ANTIARRHYTHMIC DRUGS: ELECTROPHYSIOLOGICAL ACTIONS[1]

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ARTHUR L. BASSETT[2] AND BRIAN F. HOFFMAN

Department of Pharmacology, College of Physicians and Surgeons, Columbia University, New York City

The application of several new experimental methods to the study of the electrophysiology of the heart has resulted, over the past two decades, in a better understanding of the normal and abnormal processes that can influence cardiac rate and rhythm (1–4). These methods have been used by pharmacologists and others to evaluate or explain the possible or actual clinical usefulness of antiarrhythmic drugs. One approach has been to determine the effect of a particular drug on the transmembrane action potentials recorded from single isolated cells in preparations of cardiac tissue (2, 3). Such preparations allow the *direct* study of electrophysiological actions of a drug under conditions in which the tissue is removed from most neural and humoral influences. While such studies are extremely valuable, a major limitation of the microelectrode recording technique is that it may not give information on an important indirect action of a drug; for example, quinidine and procaine amide have a vagolytic action on sinus node cells and atrial fibers in the intact animal (5). A major technical advance for in vivo studies of drug action was the development of recording and stimulating electrodes for acute and chronic implantation in the hearts of laboratory animals (6). Their use permits a direct demonstration of normal excitation and conduction in the heart and how these properties and excitability may be altered by drug action (7, 8). There are other useful techniques which have been developed to record sequential activity of pacemaker and specialized cardiac cells (9). Another approach is to determine the effectiveness of a drug in suppressing various experimentally induced arrhythmias in laboratory animals by monitoring the electrocardiogram and records from acutely and chronically implanted electrodes (10). Analysis of data from experiments utilizing these various methods does not guarantee that one can predict with certainty whether or not a drug will be a useful clinical agent since, for example, toxicity is not determined from such procedures. How-

[1]This work supported in part by Program Project Grant (1-PO1-HE 12738), and

[2] Career Development Award (1-KO4-HE 42500) from the National Heart and Lung Institute.

ever, such experimental approaches are essential because they provide a logical framework for attempting to understand the electrophysiological basis for the mechanisms of action of antiarrhythmic drugs (10–12). This review is concerned with several of the newer antiarrhythmic drugs and particularly with data obtained from experiments using microelectrode recording techniques. Wherever possible we will compare the data on newer agents to that available for the traditional antiarrhythmic drugs. We have limited ourselves to describing a comparatively few of the many papers published in this area in recent years. The reader is referred to the comprehensive review by Szekeres & Papp (13) for a complete survey of antiarrhythmic drugs and to several recent reviews for clinical indications for their use and toxic manifestations (4, 10, 14, 15). Several papers and monographs provide a full description of the techniques mentioned above and a review of the changes in transmembrane potential that accompany excitation in heart (3) and the ionic basis for these changes (16, 17).

Electrophysiological Basis for Arrhythmias

Before considering specific drugs, it would be useful to set forth our concept of the basis for the genesis of cardiac arrhythmias as conceived from studies on single cardiac cells (18–20). It has been shown that excitation of the heart originates from specific pacemaker tissue and then spreads throughout the rest of the heart over particular pathways. Arrhythmias may arise from changes in the cyclic automaticity of pacemaker cells, from alterations in conduction of the propagated impulse throughout the heart, or from some simultaneous combination of changes in automaticity and conduction.

Automatic cells are found in the specialized cells of the heart, the sinoatrial node and the His-Purkinje system. Automaticity also is a property of some parts of the specialized atrial tracts and the atrioventricular (A-V) node. The normal mechanism for automaticity is due to slow depolarization during phase 4 (electricial diastole) which lowers (less negative) transmembrane potential to the threshold potential level (3). An arrhythmia may result from enhanced normal automaticity in any specialized cardiac fiber induced, for example, by digitalis (21, 22) or catecholamine release following myocardial infarction (23). Local hypoxia (24, 25) and stretch (26, 27) accompanying myocardial infarction may also increase normal automaticity in the His-Purkinje system. Changes in P_{CO_2} and pH can alter the rate of diastolic depolarization (28, 29). Passage of weak depolarizing currents across Purkinje fiber membranes increases the slope of diastolic depolarization (30); such currents might flow between normal fibers and cells damaged by local injury or ischemia. Arrhythmias may also result from a decrease in automaticity in the sinoatrial pacemaker which allows the escape of some other automatic cell or cells. Diastolic depolarization normally is limited to the specialized cardiac fibers and it is not seen in muscle fibers of the atria or ventricles except under most unusual conditions (31) including

barium intervention (32, 33). Working myocardial fibers usually do not play any significant role in the induction of arrhythmias which result from alterations in normal automaticity.

Among the abnormal mechanisms that might induce automaticity are delayed repolarization or persistent depolarization. Either condition might generate a new action potential through local current flow at the boundary between still depolarized and just repolarized fibers. Injury, ischemia, and local changes in gaseous and ionic environment are factors that may cause persistent depolarization (3, 34, 35). Afterpotentials, and other oscillatory changes in transmembrane potential which reach threshold voltage, are abnormal mechanisms that may induce automaticity and new action potentials. Oscillatory changes in transmembrane potential may be brought about by local alteration in extracellular concentration of potassium and calcium (36, 37), temperature changes on human atria (38), and the actions of several drugs such as catecholamines (1), digitalis (39), aconitine (40), veratrine (41), and MJ 1999 [4-(2-isopropylamino-1-hydroethyl) methanesulfonanilide HCl] (42, 43). Spontaneous ectopic impulse formation and subsequent arrhythmias that result from abnormal automaticity can occur in any region or type of cell found in the heart.

Disturbances in rhythm may result from alterations in the conduction of the impulse throughout the heart. For example, when a normal action potential enters an area which is partially depolarized by local injury or ischemia, it may propagate slowly, or may be blocked. Such block may be unidirectional. Under such conditions of depressed conduction, favorable anatomical arrangements and spatial differences in refractoriness may cause reentrant excitation (11, 19, 20).

Disturbances of rhythm in man often occur as a result of conduction impairment in the A-V node (44). Decremental conduction, the probable mechanism responsible for the slowing of impulse transmission through the A-V node (45), also occurs under special circumstances in other cardiac fibers. In the His-Purkinje system, decremental conduction can occur when the transmembrane potential is diminished just prior to the initiation of an action potential (46). This decrease in transmembrane potential may result from incomplete repolarization due to premature excitation (rapid rates) or partial depolarization (from injury or ischemia), or the slow diastolic depolarization which may be enhanced under abnormal conditions. The magnitude of the transmembrane potential at the time of excitation is an important determinant of action potential characteristics and conduction velocity (47). The maximum rate of rise of phase 0 of the action potential ($\dot{V}_{MAX}$), action potential amplitude, and conduction velocity are reduced if the transmembrane potential is diminished by any mechanism (47). Action potentials elicited at diminished membrane potentials are poor stimuli to unexcited cardiac tissue (48). Further, the magnitude of these changes in the action potential may increase as the impulse propagates through a partially depolarized area (i.e., conduction becomes decremental) and complete failure of con-

duction may result. Decremental conduction also may result from an action potential slowly propagating into an area and decreasing (making less negative) the threshold potential through the effect of a slow loss of membrane potential on availability of sodium carrier (49) (see below). The propagating action potential in turn gradually becomes a poorer stimulus to unexcited tissue since, for example, any given rate of depolarization must proceed longer to reach the lower threshold potential and initiate a new regenerative response. Since the regenerative depolarization occurs at a lower membrane potential, it has a lower $\dot{V}_{MAX}$ and reduced amplitude. Decremental conduction, like depressed conduction, may also result in unidirectional block and reentrant rhythm (20).

Application of Microelectrode Techniques to Study of Antiarrhythmic Drug Action

Until procaine amide was introduced into medicine by Mark et al (50) in 1951, no drug equally effective to quinidine had been found, although many varied compounds were studied in the laboratory and subjected to clinical test. Quinidine and procaine amide were noted to have essentially similar pharmacologic actions in laboratory animals and man. Both act as local anesthetics in sufficient concentration. When acting on the heart both drugs decreased automaticity (impulse formation) and excitability and both prolonged refractoriness and slowed conduction. Further, both quinidine and procaine amide had similar toxic actions on the cardiovascular system (5, 51). Several of the other drugs tested up to 1960 were found to have some clinical applicability (13).

The failure to develop more effective drugs for the restoration of normal cardiac rate and rhythm resulted in large part from three factors: first, the electrophysiological mechanisms responsible for many clinical arrhythmias were and still are unknown; second, the effects of quinidine-like drugs on the electrical activity of the heart were not understood because of inadequate methods of study, and third, new drugs were usually selected for clinical trial on the basis of their quinidine-like properties identified by laboratory screening studies which relied on an incomplete comprehension of the causes of arrhythmias in man.

Microelectrode recording techniques allowed the fuller understanding of the mechanisms responsible for the normal control of cardiac rate and rhythm by humoral factors such as acetylcholine and catecholamines (3, 52, 53), and by changes in the ionic and gaseous environment and temperature (3). Equally important, these studies demonstrated that a drug might cause a change in excitability, threshold to electrical stimulation, refractoriness, or conduction by acting on one or more of several variables including the magnitude of the resting and threshold potential and the rate of rise, amplitude, and duration of the action potential (11). Also, a drug might cause a change in the firing rate of an automatic cell by affecting one or more of

several variables: the rate of diastolic depolarization, the level of the threshold potential, or the magnitude of the resting potential (11). Microelectrode experiments showed that normally and potentially automatic cells, including those of the specialized conducting system, usually were more affected at any given drug concentration than ordinary working myocardial fibers (54). A further advance resulted from the first efforts to make direct studies on transmembrane potentials of human cardiac tissue (38, 55, 56). Thus, comparisons could be made of the electrophysiological properties of human cardiac cells and laboratory animal cardiac cells maintained under identical experimental conditions to determine whether extrapolation of findings from experiments on animal heart could be applied to the normal and diseased human heart. Additionally, comparisons could be made between the properties of normal and abnormal cardiac tissues to determine how these properties were altered by disease.

In short, research utilizing microelectrode techniques, which was begun in the 1950s and is still in progress, permits an evaluation of the action of drugs in terms of directly demonstrated changes in electrical activity that can cause specific disturbances of rhythm, rather than in terms of the presence or absence of a drug-induced change in an arrhythmia that is identified only by its electrocardiographic appearance.

Mechanisms of Action of Quinidine and Procaine Amide

The antiarrhythmic action of the quinidine-like agents, which characteristically have local anesthetic and autonomic blocking effects (13), has been explained in terms of laboratory studies demonstrating that these agents cause decreased excitability, prolonged refractoriness, and decreased conduction velocity. These three actions are assumed to be of value in the treatment of arrhythmias largely because of certain theories concerning the genesis of certain disturbances of rhythm (1). For example, if fibrillation or flutter were due to a "circus" movement, a prolongation of refractoriness which was sufficient in relation to a decrease in conduction velocity might terminate the arrhythmia. A decrease in excitability might be an effective antiarrhythmic action if the discharge of a pacemaker were analogous to an external electrical stimulus and if that discharge were only slightly suprathreshold. This explanation has been offered in spite of evidence that a drug-induced, selective prolongation of refractoriness or depression of conduction might increase the likelihood of arrhythmias (1).

Weidmann (49) introduced a new concept to the mechanisms of antiarrhythmic action. He applied microelectrode techniques to the study of the action of several drugs, including quinidine, on the electrical properties of isolated cardiac Purkinje fibers. He studied the relationship between "clamped" membrane potential and the inward current caused by depolarization and showed that the maximum inward (depolarizing) current was related by an S-shaped curve to the magnitude of membrane potential prior to

depolarization. Under control conditions, at membrane potentials greater than −90 mV, the peak inward current was maximal while at membrane potentials of less than −55 mV, inward current approached zero. At intermediate values of membrane potential, inward current was reduced, reaching values of half maximum at a membrane potential of −70 mV. These changes in inward current were assumed to occur because of an effect of membrane potential on the availability of a sodium carrier. At membrane potentials less than −90 mV availability of Na carrier was reduced and thus the peak inward Na current caused by depolarization was reduced. Similar changes in inward current are observed when action potentials are elicited from different levels of membrane potential; with a reduction in the magnitude of the membrane potential prior to excitation there is a decrease in V_{MAX} and, with sufficient reduction in membrane potential, a decrease in the magnitude of the action potential as well. The decrease in $\dot{V}_{MAX}$ and magnitude of the action potential cause a decrease in conduction velocity and in the safety factor for propagation (48).

The S-shaped relationship between $\dot{V}_{MAX}$ and the membrane potential at which the action potential is elicited has been called membrane responsiveness (57). This relationship explains absolute and effective refractoriness (20), changes in conduction velocity of premature responses, and effects of alterations in excitability on conduction when changes in excitability are caused by a change in threshold potential or a change in resting potential (20). There is a similar relationship for atrial and ventricular muscle fibers. However, cells of the sinoatrial and A-V nodes and adjacent tissues do not demonstrate such a relationship; in such cells the restoration of responsiveness may be time-dependent (58, 58a, 58b).

The relationship between membrane potential and responsiveness also shows how the behavior of cardiac fibers might be changed by drugs which act on the availability of sodium carrier. Weidmann showed that an increase in the concentration of extracellular calcium shifted the curve describing membrane responsiveness to lower values of membrane potential (59) so that there was more available sodium carrier at any given membrane potential below −90 mV. As a result, $\dot{V}_{MAX}$ and amplitude of an action potential elicited at membrane potentials lower than −90 mV was increased. These actions would cause a decrease in effective refractoriness (propagating action potentials could be elicited at lower membrane potential) and an increase in conduction velocity of premature responses (see above). In contrast, high concentrations of quinidine, cocaine, and procaine amide shifted the curve describing membrane responsiveness to higher values of membrane potential and also depressed the maximum inward current elicited at normal (−90 mV) or higher values of membrane potential. This suggested that less sodium carrier was available at all membrane potentials. It is interesting to note that the local anesthetics procaine, cocaine, and lidocaine have marked inhibitory effects on rapid inward sodium currents during excitation in nerve (60, 61).

In the experiments described above, Weidmann showed that quinidine and procaine amide could cause both an increase in effective refractoriness and a decrease in conduction velocity through direct "depressant" actions on membrane responsiveness (59). The decrease in membrane responsiveness induced by these drugs explains why the increase in the effective refractory period that they cause is greater than one would expect to result from the drug-induced lengthening of action potential (20). Weidmann's observations were confirmed by other investigators who found that quinidine and procaine amide reduced $\dot{V}_{MAX}$ and increased effective refractoriness in several isolated preparations of cardiac tissue (62–65) and in one study on in situ dog heart (66).

The relative importance of slowed conduction versus prolonged effective refractoriness as mechanisms of antiarrhythmic action of quinidine in man is still uncertain although a recent study on intact, unanesthetized dogs showed that quinidine slows intraventricular conduction prior to causing consistent changes in ventricular refractoriness (8). Further, it has been shown that effective antiarrhythmic concentrations of quinidine consistently and significantly increase QRS duration in man (67).

There are other possible mechanisms by which quinidine and procaine amide might suppress arrhythmias. It has been shown that quinidine and procaine amide could suppress automatic rhythms originating in the His-Purkinje system directly since they decreased the slope of diastolic depolarization in automatic fibers of isolated preparations (3, 59); moreover the suppression of diastolic depolarization can occur independently of substantial alterations in refractoriness, excitability, and conduction. Further, it has been shown that the depressant drugs quinidide and procaine amide may, under certain conditions, improve conduction by suppressing diastolic depolarization of all automatic fibers (68). As a result, membrane potential is more negative at the instant of excitation. When this action occurs at a concentration that does not appreciably reduce membrane responsiveness, then the net effect is to enhance the rate of rise and magnitude of propagated action potentials. In turn, such action potentials may propagate more successfully and conduction may be improved sufficiently to interrupt a reentrant rhythm. Alternately, if the local concentration of quinidine or procaine amide is sufficient to reduce membrane responsiveness (and if phase 4 depolarization is not contributing to impaired conduction), then conduction may be blocked completely in depressed fibers of a reentrant path. This action would also abolish a reentrant rhythm. Thus, depending on the past history and condition of the cardiac fibers involved in a disturbance of rate or rhythm, the same dose of quinidine or procaine amide might suppress an automatic rhythm by decreasing diastolic depolarization or abolish a reentrant rhythm either by actually improving conduction or, as usually thought, by depressing conduction in the reentrant path.

The demonstration that enhanced excitability and conduction may be caused by depressant agents like quinidine suggested that effective antiar-

rhythmic agents might be found among compounds which would have similar actions, i.e., agents whose primary effect was to improve responsiveness. Such an effect had been shown for increased extracellular calcium concentrations (59). Agents having such effects are diphenylhydantoin and lidocaine (see below).

The use of microelectrode recording techniques has provided an understanding of several possible beneficial effects of therapeutic concentrations of quinidine and procaine amide. Further, the decreased membrane responsiveness induced by quinidine and procaine amide explains in part the "depressant" actions of therapeutic and excessive concentrations of these drugs which are manifested primarily as impaired intraventricular conduction. While excessive concentrations of quinidine and procaine amide have similar but exaggerated action on effective refractory period and membrane responsiveness to that described for therapeutic concentrations, high concentrations also cause a decrease in resting potential (partial maintained depolarization), and may actually augment slow diastolic depolarization. These findings provided additional basis for understanding the usually severe disturbances in rhythm and conduction that can occur during administration of excessive doses of quinidine and procaine amide to man (5).

β-Receptor Blocking Agents

Relationships between β-blockade and antiarrhythmic action.—Experiments have indicated that catecholamines and the sympathetic nervous system can be involved in the genesis of arrhythmias (1, 10, 13). There is evidence that arrhythmias that follow myocardial infarction or that accompany hydrocarbon anesthesia depend, to some extent, on the availability of catecholamines to the heart (23, 69, 69a). For these reasons, it was thought that agents that specifically blocked β-receptors might be useful as antiarrhythmic drugs. After introduction of the first β-blocking agent, dichloroisoproterenol (70), it was shown that it could suppress or prevent the arrhythmias that usually follow catecholamine treatment of sensitized dogs (71) as well as arrhythmias due to coronary ligation followed by catecholamine administration or treatment with excessive amounts of cardiac glycosides (72, 73). Other β-blockers, pronethalol (74) and propranolol, were shown to be useful in several experimental and clinical arrhythmias including those produced by digitalis intoxication (13, 75). Although the primary actions of pronethalol and propranolol resulted in blockade of β-receptors, it was suggested that these drugs possessed antiarrhythmic activity which was, in large part, separate from their β-blocking abilities (13). Sekiya & Vaughan Williams (76) showed by recording transmembrane potentials from isolated atrial preparations that pronethalol had quinidine-like properties in that it decreased conduction velocity and excitability (raised electrical threshold) and prolonged refractoriness. Also, the d-isomer of pronethalol, which had $\frac{1}{40}$ the potency of the l-isomer in producing blockade of β-receptors, was equal to the l-isomer in abolishing digitalis-induced arrhythmias

(77). Similarly, it has been shown that the d- and l-isomers of propranolol have antiarrhythmic activity which is unrelated to their potency as β-blockers (78, 79). It is not surprising that the d-isomers of pronethalol and propranolol, which lack substantial beta blocking abilities, are relatively ineffective in preventing catecholamine-induced disturbances of rhythm (75). It is well known that catecholamine administration or activation of the sympathetic nerve supply to the heart increases both the rate of diastolic depolarization in pacemaker and latent pacemaker cells and the temporal dispersion of repolarization in myocardial cells and thus may change the pattern of recovery of excitability (1, 80). This catecholamine-mediated effect increases the likelihood and incidence of arrhythmias and fibrillation (1, 81–83). Thus it is possible that in certain clinical and experimentally induced arrhythmias that are intimately related to the action of catecholamines, the β-blocking actions of dichloroisoproterenol, pronethalol, and propranolol are important. For example, if the arrhythmia results from β-receptor mediated increases in automaticity in pacemaker or latent pacemaker cells then administration of propranolol or a similar β-blocker may prove to be useful. Arrhythmias arising after direct current cardioversion may result from catecholamine enhancement of automaticity and one recent laboratory study suggests that β-blocking agents may be useful in suppressing such post-counter shock arrhythmias (84). For the remainder of the arrhythmias for which these three agents are effective, their action may be due to their direct quinidine-like effects on the electrical activity of cardiac cell membranes. However, this question is far from settled and the introduction of MJ 1999 (Soltalol), a β-blocker (13, 75) apparently lacking local anesthetic effects, has refocused attention on it (see below).

Recent studies on β-blocking drugs.—Vaughan Williams showed that pronethalol and propranolol are local anesthetics with greater potency than procaine; further, it was demonstrated that both β-blockers have quinidine-like properties when acting on rabbit atria (85, 86), i.e., they decrease the maximum rate of rise of the action potential, decrease conduction velocity, raise electrical threshold and prolong refractoriness. Recently, Pitt & Cox (87) have shown that propranolol also decreases the spontaneous rate of isolated rabbit atrial preparations. Since the concentrations of propranolol that were used had significant β-blocking effects, it is impossible to determine whether the drug acted by β-blockade or quinidine-like actions in suppressing the rate of spontaneous impulse formation. In an effort to dissociate beta blocking effects more precisely from quinidine-like actions, Papp & Vaughan Williams (88) studied the effects of l-propranolol and another, β-blocker, I.C.I. 50172 [4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide] on intracellular potentials recorded from rabbit atria. They showed that the minimal concentration of l-propranolol necessary for quinidine-like actions was many times that necessary to cause almost complete blockade of β-receptors. In comparison I.C.I. 50172, which has less β-blocking ability than

propranolol on a molar basis, demonstrated quinidine-like activity only when used in concentrations 30 times greater than l-propranolol. However, I.C.I. 50172 was 40 percent as effective as l-propranolol in protecting against ouabain-induced ventricular fibrillation in guinea pigs. This study emphasizes the difficulty in comparing electrophysiological actions of drugs in one test system to their actions in another system which may be influenced by very different factors. Additionally, one must carefully consider whether the determination of local anesthetic properties of a drug using frog sciatic nerve has any quantitative relation to possible quinidine-like activity in cardiac muscle. Both types of information are useful and important but the differences in the test systems (for example, kinetics of sodium influx, drug binding receptor proteins, etc.) may prevent any rigorous comparisons. Dohadwalla et al (89) have recently shown that l, d, and d-l propranolol and I.C.I. 50172 reduce the $\dot{V}_{MAX}$ recorded from rabbit atrial cells when used in concentrations demonstrating no significant effect on electrical threshold, spontaneous rate, repolarization time, or conduction.

Hoffman & Singer (90) noted that low concentrations of pronethalol, without significant effects on resting or action potential characteristics, slowed the rate of diastolic depolarization in automatic Purkinje fibers. Similar to the effects of quinidine and procaine amide, pronethalol depressed membrane responsiveness; this effect preceded the appearance of any significant changes in resting and action potential. They also noted marked depression of excitability and conduction in the hearts of intact dogs which they related to the direct quinidine-like action of pronethalol. Similar findings of a depressant action of pronethalol have been reported for action potentials recorded from dog ventricular fibers by Shigenobu et al (91).

Davis & Temte (92) have thoroughly investigated the action of propranolol on Purkinje fibers and ventricular muscle. They demonstrated that a sufficient concentration of propranolol would decrease the $\dot{V}_{MAX}$ and overshoot of the Purkinje fiber action potential. Membrane responsiveness was also depressed. Propranolol decreased the effective refractory period and accelerated repolarization in Purkinje fibers; at moderate concentrations the changes in both were such that the effective refractory period was lengthened relative to the action potential duration. This increase in the ratio of effective refractory period to action potential duration has been noted for quinidine and procaine amide although in the latter case both lengthen during the drug-action. An interesting finding was the lack of local graded responses to stimulation during the effective refractory period in propranolol-treated preparations. The earliest responses that could be elicited during propranolol intervention were relatively large and had reasonably high rates of rise; no decremental conduction was noted. This finding may explain part of the antiarrhythmic effectiveness of propranolol. Treatment with low concentrations of propranolol, which had no effects on transmembrane potentials, blocked the usual increase in diastolic depolarization induced by epinephrine.

Davis & Temte suggest that this is a mechanism by which β-receptor blockers may suppress or prevent ventricular arrhythmias induced by catecholamines. However, the direct effects of propranolol on membrane responsiveness and conduction also may suppress certain arrhythmias. Mason et al (14) have recently suggested that, depending on the clinical circumstances in which the drug is used, either of the two actions of propranolol, antiadrenergic or direct "quinidine-like" effects, can be of importance. This, we feel, is an accurate estimation of the current understanding of the antiarrhythmic effects of propranolol.

Several recent studies have attempted to evaluate the relative importance of quinidine-like actions and β-blocking effects in the treatment of clinical arrhythmias (93).

Another recently introduced β-receptor antagonist is H 56/28 [1(O-allylphenoxy-3-isopropylamino-2-propanol-HCl)] (alprenolol). Singh & Vaughan Williams (94) have reported that alprenolol has some quinidine-like properties. It had no effect on resting transmembrane potentials of isolated rabbit atrial cells even at very high concentrations. The maximum rate of rise of atrial action potentials however was reduced by some 30 percent by 0.525×10^{-6}M alprenolol. They also showed that alprenolol protected ouabain-induced ventricular fibrillation in guinea-pigs. Other studies have shown that alprenolol in concentrations as high as 2×10^{-6}M has no significant effects on resting and action potential amplitude and configuration recorded from ventricular cells of cat papillary muscle although such concentrations of the drug had significant β-blocking effects (39).

Wit & Damato (95) have studied the actions of alprenolol in a number of isolated and intact preparations. They note that alprenolol, in doses that block the effects of exogenous norepinephrine, had little effect on sinus rate and A-V conduction in intact dogs. However, in reserpinized dogs the same concentrations of alprenolol increased sinus rate and decreased A-V conduction time; this suggested that the drug has intrinsic sympathomimetic action. An initial sympathomimetic effect following alprenolol administration has been noted by others (39). Wit & Damato also showed that concentrations of alprenolol greater than those needed for β-receptor blockade slowed conduction in the His-Purkinje system. In isolated canine Purkinje fibers alprenolol decreased action potential duration and effective refractory period. However, the changes were such that the effective refractory period lengthened with respect to the action potential. This finding is similar to that noted for propranolol and the quinidine-like drugs. Relatively high concentrations of the drug were necessary to depress action potential rate of rise and conduction in Purkinje fibers. Bassett & Hoffman (39) also noted that alprenolol had a quinidine-like effect on canine Purkinje fibers at concentrations higher than those essential for β-blockade.

Alprenolol resembles propranolol in several respects. Both drugs have potent β-blocking abilities and also demonstrate direct actions on cardiac cell membranes; they differ as there are sympathomimetic effects following

alprenolol administration which may be important clinically. Presumably alprenolol may suppress catecholamine-induced clinical and experimental arrhythmias by its β-blocking effects while its direct activity may be useful in suppressing atrial and ventricular ectopic activity. This assumption is supported by one recent laboratory study (96). Both the d-isomer (lacking significant β-blocking ability) and the l-isomer were effective in suppressing glycoside-induced ventricular automaticity in dogs and both forms of the drug also suppressed ventricular ectopic tachycardia following experimental coronary ligation. Further, Katz et al (97) have shown that administration of l-alprenolol prevented anesthetic dopamine-induced arrhythmias in cats while the d-isomer was ineffective.

The search for β-receptor antagonists with more "selective" properties led to the introduction of MJ 1999. This drug has strong β-blocking effects but apparently lacks significant local anesthetic properties. Strauss et al (43) have recently evaluated the actions of MJ 1999 on isolated cardiac tissue preparations and in intact dogs. A wide range of concentrations of MJ 1999 had no effect on resting and action potential amplitude and overshoot recorded from canine ventricular muscle and Purkinje fibers and rabbit atrial fibers. Similar concentrations had no significant effect on $\dot{V}_{MAX}$ of action potentials recorded from Purkinje fibers or rabbit atrium; membrane responsiveness was unaltered in Purkinje fibers. High concentrations of MJ 1999 increased action potential duration and effective refractory period in canine Purkinje fibers and ventricular muscle; the ratio of effective refractory period to action potential duration was shortened. The actions of MJ 1999 on repolarization and refractoriness and the lack of effect on $\dot{V}_{MAX}$ differ markedly from those noted during intervention with pronethalol or propranolol or the traditional quinidine-like agents. Further, MJ 1999 does not significantly alter the rate of diastolic depolarization in spontaneously beating Purkinje fibers but it does block their usual positive chronotropic response to catecholamine. However, idioventricular rate was decreased and ideoventricular escape time was increased in dogs with A-V block after treatment with MJ 1999.

There have been a number of laboratory studies of the effectiveness of MJ 1999 in suppressing experimental arrhythmias. As expected, the drug has great efficacy in the treatment of ventricular arrhythmias induced by hydrocarbon-epinephrine (98, 99) but there are conflicting reports concerning the ability of MJ 1999 to suppress ventricular arrhythmias resulting from infusion of ouabain (100, 100a). Since the drug was shown to have minimal effects on normal Purkinje fiber automaticity but marked blocking effects on catecholamine enhanced automaticity (43), it is possible that MJ 1999 may have been effective only in those experimental ventricular arrhythmias intimately related to catecholamine action.

It is interesting to note that the available β-blocking agents are usually quite effective against arrhythmias whose etiology involves catecholamines. The inability of MJ 1999, a purer β-blocker lacking local anesthetic and quinidine-like properties, to be uniformly effective against digitalis-induced

arrhythmias suggests that certain of the digitalis arrhythmias may arise independently and with little relation to the availability of catecholamines.

Diphenylhydantoin

Diphenylhydantoin (DPH) was used in some experimental cardiac arrhythmias, including those induced by hypothermia, aconitine, digitalis toxicity, and coronary artery ligation with good results before its clinical effectiveness was rigorously tested (101). It has been found useful in a number of clinical arrhythmias including disorders of rate and rhythm caused by digitalis excess, surgical intervention, and myocardial infarction (101, 102). As with quinidine, the clinical efficacy of DPH is closely related to blood concentration (103). In contrast, DPH has effects on cardiac electrophysiological properties which are quite different from those of quinidine.

Bigger et al (57) were the first to study the effects of the drug on the electrophysiological properties of isolated perfused Purkinje fibers. They noted that a wide range of DPH concentrations caused marked acceleration of the repolarization phases of the action potential and shortening of the effective refractory period. However, the changes in action potential duration and effective refractory period were such that, although the effective refractory period shortened, it was slightly longer relative to the time course of repolarization than under control conditions. As a result the earliest propagated action potential was elicited at a more negative (higher) membrane potential and therefore had a greater $\dot{V}_{MAX}$ and amplitude. Extrapolation of this result to treatment of an arrhythmia in man caused by a partial or complete block of conduction would suggest that during DPH administration, early premature action potentials would be more effective stimuli to unexcited tissue and would propagate into more fully repolarized fibers. Either of these conditions might be sufficient to reverse conduction block by increasing conduction velocity and thus increasing the minimum necessary length of a reentrant pathway. This study also showed that DPH suppressed spontaneous automaticity of normal and depressed canine Purkinje fiber preparations as well as ouabain enhanced automaticity. Thus, an arrhythmia arising from an increased rate of firing of some automatic cell, or from a conduction disturbance induced by slow diastolic depolarization might be abolished by the direct effect of DPH on automaticity. This investigation additionally demonstrated that while DPH had little effect on membrane responsiveness of normal fibers, it markedly improved $\dot{V}_{MAX}$ in fibers that were partially depolarized or depressed by cold, digitalis excess, or stretch. This aspect of DPH action was examined in greater detail in another study on the effects of DPH on Purkinje fibers exposed to low oxygen tensions (104). Hypoxia induced a decrease in $\dot{V}_{MAX}$ of the Purkinje fiber under control conditions; during DPH administration, the depression of $\dot{V}_{MAX}$ by hypoxia was significantly delayed. Further, DPH transiently increased $\dot{V}_{MAX}$ when it had been depressed by prior exposure to a low P_{O_2}. These results suggested a partial explanation for the efficacy of DPH in the treatment of ar-

rhythmias caused by experimental coronary artery ligation in dogs and the arrhythmias accompanying myocardial infarction in man. If local ischemic hypoxia is involved in initiation of arrhythmias, these arrhythmias would be less likely if action potential rate of rise were maintained at reasonably normal values through the action of DPH.

The studies described show that DPH differs markedly in several important respects from the traditional antiarrhythmic agents quinidine and procaine amide. DPH either increases or does not substantially alter the membrane responsiveness and conduction velocity while quinidine and procaine amide may severely depress these properties. Further, DPH, in sharp contrast to quinidine and procaine amide, causes a shortening of the effective refractory period and action potential. However, all three drugs alter the effective refractory period and action potential duration so as to make the effective refractory period longer relative to the time course of repolarization than under control conditions. Quinidine and procaine amide decrease excitability (more current is necessary for stimulation) while DPH usually increases excitability. All three drugs do share the property of decreasing the rate of slow diastolic depolarization in automatic fibers.

Two groups have studied the action of DPH in isolated atrial preparations. Strauss et al (58) noted that DPH increased membrane responsiveness of working atrial fibers and specialized Bachmann's bundle fibers under control conditions and especially after responsiveness had been decreased by ouabain. Except at high concentrations, DPH had no significant effect on effective refractory period, action potential duration, and automaticity of specialized atrial fibers. They suggested that the ability of DPH to improve membrane responsiveness and conduction may be the major mechanism for its effectiveness in certain atrial arrhythmias including those produced by digitalis excess.

Jensen & Katzung (105, 106) have examined in great detail the relationship of stimulation frequency and extracellular potassium and sodium concentrations to the action of DPH on preparations of isolated rabbit and dog atrial tissues. They did not study the effect of DPH on specialized atrial fibers but found that low concentrations of DPH increase action potential rate of rise in working myocardial fibers when extracellular potassium is 4.6–5.6 mM. At the same potassium levels, and especially at rapid rates, they found that higher concentration of DPH has a depressant action on the rate of rise of the action potential. If extracellular sodium is increased at this time, the DPH induced depression in action potential rate of rise can be reversed. Modification of drug activity by alterations in extracellular ion concentration has been shown previously for quinidine. Sodium lactate reversal of quinidine-induced depression of the action potential has been noted for rabbit atria (107) and modifications of depressant effects of quinidine on cardiac electrical activity by alteration in extracellular potassium concentration have been noted by several investigators. Brandfonbrenner et al (108)

report that hypokalemia protects against quinidine-induced prolongation of intraventricular conduction in dogs while Watanabe & Dreifus (109) note that lowering extracellular potassium moderates quinidine prolongation of A-V conduction in the isolated rabbit heart. Watanabe et al (110) have reported that low potassium reverses quinidine-induced depression of $\dot{V}_{MAX}$ and amplitude of ventricular action potentials recorded from isolated perfused rabbit hearts. They also observed that low potassium alone had no significant effect on $\dot{V}_{MAX}$ of ventricular cells and that the addition of quinidine to low potassium solutions also did not affect $\dot{V}_{MAX}$. Jensen & Katzung (105, 106) cite these previous papers and their own findings as evidence for their suggestion that DPH has quinidine-like properties. However, it must be clearly understood that until the reports of Bigger (57) and Strauss (58) on the effect of DPH there was no evidence that any clinically useful antiarrhythmic agent directly increased membrane responsiveness. These papers have been considered in detail because they reemphasize several inherent difficulties in laboratory experiments involving isolated preparations of cardiac tissues. For certain drugs, the antiarrhythmic blood levels may not be known and additionally, because of factors such as plasma protein binding, route and rate of drug administration, and rate of excretion or metabolic degradation, one often must make assumptions concerning the actual concentration of drug at its tissue site of antiarrhythmic action in man and then use the appropriate "therapeutic" concentration or a range of similar concentrations in the tissue bath. Further, the wide range of concentration of extracellular ions encountered in man and their marked effects on arrhythmias (111) often necessitates many manipulations of these ions in the tissue bath to describe completely the actions of an antiarrhythmic drug. For DPH, it would be of interest to know whether alterations of extracellular potassium would affect its actions on isolated Purkinje fibers and in man.

A number of studies have been concerned with the interactions of DPH and glycosides on the in situ dog heart. It is established that DPH decreases ventricular automaticity in dogs with experimental heart block and has significant effects in reversing the enhanced ventricular automaticity induced by digitalis (112, 113). These results are in accord with the demonstration that the drug suppresses slow diastolic depolarization in isolated Purkinje fibers. This property of the drug may explain its ability to increase the energy needed to produce some types of arrhythmias which occur after direct-current shock in digitalis-treated animals (114). DPH also antagonizes the toxic effect of digitalis on the A-V node by reversing glycoside-induced A-V block in contrast to the effects of procaine amide on depressed A-V conduction (115, 116). DPH is an unusual agent in that it increases A-V conduction during digitalis intoxication but decreases ventricular automaticity. These laboratory findings suggest that DPH administration may be hazardous in cases of complete A-V block caused by digitalis since ven-

tricular automaticity may be depressed before A-V conduction is restored. DPH is also an unusual drug in that it can suppress experimental digitalis-induced arrhythmias without altering the positive inotropic effect of the glycoside (117).

Several groups have examined in detail the effects of DPH on the electrophysiological characteristics of the normal in situ dog heart. Rosati et al (112) implanted electrodes over various parts of the specialized conducting system and studied the animals in the awake state several weeks following recovery from surgery. They found that DPH increased heart rate and shortened A-V conduction time but that after cardiac denervation, DPH decreased heart rate and prolonged A-V conduction time. These findings suggest that the drug may have some anticholinergic activity although Bigger et al (118) report that cholinergic and adrenergic blockade do not affect the action of DPH on A-V conduction. Helfant et al (113) also report that DPH accelerates A-V conduction in anesthetized dogs. However, Sasyniuk & Dresel (119) showed that DPH preferentially slowed conduction in the A-V node of isolated blood perfused dog heart. Part of the difference in effects of DPH on A-V conduction may result from the varied concentrations used, effect of diluent (see below), variable levels of extracellular ions, and variations in available catecholamines.

Rosati et al (112) evaluated the effects of DPH on excitability and refractoriness of the canine atria and ventricles by obtaining strength-interval curves. DPH consistently increased the threshold for excitation throughout the strength-interval curve but had small and insignificant effect on the effective refractory period of atrial and ventricular muscle. In contrast, Bigger et al report that in anesthetized dogs with chronically implanted electrodes DPH significantly shortens the effective refractory period of atrial and ventricular muscle and has no significant effect on atrial or ventricular diastolic threshold tested with either bipolar stimuli or stigmatic anodal or cathodal stimuli. Part of the discrepancy between the reports of the two groups may result from the commercial diluent used for dissolving DPH. Bigger et al (118) showed that the diluent increases diastolic threshold, the subsequent administration of DPH in diluent moderates this effect and DPH in alkaline saline directly decreased threshold current. Previously, in microelectrode experiments (57) it was shown that the commercial diluent decreases membrane responsiveness. Further, Louis et al (120) have shown that the diluent can cause bradycardia and changes in the electrocardiogram of cats and that DPH can attenuate these effects. One further difference between reports of the two groups is that Bigger et al (118) noted that DPH increased the test pulse amplitude necessary to induce fibrillation while Rosati et al (112) state that DPH did not significantly change ventricular fibrillation threshold. This difference may also result from the unique actions of DPH and diluent. The ability of DPH to elevate the fibrillation threshold probably stems, at least in part, from its ability to increase

conduction velocity in partially refractory heart muscle. Acceleration of conduction might lead to a decrease in temporal dispersion of recovery of excitability which would tend to act against the possibility of reentry and fragmented impulse formation. Quinidine and procaine amide also increase atrial and ventricular fibrillation thresholds. The fact that drugs with such widely different electrophysiological actions act similarly on fibrillation thresholds poses some interesting and, at this time, unanswered questions.

Bigger et al (118) also pointed out one of the difficulties in determining cardiac excitability by monitoring changes in requirements for stimulus strength and duration (1). They noted that administration of their test drug (DPH) markedly altered the impedance of the silver electrodes used in the study. Changes in electrode characteristics may occur during test procedures and they should be carefully monitored and considered with respect to any conclusions reached about the action of a drug on excitability.

In summary, the effects of therapeutic concentrations of DPH on the electrophysiological properties of the heart include the following: Studies on the in situ canine heart have shown that refractoriness is somewhat shortened and intraventricular conduction is usually unaffected. However, prior depression of intraventricular condition may be partially reversed by DPH. A-V conduction usually is improved in that P-R intervals shorten and the effective refractory period of the A-V junction is decreased. Studies on transmembrane potentials of isolated Purkinje fibers and specialized atrial fibers show that repolarization is accelerated. When the fibers are depressed, DPH increases $\dot{V}_{MAX}$ and membrane responsiveness is returned towards normal. Depressed conduction is improved and tolerance to hypoxia is increased. The effects of DPH on normal automaticity are relatively slight but the drug minimizes the increase in diastolic depolarization caused by catecholamines and digitalis.

These findings suggest the following: First, since the same clinical arrhythmias may respond to DPH and quinidine, the efficacy of quinidine may not necessarily depend on its traditional depressant effects. Second, the efficacy of DPH suggests that some arrhythmias can best be countered by agents that tend to restore electrophysiological properties towards normal.

LIDOCAINE

Lidocaine was introduced as a clinical antiarrhythmic agent 20 years ago and it has gained wide use in the treatment of clinical ventricular arrhythmias; however, many atrial arrhythmias do not respond to lidocaine (51). A possible explanation for the relative ineffectiveness of lidocaine in the treatment of clinical atrial arrhythmias, other than those caused by digitalis, has been offered by Mandel & Bigger (121). Although one report suggests that lidocaine does possess some quinidine-like actions on working atrial cells of the rabbit heart (85), Mandel showed that concentrations of lidocaine that had significant effects on Purkinje fibers (see below), did not alter

sinoatrial rate or atrial action potential configuration, and did not affect other electrophysiological characteristics of specialized fibers and working fibers of isolated rabbit atria. This was a direct demonstration of the relative insensitivity of atrial tissue to lidocaine.

Laboratory investigations include reports which indicate that lidocaine is useful against arrhythmias induced by cardiac glycosides and catecholamines, and coronary artery ligation (51). In therapeutic concentrations, lidocaine has little effect on interatrial and intraventricular conduction (51). Lidocaine thus demonstrates properties different from the quinidine-like drugs while it shares the common property (along with quinidine and procaine amide) of suppressing ventricular automaticity in dogs with A-V block.

Davis & Temte (122) reported that several concentrations of lidocaine (2–20 $\times$ 10^{-5}M) accelerated repolarization (especially phase 2) of canine Purkinje fibers but did not affect repolarization of ventricular muscle fibers. Action potential rate of rise of Purkinje fibers was unaffected except for a slight decrease at high concentrations (20 $\times$ 10^{-5}M) while rate of rise of action potentials recorded from ventricular muscle was unaffected at any concentration used. Davis & Temte reported that membrane responsiveness was unaffected by 2 $\times$ 10^{-5}M lidocaine but was depressed by higher concentrations of the drug (4–20 $\times$ 10^{-5}M). They noted in their measurements of membrane responsiveness that, during lidocaine action, the levels of membrane potential necessary for eliciting propagated premature action potentials in Purkinje fibers increased. Such premature responses had much greater rates of rise than those elicited under control conditions. The effective refractory period of Purkinje fibers shortened with 2 $\times$ 10^{-5}M lidocaine and lengthened with 20 $\times$ 10^{-5}M. More importantly, conduction from ventricular muscle to Purkinje fibers was improved with all concentrations of lidocaine. Under control conditions, when Purkinje fibers are excited by action potentials propagating from ventricular muscle, often there are local or graded responses at the Purkinje fiber papillary muscle junction (PPJ) (3); however, Davis & Temte noted lidocaine increased the amplitude and rate of rise of the rise of premature action potentials propagating from ventricular muscle to Purkinje fiber recorded at the PPJ. They also showed that lidocaine decreased the rate of diastolic depolarization in stimulated, spontaneous, and catecholamine-treated Purkinje fibers. These results will be considered in relation to the clinical efficacy of lidocaine after reviewing the data of Bigger & Mandel (123, 124). They state that 1 $\times$ 10^{-5}M lidocaine (a concentration they considered equivalent to therapeutic concentrations in man) had a number of significant effects on Purkinje fibers. This concentration reduced automaticity by a reduction in the slope of slow diastolic depolarization. It also maximally decreased action potential duration and effective refractory period without affecting maximal diastolic potential or action potential amplitude and overshoot. The changes in action potential duration and effective refractory period were such that the effective refractory period

became longer relative to action potential duration. Bigger & Mandel found, as had Davis & Temte, that this concentration of lidocaine increased (made more negative) the level of membrane potential required for stimuli to elicit a propagated response from Purkinje fibers. They also showed that 1×10^{-5}M lidocaine increased membrane responsiveness and additionally increased $\dot{V}_{MAX}$ of action potentials elicited at maximum diastolic potential. (Davis & Temte did not use concentrations lower than 2×10^{-5}M). Bigger & Mandel also found that conduction velocity in Purkinje fibers increased or was not changed significantly during perfusion with lidocaine at 1×10^{-5}M; however this concentration markedly improved conduction and decreased refractoriness at the ventricular muscle-Purkinje fiber junction.

Lidocaine is effective against many of the same experimental arrhythmias that respond to DPH, and its actions on isolated Purkinje fibers are also quite similar to those of DPH. In therapeutic concentrations both drugs may enhance membrane responsiveness. The importance of such action with respect to termination of arrhythmias has been discussed previously. Further, lidocaine increases the duration of effective refractory period relative to action potential duration; an effect also induced by DPH, quinidine, and procaine amide. However, it should be emphasized once more, that although all four drugs induce similar changes in the ratio of effective refractory period to action potential duration, because of the different effects on membrane responsiveness, premature action potentials elicited during DPH and lidocaine perfusion, will be larger in amplitude and have a higher $\dot{V}_{MAX}$ than those elicited during quinidine and procaine amide intervention. Thus DPH and lidocaine may abolish a reentrant rhythm by improving conduction, while quinidine and procaine amide may break such a rhythm by decreasing the rate of rise and amplitude and thus conduction of premature impulses. The demonstration that lidocaine shortens refractoriness and improves conduction of both normal and premature impulses at the ventricular muscle-Purkinje fiber junction suggests that it can reverse arrhythmias which arise due to block and reentry in this area. In contrast, Bigger & Mandel reported quinidine impairs conduction at the ventricular muscle-Purkinje fiber junction in their preparations. Lidocaine shares with procaine amide, quinidine, and DPH the property of suppressing automaticity in Purkinje fibers. Clinical and experimental ventricular arrhythmias caused by enhanced automaticity in the His-Purkinje system thus may be abolished by lidocaine.

High (toxic) concentrations (1×10^{-4}M) of lidocaine depressed membrane responsiveness and conduction velocity in Purkinje fibers while refractoriness at the ventricular muscle-Purkinje fiber junction was increased (122–124). Often these high concentrations of lidocaine caused a decrease in resting potential or maximum diastolic potential and action potential amplitude. Bizarre action potential complexes were noted and, ultimately, the drug effect caused inexcitability.

There are few reports indicating that lidocaine has a direct toxic effect on the electrical characteristics of myocardium after antiarrhythmic doses have been administered (51). This lack of toxicity is understandable since the microelectrode experiments have shown the drug actually may increase membrane responsiveness and improve conduction when administered in therapeutic concentrations. Thus lidocaine is similar to DPH in its rather benign affects on, for example, intraventricular conduction in man and quite different from quinidine and procaine amide which may cause conduction disturbances following administration of therapeutic doses. The differences in the effects of these drugs on conduction in man probably relate directly to their differing effects on membrane responsiveness.

Bretylium

A number of adrenergic neuron blocking drugs are reported to have some antiarrhythmic activity (13). Bretylium is such a drug and also demonstrates weak local anesthetic activity. Bretylium has attracted recent attention because of reports that it is apparently successful in treating a number of arrhythmias in man including those induced by myocardial infarction, digitalis intoxication, and open heart surgery (14). Leveque in 1965 (125) reported that bretylium was effective against atrial fibrillation induced in dogs rendered hypokalemic by pretreatment with insulin and glucose. Other laboratory studies report that bretylium increases the ventricular fibrillation threshold in the dog (126). It also has been said to be effective against several other experimental ventricular arrhythmias including those following hypothermia, acute coronary ligation, and digitalis excess in dogs (13, 127–129).

Four groups have used microelectrodes to examine the effects of bretylium on isolated cardiac tissues in efforts to determine whether the drug acts by local anesthetic (quinidine-like), anti-adrenergic or by some other mechanisms.

Papp & Vaughan Williams (130) studied the action of bretylium on single cells of isolated rabbit atria. At most concentrations of bretylium, there was an initial increase in conduction velocity, spontaneous rate, and maximum stimulation frequency, and a decrease in voltage necessary to stimulate. At very high concentrations the initial actions were followed by a reduction in conduction velocity, spontaneous and maximum stimulation frequency, and an increase in electrical threshold. They concluded the initial effects of bretylium were due to its sympathomimetic actions and the subsequent effects to the quinidine-like local anesthetic activity. The latter effects, which occurred at high concentrations, were not likely to be obtained clinically because of the concentrations used. Papp & Vaughan Williams also directly measured the local anesthetic activity of bretylium and confirmed earlier reports of its weak local anesthetic activity. Watanabe et al (131) report that bretylium increases resting and action potential amplitude and rate of rise of action potentials, shortens effective refractory period, and

improves conduction of premature responses in isolated rabbit ventricular strips.

Wit et al (132) and Bigger & Jaffe (133) have examined the action of bretylium on the electrophysiological properties of canine Purkinje fibers and ventricular muscle. Both groups found that, except for high concentrations, bretylium usually did not affect resting potential and action potential $\dot{V}_{MAX}$ and amplitude, membrane responsiveness, or conduction velocity. Both groups reported a transient hyperpolarization in partially depolarized Purkinje fibers. This effect was not observed in fibers from reserpinized dogs. Thus, this drug does not resemble either quinidine or DPH and lidocaine in several of its electrophysiological actions. Both groups also reported that bretylium produces an initial increase in the rate of spontaneously beating Purkinje fibers by increasing the slope of slow diastolic depolarization. Initial increases in spontaneous rate were blocked by β-receptor blockade and were not observed in preparations from dogs pretreated with reserpine. Bretylium prolonged action potential duration and effective refractory period of Purkinje fibers and ventricular muscle cells at several rates of stimulation but did not lengthen the effective refractory period relative to action potential duration. Both groups concluded that the actions of bretylium on isolated Purkinje fiber and ventricular tissue probably result from some effect on nerve terminal stores of catecholamines.

The increases in effective refractory period and action potential duration induced by bretylium are similar to those caused by quinidine and procaine amide in Purkinje fibers; however since membrane responsiveness is not depressed by bretylium the effective refractory period does not lengthen relative to action potential duration. Thus, bretylium does not resemble either the quinidine-like drugs or DPH and lidocaine in its effects on the relative magnitude of changes in effective refractory period and action potential duration. This fact, plus the failure of bretylium to decrease automaticity, suggests that its antiarrhythmic efficacy in laboratory studies is not due to any intrinsic direct electrophysiological effects. Several of the laboratory-induced arrhythmias previously treated successfully with bretylium arise, at least in part, from action of the sympathetic nervous system. Certainly, there are sympathetic factors involved in arrhythmias arising during hypothermia, hemorrhage, and digitalis excess. It has been shown that stimulation of cardiac sympathetic nerves, ouabain intoxication, hypothermia, and myocardial ischemia increase the temporal dispersion of recovery of excitability in the dog ventricle and this would tend to favor reentrant rhythm and fibrillation. More recently it has been shown that changes in the activity of sympathetic cardiac nerves can drastically change the pattern of repolarization in the dog ventricle (134). Bretylium may be useful in arrhythmias arising from "noncoordinated" cardiac sympathetic nerve activity through its ability to block adrenergic neurons. Han et al (80) have shown that stimulation of the cardiac sympathetic nerves decreases the fibrillation

threshold of the canine ventricle. Again, the fact that bretylium is an adrenergic neuron blocker may explain the reports from one laboratory on its effectiveness in increasing the ventricular fibrillation threshold in dogs. A final judgment as to the clinical efficacy of bretylium awaits further well controlled clinical trials. A possible drawback to its clinical usefulness may result from possible antiadrenergic effects or interference with catecholamine release. Data in two recent abstracts (135, 136) suggest bretylium may have an antiadrenergic action in intact dogs following its initial sympathomimetic effects. In any event, the reports of its clinical usefulness have lent some strength to the concept that various drugs exert their antiarrhythmic action through depression of neural function (137, 138).

Glucagon

The attention focused on the adenyl cyclase system as a possible mechanism by which catecholamines exert their actions on β-receptors has led investigators to examine the electrophysiological effects of other activators of this system. The pancreatic hormone glucagon is such an agent and it has been shown to have a "catecholamine-like" positive chronotropic effect. Glucagon has been used in several recent experimental studies. Whitsitt & Lucchesi (139) report that glucagon improves A-V conduction in dogs treated with dl-propranolol. In the reverse experiment, Steiner et al (140) have shown that glucagon improves A-V conduction in dogs and that this is not affected by propranolol. Glucagon had no significant affect on normal ventricular automaticity. Cohn et al (141) have recently demonstrated in intact dogs that glucagon is effective against ouabain-induced arrhythmias through its positive chronotropic action. However, in these ouabain-treated animals, glucagon had no consistent action on ventricular automaticity. In microelectrode studies, Greenspan et al (142) noted that glucagon shortened Purkinje fiber action potential while Stewart et al (143) stated that the drug has only slight effects on action potential characteristics in normal canine Purkinje fibers and working myocardial cells as $\dot{V}_{MAX}$ and membrane responsiveness were unchanged. Glucagon increased spontaneous rate in automatic fibers. Glucagon, similar to catecholamines (see below) had restorative effects in quinidine-intoxicated Purkinje fibers (143). The drug improved $\dot{V}_{MAX}$ and membrane responsiveness in quinidine-intoxicated preparations and decreased action potential duration and effective refractory period when these had been modified by quinidine. These restorative effects of glucagon are interesting since glucagon shares with the catecholamines the property of activation of the adenyl cyclase system while the experiments on intact animals suggest that glucagon probably does not work through interaction with β-receptors. The antiarrhythmic importance of glucagon remains to be determined but the drug may prove to be useful in reversing propranolol-induced depression of A-V conduction and toxic effects of quinidine on conduction.

Catecholamines

Catecholamines may, under certain conditions, be used as antiarrhythmic drugs. They can be effective in suppressing some forms of ventricular tachycardia and in reversing the depressed conduction following excessive administration of procaine amide or quinidine. A possible explanation for such actions has been offered by Hoffman & Singer (48, 90). They noted that catecholamines increased resting potential and the maximum diastolic potential in automatic cells when these properties had been decreased by stretch, hypoxia, and toxic concentrations of ouabain and procaine amide. The restoration of membrane potential toward normal values reversed the abnormalities of the action potential, excitability, and conduction caused by a low membrane potential while membrane responsiveness was unaffected. Normalization of conduction might abolish a reentrant rhythm which was due to local areas of unidirectional block in partially depolarized cells of the His-Purkinje system. Restoration of normal membrane potential would also improve conduction in Purkinje fibers partially depolarized by excessive therapy with procaine amide or quinidine.

Conclusion

We have discussed a number of drugs including those most widely used in the treatment of clinical arrhythmias (4, 10, 14, 144). In addition, we reviewed the actions of several agents of particular interest to us. Many other chemically different drugs which have not been studied in any great detail with microelectrode recording techniques are being tested in the clinic and in the laboratory for antiarrhythmic activity (13). From microelectrode studies, a substantial amount of data has been accumulated with respect to the effects of quinidine, procaine amide, propranolol, DPH, and lidocaine on the electrophysiological properties of single cardiac cells. Hoffman & Bigger (4) have recently summarized several of the electrophysiological actions of these five agents. From studies on isolated Purkinje fibers, it is known that quinidine, procaine amide, and propranolol decrease membrane responsiveness while in contrast diphenylhydantoin and lidocaine may increase responsiveness. On this basis, antiarrhythmic drugs may be separated into two groups (Table I). Quinidine, procaine amide, and propranolol represent Group I while diphenylhydantoin and lidocaine constitute Group II. Quinidine and procaine amide increase both action potential duration and effective refractory period while diphenylhydantoin and lidocaine decrease both of these properties. Propranolol differs from the other two Group I drugs in that it causes a decrease in action potential duration and effective refractory period similar to that of the Group II drugs. However, all five drugs share the property of increasing the duration of the effective refractory period relative to that of action potential duration. All five drugs also decrease automaticity (slow the rate of diastolic depolarization) in Purkinje fibers. At present, it is impossible to state which of these charac-

teristics act to suppress many ventricular arrhythmias. This information may be gained from a *systematic* application of these five drugs to the treatment of clinical arrhythmias.

TABLE 1. CHARACTERISTIC ELECTROPHYSIOLOGIC ACTIONS

Electrophysiological Properties Purkinje Fibers	Group I		Group II
	Procaine Amide Quinidine	Propranolol	Diphenyl-hydantoin Lidocaine
Automaticity	↓	↓	↓
Membrane Responsiveness	↓	↓	→ or ↑
Conduction Velocity	↓	↓	→ or ↑
Effective Refractory Period (ERP)	↑	↓	↓
Action Potential Duration (APD)	↑	↓	↓
ΔERP Relative to APD	↑	↑	↑
Excitability	↓	↓	→

↑ Increased, ↓ Decreased, → No change. Arrows indicate *direction* and *not magnitude* of change.

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