is almost completely absorbed after oral administration. Peak plasma concentrations occur 2-4 hours after administration. The elimination half-life is about 10 hours in normal volunteers but may be longer in patients with heart disease. In one study of patients with acute infarction, the half-life was 16.7 hours. It is metabolized by the liver. Less than 10% of the unchanged drug is excreted in the urine. Therapeutic blood levels of 0.75-2μg/ml have been suggested. These levels can be achieved in most patients with administration of 200-300mg every 6-8 hours. Intravenous infusion is not commonly used, but a regimen that has been recommended is to give an initial bolus of 150-250mg over 2-5 min followed by a loading infusion of 250mg in 30 min, 250mg in 2.5 hr, and 500mg in 8 hr. The maintenance infusion was 500-1000mg over 24 hr.

CLINICAL UTILITY

Like tocainide, mexiletine has been most extensively studied in the setting of ventricular rhythm disturbances. Very few data are available regarding its efficacy and role in the management of supra-ventricular rhythm disturbances. There are also similar problems to tocainide in determining the efficacy because of a similar tendency for it to be used in patients who were refractory to other oral agents and who had responded to intravenous lidocaine. The efficacy appears to closely parallel that of tocainide although some patients who respond to mexiletine may not respond to tocainide and vice versa. Reduction of the frequency of ventricular premature beats by more than 75% and suppression of the majority of patients with serious recurrent ventricular rhythm disturbances have been reported. It has been studied extensively after myocardial infarction and appears to be highly efficacious in reducing serious ventricular rhythm disturbances in that setting.

ADVERSE SIDE EFFECTS

The hemodynamic effects of orally administered mexiletine are similar to those of tocainide. Depression of contractility of the heart is slight. Slight elevations of systemic vascular resistance and blood pressure are common. There is usually no adverse effect on sinus node function or cardiac impulse conduction in patients with no disease of the sinus node or the conduction system but bradycardia and heart block have been noted in some patients with sinus node and conduction system disease. The hemodynamic and cardiac effects are usually considerably more marked with intravenous administration.

Side effects of orally administered mexiletine are also similar to those of tocainide but are chiefly neurological. They are dose-related and frequent but usually minor and well-tolerated. Neurological side effects include tremors, nystagmus, blurred vision, dizziness, drowsiness, confusion, mild ataxia, paresthesias, dysarthria, insomnia, tinnitus, nausea, and seizures. Side effects of intravenously administered mexiletine are usually more marked.

APRINDINE

Aprindine is a tertiary amine with potent local anesthetic activity and the electrophysiological properties of a class I drug. It was introduced for antiarrhythmic studies in man in 1973. It has been tested and used extensively in Europe and has undergone testing in several centers in the USA. It was developed in Belgium by the Christiaens Co. Although it is frequently (but not always) grouped as a class IB agent, it shares properties with the class IA drugs. As the classification system is further refined in the future, aprindine may well be re-classified in a different way. While it is approved for clinical testing in the USA, it has not received FDA approval for marketing. The rather low therapeutic:toxic ratio makes it somewhat questionable if it will be approved for general clinical use in the near future. There are several recent reviews of aprindine. (28, 87-88, 99-101)

CLINICAL PHARMACOLOGY

The major effect of aprindine in therapeutically meaningful concentrations is depression of the upstroke velocity of phase 0 depolarization in atrial, ventricular, and Purkinje fibers (a quinidine-like property). In addition it shortens the action potential duration (APD) and the effect refractory period (ERP), but the ratio of the ERP/APD is increased (a lidocaine-like property).

Aprindine can be administered orally or intravenously. It appears that oral aprindine is well absorbed. The therapeutic range has not been well established but is in the range of 1-2µg/ml. Levels above 2µg/ml frequently cause toxic side effects. Aprindine is extensively metabolized in the liver and very little is excreted unchanged in the liver. The elimination half-life is long in normal volunteers and longer in patients with heart disease. There is considerable variation in the reported half-lives. Values from 30-60 hours and 13-50 hours have been reported. The full antiarrhythmic effects of aprindine may not become manifest until several days of beginning therapy, even when a loading dose is used. Doses from 100-150 mg/day achieve therapeutic results. A loading regimen is usually employed before beginning maintenance therapy (100mg every 6 hours the first day, 75mg every hours the second day and then 50mg every 6 hours the third day).

CLINICAL UTILITY

Aprindine has been found to be useful in a wide range of rhythm disturbances. In patients with stable ventricular premature beats, a suppression rate of about 70% has been found. The majority of patients with recurrent ventricular tachycardia or fibrillation who were refractory to other drugs were adequately controlled with aprindine;

in one study the value was over 80%. Aprindine has been particularly effective in preventing recurrent ventricular tachycardia and fibrillation in patients with mitral valve prolapse.

Aprindine has also been very successful in the management of supraventricular rhythm disturances associated with anomalous bypass tracts. This drug blocks conduction or markedly increases refractoriness in the aberrant pathway and abolishes reentrant supraventricular tachycardia. It also is useful in controlling the ventricular response to atrial fibrillation and atrial flutter in pre-excitation syndromes. Aprindine has not been very successful in the treatment of supraventricular rhythm disturances in the absence of an anomalous pathway.

ADVERSE SIDE EFFECTS

Aprindine has a very high incidence of adverse side effects and a very narrow dose range in which efficacy can be expected without toxicity. It does not cause major hemodynamic side effects, but there are a number of non-cardiac side effects that are associated with short-term or long-term use. Dose-related effects with short-term administration include hypotension, visual disturbances, somnolence, slurred speech and paresthesias. Long-term administration is commonly associated with dose-related neurological symptoms which range from tremor, dizziness, ataxia, diplopia and memory impairment to hallucinations and acute psychosis. Neurological side-effects (except vertigo, which may persist) are rare with serum concentrations less than 1µg/ml. Of greater concern are two serious side-effects associated with long-term use. Hepatitis, which is almost always reversible with therapy, has been reported rarely. Agranulocytosis has been reported. The exact incidence is unclear but is probably between 0.2 and 1%. Two of eight cases reported in Holland with this complication died.

ETHMOZIN

Ethmozin is a phenothiazine derivative that was developed in the Soviet Union in 1964. Until recently, most of the testing and experience was in the Soviet Union. The drug is now being tested in the USA by the Endo division of DuPont. Its electrophysiologic properties are somewhat similar to lidocaine in that it decreases the slope of phase 0 depolarization but shortens the action potential duration. Ethmozin has been used with success in both ventricular and atrial arrhythmias. Very few adverse side effects have been reported and it has none of the usual effects observed with phenothiazines. More studies will be required to establish its potential role as an antiarrhythmic agent. (28, 109).

CLASS IC DRUGS

Three drugs that have been developed in the last few years appear to have properties and clinical actions that are similar enough to lump them for the purposes of classification. As noted above, these properties are sufficiently different from the other class I anti-arrhythmic drugs that Harrison and his colleagues (28-29) have suggested that they be put into a separate sub-division. All three

of these drugs are currently undergoing extensive investigation in the USA and Europe. Encainide is a benzanilide derivative that is being tested by Mead Johnson. Flecainide is somewhat similar to encainide and is being tested by Riker. Lorcainide is an acetanilide derivative being tested by Janssen Pharmaceutica. These drugs markedly depress phase 0 depolarization without much effect on the action potential duration or refractoriness. In men, these drugs slow conduction in the heart, especially in the His-Purkinje system. This is reflected in the electrocardiogram by prolongation of the QRS, especially with encainide, and of the PR interval to a lesser degree. QT prolongation is not as marked and has not always been observed. It is interesting to speculate that the potent effects sometimes seen in the suppression of ventricular rhythm disturbances may owe to abolition of reentrant circuits that had within their loop Purkinje fibers with conduction markedly slowed by drug administration. A flurry of reports in the last year has added to our knowledge about these drugs but have also raised some uncertainties. These drugs, especially encainide and flecanide, appear to be remarkably effective in almost totally abolishing ventricular premature beats and do so with drug levels below 1ug/ml. (102-104) In this regard they appear to be unequivocally superior to any previous drug therapy and so have gained the nickname "VPB-killers." The role of these drugs in life-threatening recurrent ventricular tachycardia and ventricular fibrillation is less certain. Both encainide and lorcainide have suppressed these serious rhythm disturbances in some patients (105-106), but encainide administration was associated with polymorphic ventricular tachycardia and ventricular flutter in a few patients that was difficult to abort. (107) In another report, encainide administration to a patient with nonlife-threatening ventricular rhythm disorders was associated with induction of ventricular fibrillation by an electrophysiological technique that has been felt to virtually never induce this rhythm. (108) Of course, these drugs may not have been causal in these episodes, but further testing will be necessary to determine the proper role for these drugs in the treatment of ventricular rhythm disturbances. There are only limited data available on the use of these drugs for supraventricular rhythm disturbances. Some of those data appear promising.

None of these drugs have major deleterious effects on cardiac contractility or blood pressure. None have important depressant effects upon sinus node impulse formation. The marked depressant effect of these drugs on His-Purkinje system conduction time makes them potentially risky for the patient with disease of the atrioventricular node or the His-Purkinje system.

Troublesome side effects with long-term oral therapy for all three drugs have been neurological. By far the most troublesome adverse effects with lorcainide are sleep disturbances: insomnia, nightmares, vivid dreams, and increased perspiration in up to 40% of patients. The sleep disturbances may diminish with time. Side effects with flecainide occur in most patients but are usually minor and well-tolerated. They include transient blurred vision, unsteadiness, dizziness, abnormal taste sensations, flushing, tinnitis, and sleepiness. Most patients who received encainide also experienced minor side effects, usually diplopia and ataxia, that were well-tolerated and were dose-related. (109)

CLASS II DRUG - BETA-ADRENERGIC BLOCKING AGENTS (110-113)

The beta-adrenergic blocking agents were initially included among the class I drugs with regard to their antiarrhythmic properties because of their membrane-active properties. It subsequently became clear that the local anesthetic properties were present only at doses far beyond those necessary to achieve cardiac beta-adrenergic blockade and far beyond clinically relevant doses. Consensus now is that the beta-adrenergic blocking drugs act as antiarrhythmic drugs exclusively or virtually exclusively through blockade of arrhythmias induced by catecholamines. The only effect of beta-blockers on the cardiac action potential is a decrease in the slope of phase 4 depolarization of cells with pacemaker potential.

There is also a current consensus that there are no important differences in the antiarrhythmic properties among the currently available beta-blockers and that equivalent degrees of beta-blockade have equivalent degress of antiarrhythmic potential. The only exception to this might lie in differences in cardiac selectivity. If one drug had more potent non-cardiac effects or side effects in a given patient than another, e.g. bronchospasm and hypoxia, the resulting indirect effects on the heart could alter the direct effects. The greatest experience by far with antiarrhythmic effects of a beta blocker, however, are with propranolol and it is the only beta-blocker currently marketed in the USA that is approved by the FDA for that indication.

A discussion of the clinical pharmacology of the beta-blockers is beyond the scope of this discussion, but it is worthwhile to consider probable mechanisms for the antiarrhythmic effects of these drugs. The heart is richly supplied with sympathetic nervous system fibers. At least three potential mechanisms have been established by which increased sympathetic tone and catecholamines may cause arrhythmias and hence beta-blockers could prevent them.

Catecholamines increase the rate of spontaneous diastolic depolarization of cells with pacemaker potential and thus increase the firing rate of those cells. Normally the sinus firing rate is increased more than that of subsidiary pacemaker cells so that sinus tachycardia results. In some circumstances, however, the firing rate of ectopic pacemaker cells may accelerate disproportionately and cause arrhythmias owing to this increase in automaticity. Myocardial ischemia and digitalis excess particularly sensitize subsidiary pacemaker cells to these effects of catecholamines.

Cardiac arrhythmias resulting from sympathetic effects on the heart may also result from reentry. Catecholamines shorten the refractory period. Increased sympathetic tone may shorten refractory period in some areas more than others and thus cause wider dispersion of the refractory period in nearby cells. These differences might be augmented by coexisting myocardial ischemia.

With the proper conditions, sympathetic activation also might elicit slow response action potentials and cause reentry to occur by the mechanism of slow conduction and unidirectional block. In the face of severe myocardial ischemia (or possibly other diseases), ventricular muscle cells leak potassium. It is conceivable that potassium concentration outside the cell could rise to such high levels that the decrease in resting membrane potential which it causes

completely inactivates the fast inward sodium current in some fibers and they come inexcitable. Under these conditions, catecholamine stimulation might cause slow response action potentials to appear. These slow potentials might then set in motion a reentrant arrhythmia from the resulting conduction delay and unidirectional.

Beta-blockers may also exert an antiarrhythmic effect by slowing conduction in the atrioventricular node. Sympathetic tone speeds conduction through the AV node. The mechanisms are not completely worked out because of the difficulties in studying the AV node but the effect appears to be an increase in the rate of rise of phase 0 of the action potential of cells in the upper part of the AV node. This effect is blocked by beta-blockade. Slowing of conduction in the AV node may abort a reentrant arrhythmia with the AV node in the loop of tissue involved. Beta-blockade does not, however, slow conduction in accessory bypass tracts.

Paroxysmal atrial arrhythmias, including atrial premature beats, paroxysmal supraventricular tachycardia, and paroxysmal atrial fibrillation may occur in response to exercise or emotion. Long-term beta-blockade has been highly effective in preventing these arrhythmias. Paroxysmal supraventricular tachycardia with or without a demonstrated aberrant pathway and paroxysmal atrial fibrillation, which are not exercise - or emotion - induced may also be reduced in frequency or abolished by long-term beta-blockade. Paroxysmal atrial flutter, atrial fibrillation, and tachycardia resulting from acute myocardial infarction also often respond to acute beta-blocker administration although that may often not be the treatment of choice because of the potential hemodynamic consequences. Chronic atrial tachyarrhythmias are rarely reverted to sinus rhythm by beta-blockers, but they are a useful adjunct to digitalis glycosides in controlling the ventricular response in these disorders.

Propranolol is often effective in the treatment of digitalis-induced atrial tachycardia and ventricular rhythm disturbances, but this is often not the treatment of choice because of deleterious consequences on AV conduction and hemodynamics.

Ventricular rhythm disturbances induced by exercise and emotion and other causes of sympathetic stimulation also often respond well to beta-blockade. Other ventricular rhythm disturbances, however, do not usually respond to beta-blockade.

The possibility that long-term beta-blockade in the six months to a year after myocardial infarction may decrease the incidence of sudden death, presumably by decreasing the incidence of ventricular fibrillation, is an exciting recent finding. The studies supporting that concept were reviewed by Dr. James Willerson at these exercises on June 24, 1982.

CLASS III DRUGS

The observations that the sole changes in the cardiac action potential in hypothyroidism and hyperthyroidism were shortening (hyperthyroidism) or lengthening (hypothyroidism) of the actual potential duration gave rise to the notion that drugs that shortened the action potential duration might be effective anti-arrhythmic agents. Two drugs, bretylium and amiodarone, are now placed into

that category. The antiarrhythmic actions of these drugs are attributed to the lengthening of the effective refractory period as a result of prolongation of the action potential duration.

BRETYLIUM

Bretylium tosylate, a quarternary ammonium compound, was introduced as an antihypertensive drug in 1959. Antiarrhythmic effects were first noted in 1965. It was approved by the FDA for intravenous administration for the treatment of certain ventricular rhythm disturbances a few years ago. An oral preparation was tested extensively but is not likely to ever become clinically available because of poor and unpredictable bioavailability. Related compounds with better bioavailability appear promising for oral use. There are recent reviews of the use of bretylium. (28, 87-88, 114-115)

CLINICAL PHARMACOLOGY

Bretylium homogeneously lengthens the action potential duration and the effective refractory period in normal Purkinje fibers and ventricular myocardial cells but not in atrial myocardial cells. In ischemically injured cells that are partially depolarized with decreased velocity of phase 0 and decreased action potential amplitude, bretylium tends to return the action potential characteristics toward normal. The net effect is to decrease the dispersion of local excited states induced by asymmetric ischemia which would reduce the vulnerability to ventricular fibrillation. Its effects on the heart, and an understanding of the mechanism of its antiarrhythmic properties, are confounded by effects on neuronal catecholamine release and uptake and by its vasodilator action. Soon after drug administration, at low drug concentrations, catecholamines are released from the adrenergic post-ganglionic nerve terminals and may transiently cause an increase in rhythm disturbances, an increase in the heart rate, and hypertension. Later, and with higher drug concentrations, neuronal uptake of catecholamines is inhibited and postural hypotension ensues and lasts several days until tolerance develops. Bretylium is eliminated almost totally unchanged in the urine. Following intravenous administration, the half-life of elimination was reported to be 13.5 hours. In emergency situations, 5mg/kg is administered by rapid intravenous injection. This dose may be increased to 10 mg/kg and repeated at 15-30 minute intervals until a total dose of 30 mg/kg has been given. The onset of action is usually delayed until at least 20-30 minutes after the dose is given. In less emergent situations, 5-10 mg is given intravenously over at least 8 minutes and may be repeated in 1-2 hours. Maintenance bretylium may be administered by a constant infusion of 1-2mg/min or 5-10mg/kg given over at least 8 minutes every 6 hours.

CLINICAL UTILITY

Bretylium has been useful in ventricular rhythm disturbances, especially ventricular tachycardia and ventricular fibrillation that are resistant to treatment with lidocaine. It has not been effective in atrial rhythm disturbances. This is not surprising in light of the absence of an effect on the action potential of atrial cells.

ADVERSE SIDE EFFECTS

The adverse side effects owe primarily to the perturbations of the drug on catecholamine release and uptake. The rhythm disturbance may transiently worsen after the first dose. The raised blood pressure and heart rate and inotropic state that occur soon after administration may worsen myocardial ischemia because of increased myocardial oxygen demand. Later the postural hypotension and bradycardia may cause some problems.

Nausea and vomiting may complicate rapid administration.

Bethanidine sulfate is a closely related chemical analog of bretylium that has virtually identical pharmacologic and antifibrillatory actions on the ventricle. Unlike bretylium, it is rapidly and effectively absorbed when administered orally. Bethanidine has been studied since the early 1960s by Bacaner and his colleagues along with their studies of bretylium. The disappointing results with oral bretylium led them to recently reevaluate bethanidine for oral and intravenous use. (116) The actions of bethanidine on the heart and sympathetic nervous system are almost identical to those of bretylium. Bethanidine increased the fibrillatory threshold in dogs with experimental infarction when administered orally or intravenously. The onset of action began as early as two minutes after intravenous administration and 15-30 minutes after oral administration. It is likely that the effects on the cardiac action potential are identical or similar to those of bretylium.

AMIODARONE (28, 87-88)

Amiodarone is a fascinating drug. While it is not the proverbial "ideal" antiarrhythmic agent, it may well be the closest to one now available. It is the product of Labaz, a Belgium company. It has been in clinical use in parts of Europe for over 15 years. It is now in wide-spread use in Europe, especially Belgium and France and elsewhere in the world, especially South America. It is my understanding that it is probably the most frequently prescribed antiarrhythmic in many countries in South America. Labaz has not shown any interest in marketing the drug in the USA. Initially patients who received it abroad maintained drug supplies from their foreign physicians by hook or crook. As interest grew in the USA, a number of physicians obtained individual INDs for amiodarone and Labaz supplied the medication free of charge. There has been an extraordinary burst of interest in amiodarone among American cardiologists in the last few years. There are now roughly 300 individual INH holders. This is unprecedented for any drug ever investigated in the USA. Needless to say, the FDA is concerned about this unusual approach to drug testing and is currently trying to help arrange for sponsorship of drug testing by an American Pharmaceutical firm. This is complicated by the unfortunate timing of the patent rights. They are about to expire. It is likely that the FDA will declare amiodarone a drug orphan which may make an American firm more interested in sponsoring amiodarone testing.

CLINICAL PHARMACOLOGY

Amiodarone is a di-iodinated benzofuran derivative. It was introduced initially as an antianginal drug with smooth muscle relaxing and coronary vasodilating properties. It was later found to have

negative chronotropic effect but only a slight negative inotropic effect; these two effects are probably mediated via non-competitive inhibition of cardiac beta-adrenergic receptors.

The electrophysiologic effects on the heart are to lengthen AV nodal conduction time and refractory period, to increase the atrial and ventricular action potential durations and refractory periods, and to increase the effective refractory period of accessory bypass tracts. Like bretylium and bethanidine, amiodarone increases the threshold to ventricular fibrillation in experimental animals. The effects on the cardiac action potential are virtually identical to the effects of hypothyroidism and it is possible that the electrophysiologic effects of amiodarone owe to selective depressant effect on cardiac metabolism in parallel, as it were, to thyroxine-dependent pathways. The structure of amiodarone has some similarities to thyroid hormones. Amiodarone blocks the peripheral conversion of thyroxine to triiodothyronine.

The pharmacokinetics of amiodarone are very poorly understood. They are completely unlike the pharmacokinetics of any other anti-arrhythmic drug. It often requires several weeks to achieve a maximum cardiac effect after initiating long-term oral therapy. The half-life is not accurately established but appears to be in the range of 16-65 days with long-term oral therapy. With a single dose, it is 7-10 hours. As much as a third of amiodarone is retained in the body one month after cessation of therapy. Both amiodarone and its desethyl metabolite (which may be active) are detectable a year after stopping treatment. Amiodarone and its metabolites are not excreted by the kidneys. Elimination may be through the skin and tears. The value of blood levels is not yet established. It may be that measurement of reverse triiodothyronine is the best chemical measure of amiodarone effect.

Amiodarone may be administered intravenously or orally, but the greatest utility appears to be for long-term oral administration in light of its pharmacokinetic properties. Almost all of the American use of amiodarone has been with oral administration.

The bioavailability of a single oral dose is about 50%. With long term administration, levels are higher in fat and fat-laden organs than in the plasma. The ideal dose of amiodarone has not yet been determined. Much of the European and South American experience has been with doses of about 400mg/day. Loading doses as high as 1200-2000mg/day for 2-4 days have been used by some in order to shorten the time for maximum cardiac effects to about one week. In the USA, most of the experience with amiodarone has been with refractory, life-threatening ventricular rhythm disturbances and doses of 200-800 have typically been employed. Some difficult patients were controlled with even higher doses.

CLINICAL UTILITY

Amiodarone has proved to be effective in a very wide array of rhythm disturbances. It is highly effective in preventing rhythm disturbances associated with pre-excitation syndromes and in blocking conduction through the accessory pathways when atrial fibrillation and atrial flutter complicate these syndromes. It is also highly successful in preventing paroxysmal supraventricular tachycardia not associated

with pre-excitation syndromes. Amiodarone has found its greatest use so far in the USA in the prevention of recurrent, sustained ventricular tachyarrhythmias. In the experiences in the USA and abroad, amiodarone has been effective in preventing recurrences of these rhythms in a majority of cases of recurrent ventricular fibrillation and most cases of recurrent ventricular tachycardia.

ADVERSE SIDE EFFECTS

Amiodarone use has been remarkably free of serious side effects but has been associated with a number of nonlife-threatening but bizarre side effects. With oral administration, death owing to amiodarone is exceedingly rare. Torsade de pointes is very rare but recently a 5% incidence of incessant ventricular tachycardia was reported by one group. (117)

With long term administration, yellow-brown granular micro-deposits in the cornea are virtually invariable. They do not interfere with vision and may be diminished by the frequent use of eyedrops and occasional transient cessation of therapy. They regress after stopping therapy.

A peculiar slate-gray or blue skin discoloration occurs occasionally. It is more common with higher doses and occurs predominantly in sun-exposed areas. It is probably due to deposition of lipofuscin.

Chemical and clinical disorders of thyroid function occur occasionally. Thyroxine levels usually increase slightly and triiodothyronine levels fall slightly. Usually these values remain in the normal range but reverse triiodothyronine levels rise considerably, presumably reflecting peripheral blockade of T-4 to T-3 conversion. The T-4 to T-3 conversion inhibition rarely leads to clinical hypothyroidism, but rare cases of both hypothyroidism and hyperthyroidism have been reported.

Use of amiodarone in patient with sick sinus syndrome or marked abnormalities of AV conduction can lead to symptomatic bradycardia owing to amiodarone effects on sinus node function and AV conduction in these patients.

There is a drug/drug interaction of amiodarone with warfarin anticoagulation which requires reduction of the dose of anticoagulation.

There are occasional abnormalities of liver function tests, proximal weakness, nausea, and minor neurological side effects, such as tremor, pyramidal signs, paresthesias, etc.

The most disturbing report of adverse side effects has come from the American experience. Rare cases of pulmonary fibrosis have been reported. They have ranged from mild and reversible to severe and non-reversible. While it is not yet absolutely established that these cases are drug-induced, more cases have been discovered in recent months suggesting a drug relationship. It has generally been observed in patients receiving fairly high doses. Use of amiodarone dictates careful clinical and radiographic evaluation of pulmonary function.

CLASS IV DRUGS

The class IV drugs are those agents that inhibit the slow calcium channel of the cardiac action potential and thus depress slow responses. Their antiarrhythmic actions can be attributed to slowing of conduction in the AV node and depression of slow responses generated by abnormal cells. Use of the calcium blockers for arrhythmias was extensively reviewed by Dr. David Hillis at these exercises on September 9, 1982 and so will not be discussed here in detail. The efficacy of calcium blockers for treatment of arrhythmias and the mechanism for these effects are outlined in table 5.

TABLE 5

EFFICACY & MECHANISMS OF CALCIUM BLOCKERS IN TREATMENT OF ARRHYTHMIAS

ARRHYTHMIA	DRUG	EFFECT	MECHANISM
Paroxysmal supraventricular tachycardia with AV node entry or reciprocating tachycardia utilizing an anomalous bypass tract.	Intravenous verapamil	Reverts most episodes to normal sinus rhythm	Slows AV conduction
	Long-term oral verapamil	Effective in reducing frequency and duration of the episodes	Slows AV conduction
Atrial fibrillation and flutter	Intravenous verapamil	Occasionally (flutter) or rarely (fibrillation) reverts to sinus rhythm. Reliably slows ventricular response*	Slows AV conduction
	Long-term oral verapamil	Controls ventricular response	
Ventricular rhythm disturbances A. Associated with acute myocardial infarction	Verapamil Nifedipine Diltiazem	Occasionally reduces or eliminates	Uncertain ?depression of slow response ?improved flow ?metabolic
B. Associated with vasospastic angina pectoris	Verapamil Nifedipine Diltiazem	Eliminates or markedly reduces	Eliminates or mitigates coronary vasospasm abolishing "reperfusion" arrhythmias

*Verapamil may accelerate the ventricular response in patients with Wolff-Parkinson-White syndrome who are conducting through the accessory pathway.

CLOSING COMMENTS

In closing this discussion, it is fair to compare the agents we now have with an ideal antiarrhythmic drug. (118) Dreifus and Ogawa suggested that the ideal agent should meet most, if not all, of the following criteria:

1. Wide therapeutic range with a low level of toxicity.
2. Minimal side effects.
3. Effectiveness in the presence of all abnormalities of impulse formation and conduction such as automaticity, reentry and rhythms produced by the calcium-mediated slow response.
4. Favorable hemodynamic effects.
5. Availability in intravenous and oral preparations.
6. Few drug interactions but favorable additive or synergistic effects with other antiarrhythmic agents so that small doses of several drugs can be used concurrently.
7. Minimal effects on normal impulse formation and conduction.
8. Prolonged action to provide sustained antiarrhythmic control.

Clearly no antiarrhythmic drug now available or immediately on the horizon meets these criteria. Nevertheless, the future has never looked so bright. The scientific basis for antiarrhythmic action is better established. There is reason to be hopeful that in the future the scientific community, the pharmaceutical industry, and the FDA will work together more effectively in speeding up the process of evaluating and testing new drugs.

Development of more effective and safer drugs will allow testing of one of the most vexing issues facing today's internist - does effective drug treatment of ventricular rhythm disorders reduce the incidence of sudden death?

Other approaches to management of arrhythmias are also advancing rapidly. Pacemaker techniques, implantable cardioverters and defibrillators, and surgical and non-surgical ablative procedures hold great promise for some rhythm disturbances. I am happy to conclude that what I have outlined today will be obsolete to a large degree ten years from now.

REFERENCES

1. Einthoven W; Die galvanometrische Registrirung des menschlichen Electrokardiogramms, Zugleicheine beurtheilung der Answendung des Capillarelektrometers in der Physiologie. Pflugers Arch. 99;472, 1903.
2. Wenckebach KF: Die unregelmässige Herztätigkeit und ihre klinische Bedeutung. W. Engelman, Leipzig, 1914.
3. Frey W: Weitere Erfahrungen mit chinidin bei absoluter Herzunregelmassigkeit. Klin. Wehnschr. 55:849, 1918.
4. Mautz FR: Reduction of cardiac irritability by the epicardial and systemic administration of drugs as a protection in cardiac surgery. J. Thoracic Surg.5:612,1936.
5. Mayer AG: Rhythmical pulsation in scyphomedusal II. Papers from the Tortugar Laboratory of the Carnegie Institute of Washington 1:113. Carnegie Institution of Washington. Publication No. 102, part VII, 1908.
6. Mines GR: On circulating excitations in heart muscle and their possible relation to tachycardia and fibrillation. Trans. Roy. Soc. Can. 8:43-52, 1914.
7. Moe GK: Evidence for reentry as a mechanism for cardiac arrhythmias. Rev. Physiol. Biochem. Pharmacol. 72:56, 1975.
8. Katz MA: Cardiac action potential, in Physiology of the Heart, pp. 229-256, Raven Press, New York, 1977.
9. Katz MA: The arrhythmias, in Physiology of the Heart, pp. 293-353, Raven Press, New York, 1977.
10. Gadsby DG and Wit AL: Normal and abnormal electrophysiology of cardiac cells, in Mandel WJ (ed) Cardiac Arrhythmias, pp. 55-81, Lippincott, Philadelphia and Toronto, 1980.
11. Rosen MR: Cellular basis of cardiac arrhythmias, in Harrison DC (ed) Cardiac Arrhythmias: A Decade of Progress, pp. 25-38, GK Hall Medical Publishers, Boston, 1981.
12. Hauswirth O, Singh BN: Ionic mechanisms in heart muscle in relation to the genesis and the pharmacological control of cardiac arrhythmias. Pharmacol Rev 30:5-63, 1978.
13. Bigger JT: Arrhythmias and antiarrhythmic drugs. Ann Intern Med 18:251-278, 1972.
14. Rosen MR, Hoffman BF: Mechanisms of action of antiarrhythmic drugs. Circ. Res. 32:1-8, 1973.
15. Gettes LS: On the classification of antiarrhythmic drugs. Modern Concepts of Cardiovascular Disease 48:13-18, 1979.
16. Vaughan Williams EM: Classification of anti-arrhythmic drugs; in Sandoe et al. (Eds). Symposium on Cardiac Arrhythmias, pp.449-469 (A.B.Astra, Sodertalji, Sweden 1970).
17. Opie LH: Calcium antagonists. Lancet 2:806-809, 1980.
18. Singh BN, Hauswirth O: Comparative mechanisms of action of antiarrhythmic drugs. Am.Heart J. 87:367-382, 1974.
19. Singh BN, Vaughan Williams EM: A third class of antiarrhythmic action. Brit. J. Pharmacol.39;675-687, 1970.
20. Singh BN, Vaughan Williams EM: A fourth class of antidysrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials and on other features of cardiac function. Cardiovasc. Res. 6:109-114, 1972.

21. Vaughan-Williams GM: Anti-disrhythmic drugs - their mode of action, in Nayler WG (ed), Contraction and Relaxation in the Myocardium, Academic Press, London, 1975.
22. Singh BN, Vaughan Williams EM: Local anesthetic and antiarrhythmic actions of alprenolol relative to its effect on intracellular potentials and other properties of isolated cardiac muscle. Br. J. Pharmacol. 38:749-757, 1970.
23. Singh BN, Jewett DE: Beta-adrenergic receptor blocking drugs in cardiac arrhythmias. Drugs 7:426-461, 1974.
24. Vaughan Williams EM: Mode of action of beta-receptor antagonists on cardiac muscle. Am. J. Cardiol. 18:399-409, 1966.
25. Freedberg AS, Papp JG, Vaughan Williams EM: The effect of altered thyroid state on atrial intracellular potentials. J. Physiol. 207:357-370, 1970.
26. Heng MK, Singh BN, Roche AHG, et al: Effects of intravenous verapamil on cardiac arrhythmias and on the electrocardiogram. Am. Heart J. 90:487-498, 1975.
27. Singh BN, Ellrodt G, Peter CT: Verapamil: A review of its pharmacological properties and therapeutic uses. Drugs 15: 169-197, 1978.
28. Keefe DLD, Kates RE, Harrison DC: New antiarrhythmic drugs: Their place in therapy. Drugs 22:363-400, 1981.
29. Harrison DC, Winkle RA, Sami M, Mason JW: Encainide: A new and potent antiarrhythmic agent, in Harrison DC (ed) Cardiac Arrhythmias: A Decade of Progress, pp. 315-330, GK Hall Medical Publishers, Boston, 1981.
30. Bigger JT,Jr., Mandel WJ: Effect of lidocaine on conduction in canine Purkinje fibers and at the ventricular muscle Purkinje fiber junction. J. Pharmacol. Exp. Ther., 174:487-499, 1970.
31. Rosen MR, Merker C, Pippenger CE: The effects of lidocaine on the canine ECG and electrophysiological properties of Purkinje fibers. Am. Heart J., 91:191-202, 1976.
32. Willus FA, Keys TE: Cardiac clinics XCIV: A remarkable early reference to the use of cinchona in cardiac arrhythmia. Mayo Clin Proc 17:294-296, 1942.
33. Singh BN: Antiarrhythmic effects of local anesthetics and calcium antagonists. J. Pharmacol. Ther. 2:125-150, 1977.
34. Seller TD, Campbell RWF et al: Effects of procainamide and quinidine sulphate in the Wolff-Parkinson-White syndrome. Circulation 55:15-22,1977.
35. Heissenbuttel RH, Bigger JT, Jr: The effect of oral quinidine on intraventricular conduction in man: correlation of plasma quinidine with changes in QRS duration. Am. Heart J. 80:453-462, 1970.
36. Greenblatt DJ, Pfeifer HJ, Ochs HR, et al: Pharmacokinetics of quinidine in humans after intravenous, intramuscular, and oral administration. J. Pharmacol. Exp. Ther. 202:365-378, 1977.
37. Woo E, Greenblatt DH: A reevaluation of intravenous quinidine. Am Heart J. 96:829-832, 1978.
38. Mason WD, Covinsky JO, et al: Comparative plasma concentration of quinidine following administration of one intramuscular and three oral formulations to 13 subjects. J. Pharmacol. Sci. 65:1325-1329, 1976.

39. Covinsky JO, Russo J Jr, et al; Relative bioavailability of quinidine gluconate and quinidine sulfate in healthy volunteers. J. Clin. Pharmacol. 19:261, 1979.
40. Ochs HR, Greenblatt DJ, Woo E, et al: Single and multiple dose pharmacokinetics of oral quinidine sulfate and gluconate. Am. J. Cardiol. 41:770, 1978.
41. Kessler KM, Lowenthal DT, Warner H, Gibson T, et al: Quinidine elimination in patients with congestive heart failure or poor renal function. N. Engl.J. Med. 290:707-709, 1974.
42. Cramer G, Isaksson B; Quantitative determination of quinidine in plasma. Scand. J. Clin. Lab. Invest. 15:553-556, 1963.
43. Carliner NH, Crowthamel WG, et al: Quinidine therapy in hospitalized patients with ventricular arrhythmias. Am. Heart J. 98:708, 1979.
44. Powers JL, Sadee W: Determination of quinidine by high-performance liquid chromatography. Clin. Chem. 24:299-302, 1978.
45. Torok E, Bajkay G, Gulyas A, Maklary E: Comparative study of a long acting quinidine preparation and quinidine sulphate in chronic atrial fibrillation. Pharmacologia Clinica 2:90-93, 1970.
46. Wellens HJ, Durrer, D: Effect of procainamide, quinidine, and ajmaline in the Wolff-Parkinson-White syndrome. Circulation 50: 116-120, 1974.
47. Krikler DM, Curry PVL: Torsade de pointes, an atypical ventricular tachycardia. Br. Heart J. 38:117-120, 1976.
48. Smitherman TC, Gottlich CM, Narahara KA, et al: Myocardial contractility in patients with ischemic heart disease during long-term administration of quinidine and procainamide. Chest 76:552-556, 1979.
49. Singh BN: Side effects of antiarrhythmic drugs. J. Pharmacol. Ther. 2:151-166, 1977.
50. Selzer A, Wray HW: Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial fibrillation. Circulation 30:17-26, 1964.
51. Rosen MR, Gelband H, Hoffman BF: Canine electrocardiographic and cardiac electrophysiologic changes induced by procainamide. Circulation 46:528-536, 1972.
52. Giardina EG, Bigger JT: Procaine amide against reentrant ventricular arrhythmias. Lengthening R-V intervals of coupled ventricular premature depolarization as an insight into the mechanisms of action of procaine amide. Circulation 48:959-968, 1973.
53. Josephson ME, Caracta AR, Ricciutti MA, et al: Electrophysiologic properties of procainamide in man. Am. J. Cardiol. 33:596-603, 1974.
54. Helfant RH, Scherlag BJ, Damato AN: The electrophysiological properties of diphenylhydantoin sodium as compared to procainamide in the normal and digitalis-intoxicated dog. Circulation 36: 108-118, 1967.
55. Helfant RH, Scherlag BJ, Damata AN: Use of diphenylhydantoin sodium to dissociate the effects of procainamide on automaticity and conduction in the normal and arrhythmic heart. Am. J. Cardiol. 20:820-825, 1967.

56. Graffner C, Johnsson G, Sjogren J: Pharmacokinetics of procainamide intravenously and orally as conventional slow-release tablets. Clin. Pharmacol. Ther. 17:414-423, 1975.
57. Koch-Weser J: Pharmacokinetics of procainamide in man. Ann. N.Y. Acad. Sci. 179:370-382, 1971.
58. Gibson TP, Matusik J, Matusik E, et al: Acetylation of procainamide in man and its relationship to isonicotinic acid hydrazide acetylation phenotype. Clin. Pharmacol. Ther. 17;395-399, 1975.
59. Gibson RP, Matuski EJ, Briggs WA: N-acetylprocainamide levels in patients with end-stage renal failure. Clin. Pharmacol. Ther. 19:206-212, 1976.
60. Reidenberg MM, Drayer DE, Levy M, et al: Polymorphic acetylation of procainamide in man. Clin. Pharmacol. Ther. 17:722-730, 1975.
61. Strong JM, Dutcher JS, Lee W-K, et al: Pharmacokinetics in man of the N-acetylated metabolite of procainamide. J. Pharmacokinet. Biopharm. 3:223-235, 1975.
62. Giardina EG, Heissenbuttel RH, Bigger JT: Intermittent intravenous procainamide to treat ventricular arrhythmias. Ann. Intern. Med. 78;183-193, 1973.
63. Kock-Weser J, Klein SW: Procainamide dosage schedules, plasma concentrations, and clinical effects. JAMA 215:1454-1460, 1971.
64. Kock-Weser J: Correlation of serum concentrations and pharmacological effects of antiarrhythmic drugs. In Proceedings of the 5th International Congress of Pharmacology. San Francisco, 1972, 69-85.
65. Collste P, Karlsson E: Arrhythmia prophylaxis with procainamide: plasma concentrations in relation to dose. Acta Med. Scand. 194:405-411, 1973.
66. Bigger JT Jr, Heissenbuttel RH: The use of procainamide and lidocaine in the treatment of cardiac arrhythmias. Prog. Cardiovasc. Dis. 11:515-534, 1969.
67. McClendon RL, Hanse WR, Kinsman JM: Hemodynamic changes following procaineamide administered intravenously. Am. J. Med. Sci. 222:375-381, 1951.
68. Inouye M, Millar J, Townsend JH: Agranulocytosis following maintenance dosage of pronestyl. Report of severe case with recovery. JAMA 147:652-653, 1951.
69. Blomgren SE, Condemi JJ, Vaughan JH: Procainamide-induced lupus erythematosus. Clinical and laboratory observations. Am. J. Med. 52:338-348, 1972.
70. Drayer DC, Reidenberg MM, Sevy RW: N-Acetylprocainamide: An active metabolite of procainamide. Proceedings of the Society for Experimental Biology and Medicine 146:358-363, 1974.
71. Jaillon P, Winkle RA: Electrophysiologic comparative study of procainamide and N-acetylprocainamide in anesthetized dogs: Concentration response relationships. Circulation 60:1385-1394, 1979.
72. Dangman KH, Hoffman BF: Effects of N-acetylprocainamide on cardiac Purkinje fibers (abstr.). Pharmacologist 20:150, 1978.
73. Strong JM, Dutcher JS, Lee WK, Atkinson AJ: Absolute bioavailability in man of N-acetylprocainamide determined by a novel stable isotope method. Clin. Pharmocol. Ther. 18:613-622, 1975.

74. Kates RE, Jaillon P, Rubenson DS, Winkle RA: Intravenous N-acetylprocainamide disposition kinetics in coronary artery disease. Clin. Pharmacol. Ther. 28:52-57, 1980.
75. Atkinson AJ, Lee WK, Quinn ML, Kushner W, Nevin MJ, Strong JM: Dose-ranging trial of N-acetylprocainamide in patients with premature ventricular contractions. Clin. Pharmacol. Ther. 21:575-587, 1977.
76. Roden DM, Reele SB, Wilkinson OR, Smith RF, Oates JA, Woolsey RL: Antiarrhythmic efficacy, pharmacokinetics and safety of N-acetylprocainamide in human subjects: Comparison with procainamide. Am. Jour. Card. 46:463-468, 1980.
77. Kluger J, Drayer D, Reidenberg M, Ellis G, Lloyd V, Tyberg T, Hayes J: The clinical pharmacological and antiarrhythmic efficacy of acetylprocainamide in patients with arrhythmias. Am. Jour. Cardio. 45:1250-1257, 1980.
78. Lertora JJL, Atkinson AJ, Kushner W, Nevin MJ, Lee W, Jones C, Schmid FR: Long-term antiarrhythmic therapy with N-acetylprocainide. Clin. Pharmacol. Ther. 25:273-282, 1979.
79. Winkle RA, Peters F, Kates RE, Tucker C, Harrison DC: The clinical parmacology and antiarrhythmic efficacy of encainide in patients with chronic ventricular arrhythmias. Circulation In press, 1981.
80. Mokler CM, Van Arman CG: Pharmacology of a new antiarrhythmic agent, gamadiisopropylamino-alpha-phenyl-alpha (2-pyridyl)-butyramide (SC 7031). J. Pharmacol. Exp. Ther. 136:114-124, 1962.
81. Katz MJ, Meyer CE, Eletr A, et al: Clinical evaluation of a new antiarrhythmic agent, SC 7031. Curr. Ther. Res. 5:343-350, 1963.
82. Heel RC, Brogden RN, Speight TM, Avery GS: Disopyramide: A review of its pharmacological properites and therapeutic use in treating cardiac arrhythmias. Drugs 15: 331-368, 1978.
83. Koch-Weser J: Drug therapy: Disopyramide. N. Engl. J. Med. 300 (17):957-962, 1979.
84. Gee JP: Disopyramide. Drug Intel. Clin. Pharm. 12:660-663, 1978.
85. Anderson JL, Harrison DC, Meffin PJ, Winkle RA: Antiarrhythmic drugs: Clinical pharmacology and therapeutic uses. Drugs 15:271-309, 1978.
86. Zipes DP, Troup PJ: New antiarrhythmic agents. Aminodarone, Aprindine, Disopyramide, Ethmozin, Mexiletine, Tocainide, Verapamil. Am. J. Cardiol. 41:1005-1024, 1978.
87. Singh BN, Collett JT, Chew YC: New perspectives in the pharmacologic therapy of cardiac arrhythmias. Progress in Cardio. Disease 22:243-301, 1980.
88. Singh BH, Mandel WJ: Antiarrhythmic Drugs: Basic concepts of their actions, pharmacokinetic characteristics and clinical applications in Mandel WJ (ed) Cardiac Arrhythmias, Lippincott, Philadelphia and Toronto, 1980.
89. Rosen MR, Hoffman BF, Wit AL: Appraisal and reappraisal of cardiac therapy: Electrophysiology and pharmacology of cardiac arrhythmias. V. Cardiac anitarrhythmic effects of lidocaine. Am. Heart J. 89:526-536, 1975.

90. Lie KI, et al: Lidocaine in the prevention of primary ventricular fibrillation. New Engl. J. Med. 29:1324-1326, 1974.
91. Wit AL, Rosen MR, Hoffman BF: Appraisal and reappraisal of cardiac therapy: Electrophysiology and pharmacology of cardiac arrhythmias. VIII. Cardiac effects of diphenylhydantoin. A. Am. Heart J. 90:265-272, 1975.
92. Danilo P: Aprindine. Am. Heart J. 97:259-262, 1979 .
93. Zipes DP, Troup PJ: New antiarrhythmic agents. Am. J. Cardio. 41:1005, 1978.
94. Harrison DC (ed): Symposium on Tocainide, American Heart Journal, December 1980, Vol 100(6) part 2.
95. Harrison DC: Cardiac arrhythmias: A Decade of Progress, Chapters 14-20, GK Hall Medical Publishers, Boston, 1981.
96. Chew CYC, Collett J, Singh BN: Mexilitine: A review of its pharmacologic properties and therapeutic efficacy in arrhythmias. Drugs 17:161-181, 1979.
97. Leahy EB, Bigger JT: Mexilitine: A new antiarrhythmic drug. Annal. of Int. Med. 68:839-429, 1980.
98. Symposium on Mexilitine. Acta Cardiologica, Suppl 25, 1980.
99. Danilo P: Aprindine. Am. Heart J. 97:119-124, 1979 .
100. Zipes DP, Elharrar V, Gilmour RF Jr, Heger JJ, Prystowsky EN: Studies with aprindine. Ame. Heart J. 100:1055-1062, 1980.
101. Stoel I, Hagemeijer F: Aprindine: A review. Eur. Heart J. 1:147-156, 1980.
102. Anderson JL, Stewart JR, Perry BA, et al: Oral flecainide acetate for the treatment of ventricular arrhythmias. New Eng. J. Med. 305:473-477, 1981.
103. Hodges M, Haugland JM, Granrud G, et al: Suppression of ventricular ectopic depolarizations by flecainide acetate, a new antiarrhythmic agent. Circ. 65:879-885, 1982.
104. Roden DM, Reele SB, Higgins SB, et al: Total suppression of ventricular arrhythmias by encainide: pharmacokinetic and and electrocardiographic characteristics. N. Eng. J. Med. 302:877-882, 1980.
105. Mason JW, Peters FA: Antiarrhythmic efficacy of encainide in patients with refractory recurrent ventricular tachycardia. Cir. 63:670-675, 1981.
106. Keefe DL, Peters F, Winkle RA: Randomized double-blind placebo controlled crossover trial documenting oral lorcainide efficacy in suppression of symptomatic ventricular tachy-arrhythmias. Am. Heart J. 103:511-518, 1982.
107. Winkle RA, Mason JW, Griffin JC, Ross D: Malignant ventricular tachyarrhythmias associated with the use of encainide. Am. Heart J. 102:857-864, 1981.
108. Duff HJ, Roden DM, Dawson AK, et al: Comparison of the effects of placebo and encainide on programmed electrical stimulation and ventricular arrhythmia frequency. Am. J. Cardio. 50:305-312, 1982.
109. Swartz JB, Keefe D, Harrison DC: Adverse effects of antiarrhythmic drugs. Drugs 21:23-45, 1981.
110. Wit AL, Hoffman BF, Rosen MR: Electrophysiology and pharmacology of cardiac arrhythmias IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade. Part A. Am. Heart J. 90:521-533, 1975.

111. Wit AL, Hoffman BF, Rosen MR: Electrophysiology and pharmacology of cardiac arrhythmias. IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade. Part B. Am. Heart J. 90:665-675, 1975.
112. Wit AL, Hoffman BF, Rosen MR: Electrophysiology and pharmacology of cardiac arrhythmias IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade. Part C. Am. Heart J. 90:795-803, 1975.
113. Nixon JV, Pennington W, Ritter W, Shapiro W: Efficacy of propranolol in the control of exercise-induced or augmented ventricular ectopic activity. Cir. 57, No. 1, January 1978.
114. Heissenbuttel RH, Bigger JT: Bretylium tosylate: A newly available antiarrhythmic drug for ventricualr arrhythmias. Ann. Int. Med. 91:229, 1979.
115. Koch-Weser J: Bretylium. New Eng. J. Med. 300:473-477, 1979b.
116. Bacaner MB, Hoey MF, Macres MG: Suppression of ventricular fibrillation and positive inotropic action of bethanidine sulfate, a chemical analog of bretylium tosylate that is well absorbed orally. Am. J. Cardio. 49:45-55, 1982.
117. McGovern B, Garan H, Kelly JN, Ruskin JN: Life-threatening reactions during amiodarone therapy. Cir. 66 (Suppl II): II-224 (abstr) 1982.
118. Dreifus LS, Ogawa S: Quality of the ideal antiarrhythmic drug. Am. J. Cardio. 39:466-468, 1977. (editorial)