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REVIEW ARTICLE

Arrhythmias and Antiarrhythmic Drugs: Mechanism of Action and Structure–Activity Relationships I ▲

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Keyphrases □ Antiarrhythmic drugs—classifications, mechanism of action, structure–activity relationships, review □ Structure–activity relationships—antiarrhythmic drugs, review □ Arrhythmias—related to changes in normal transmembrane action potential and electrophysiological parameters, antiarrhythmic drugs, review

CONTENTS

The drug therapy of disturbances in cardiac rhythm had its beginning in 1914 when Wenckebach (1) reported that the cardiac arrhythmia of a patient with malaria, being treated with cinchona alkaloids (which contain mainly quinine), was converted to normal sinus rhythm. In 1918, Frey (2) studied cinchonine, quinine, and quinidine (I) and found that all three had similar properties in converting atrial fibrillation to normal rhythm but that quinidine was the most potent. Since this initial use, quinidine has remained one of the most important and efficacious drugs for maintaining normal heart rhythm (3).

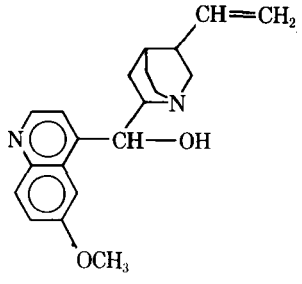
DEVELOPMENT OF CURRENTLY USED AND EXPERIMENTAL ANTIARRHYTHMIC DRUGS

In 1951, Mark *et al.* (4) found that procainamide (II) was effective as an antiarrhythmic agent; it has been widely used since then in treating arrhythmias. Southworth *et al.* (5) reported in 1950 that the local anesthetic lidocaine[1] (III) was successful in terminating ventricular tachycardia, and this drug has become important in the early treatment of ventricular arrhythmias associated with acute myocardial infarction due to its relatively safe intravenous route of administration.

Phenytoin[2] (IV), an anticonvulsant drug in use since 1938, was reported in 1958 to be effective in ventricular arrhythmias in humans (6). Since then, phenytoin has been used quite widely, particularly against ventricular arrhythmias caused by digitalis toxicity (3). Another drug discovered to have antiar-

▲ *Editor's note:* Part II of this article will appear in the May 1976 issue of the *Journal of Pharmaceutical Sciences.*

[1] Xylocaine or lignocaine.
[2] Dilantin.



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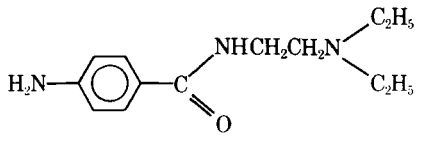

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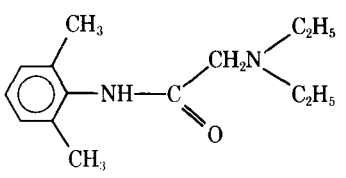

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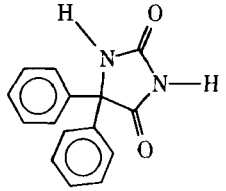

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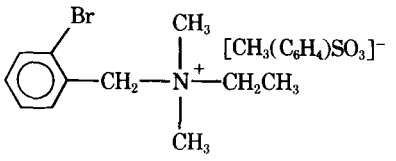

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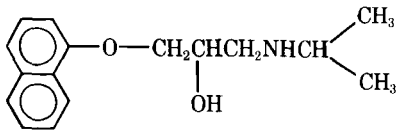


VI

rhythmic properties (7) is bretylium tosylate (V). Subsequent studies on bretylium showed that it is effective in the treatment of disturbances of ventricular rhythm that were not successfully abolished by conventional drugs; on this basis, it has achieved limited clinical use (3).

Propranolol (VI) also has gained widespread clinical use as an antiarrhythmic agent. This drug, developed in 1964, is a potent β-adrenergic blocking agent (8). However, subsequent studies indicated that propranolol had, in addition to β-blocking properties, a quinidine-like action on the heart (9, 10). Which of these factors represents the more important antiarrhythmic property is still a matter of controversy (11, 12), although it is generally accepted that β-blockade is the primary therapeutic effect at normal blood levels (13).

Several other drugs not normally classified as antiarrhythmic agents have been used in the therapy of certain cardiac rhythm disturbances, *e.g.*, digitalis (14). Many compounds in the early stages of pharmacological and clinical evaluation have proved to be effective in the treatment of experimentally induced arrhythmias in animals (15–25).

Disopyramide[3] (VII) is currently being used successfully in Europe and appears to manifest its antiarrhythmic properties in much the same way as quinidine while having a wider margin of safety (26, 27).

Verapamil (VIII), a derivative of papaverine, has been in clinical use in Europe since 1966. It is reported to be most successful against atrial fibrillation and flutters and paroxysmal supraventricular and preexcitatory tachycardia but less successful against ventricular arrhythmias. This drug has evoked considerable interest recently due to its novel mechanism of action (28–30).

Mexiletine[4] (IX) has successfully passed several clinical trials and has demonstrated efficacy against ventricular arrhythmias equal to, or greater than, currently available drugs (31, 32). In addition, mexiletine is reported to be effective when taken orally and to possess a long half-life in the body at effective levels without the toxic side effects seen with the most commonly used long-term oral antiarrhythmic drugs. A preliminary report of a pharmacokinetic study claimed that plasma mexiletine levels are linearly related to salivary concentrations (33). Use of this relationship is proposed as a rapid and convenient analytical method for determining blood drug levels during antiarrhythmic therapy.

A new drug, 2-amino-2′,6′-propionoxyxylidide hydrochloride (X), possessing a structure similar to lidocaine and mexiletine, has proved successful in treating experimental ventricular arrhythmias in animals (34). It is orally absorbed, has a rapid onset of action and long duration, and is currently being studied in humans.

Amiodarone[5] (XI), initially used in the treatment of angina pectoris (35), has been reported to be an effective antiarrhythmic agent after prolonged oral administration in both animals and humans (36). This drug possesses an unusual mechanism of action, mimicking the lengthening of the duration of the cardiac action potential seen in hypothyroidism, although no evidence of this condition has been reported in patients receiving the drug (37).

Aprindine (XII) is reported to be an orally effective, long-acting drug, efficacious in preventing ventricular arrhythmias associated with acute myocardial infarction (38, 39). One clinical study suggested that one dose per day is sufficient for maintenance therapy (40).

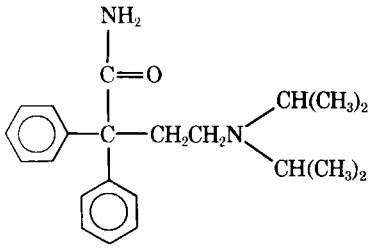
Another drug that has shown promising antiarrhythmic properties in animal tests is a decahydroquinoline derivative, 4-carbamoyloxy-1-[4-(4-fluorophenyl)-4-oxybutyl]decahydroquinoline[6] (XIII). It is reported to be orally effective and long acting, possessing similar actions on the heart as quinidine (41).

Propafenone[7] (XIV) underwent clinical trials in Germany and is effective in humans. Its effectiveness may result from both its β-adrenergic blocking properties and its local anesthetic, quinidine-like actions (42).

Diphenidol (XV) is reported to be efficacious in

[3] Norpace.

[4] Kö 1173.
[5] Cardarone.
[6] L 7810.
[7] 5A-79.



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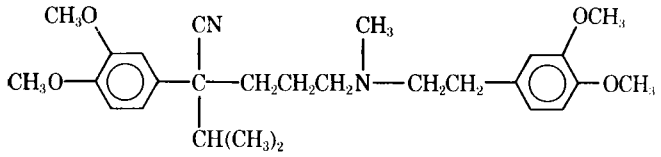

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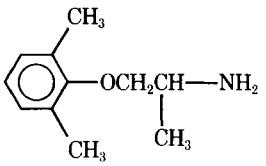

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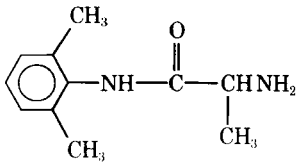

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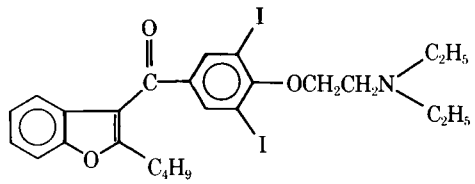

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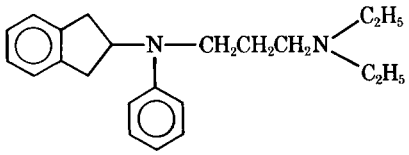

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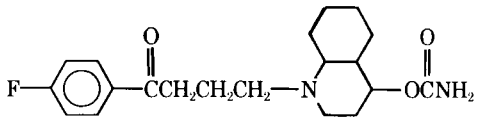

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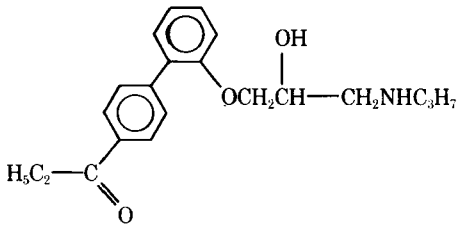

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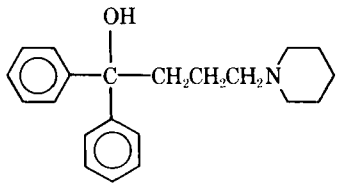

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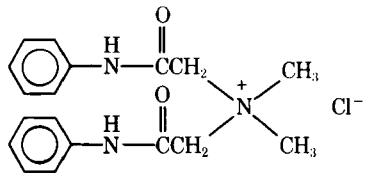

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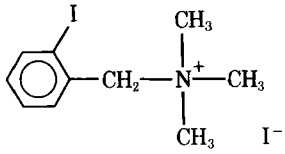
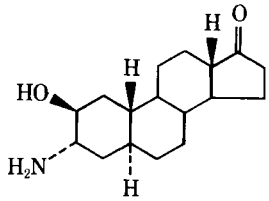


XVII



XVIII

both digitalis-induced arrhythmias in dogs and in digitalis intoxication in humans. Its usefulness as a clinical drug has been proposed (43).

N,N-Bis(phenylcarbamoylmethyl)dimethylammonium chloride[8] (XVI), a quaternary ammonium derivative of lidocaine synthesized several years ago (44), has recently received renewed interest as a supplement to lidocaine in intravenous treatment of arrhythmias in the coronary care unit (45). The compound is reported to be successful in the treatment of most types of ventricular arrhythmias and is suggested especially for arrhythmias that have proved refractory to other antiarrhythmic drugs (46). Compound XVI has a rapid onset of action and long duration. Moreover, due to the presence in the molecule of a permanently charged cation, it fails to pass through the blood–brain barrier and thus elicits much fewer central nervous system (CNS) side effects than does lidocaine (47).

o-Iodobenzyltrimethylammonium chloride[9] (XVII), an analog of bretylium, has demonstrated effectiveness in raising the ventricular fibrillation threshold to electroshock, preventing ventricular fibrillation in dogs suffering from experimentally induced myocardial infarction, and, in contrast to bretylium, reversing ouabain-induced arrhythmias. Compound XVII lacks the initial and potentially dangerous sympathomimetic effects of bretylium (48). The ^{131}I-labeled analog of XVII is highly localized in cardiac tissue and has been proposed as a heart scanning agent for use in radiology (49, 50).

A steroid, 3α-amino-5α-androstan-2β-ol-17-one[10] (XVIII), possesses potent antiarrhythmic activity (51, 52). Compound XVIII proved effective in antagonizing aconitine-induced arrhythmias in rats, being seven times more potent and five times less toxic than lidocaine by the intravenous route. The

[8] QX-572.

[9] UM-360.

[10] ORG-6001.

Table I—Etiological Factors that May Give Rise to Cardiac Arrhythmias[a]

Local cardiac factors
1. Hypertensive heart disease
2. Rheumatic, diphtheric, and viral types of heart disease
3. Degenerative states, especially coronary artery disease
4. Congenital abnormalities
5. Congestive heart failure

Cardiac factors resulting from disturbances in other organs
1. CNS (mediated by sympathetic and vagal stimulation)
2. Pulmonary disease (emphysema)
3. Endocrine (hypo- and hyperthyroidism, hypo- and hyperaldosteronism, diabetic acidosis, and hypoglycemia)
4. GI (fluid and electrolyte loss by vomiting and diarrhea)
5. Renal disturbances (renal insufficiency and alterations in fluid balance)

General factors
1. Infections and toxic states
2. Anemia and avitaminosis
3. Electrolyte disturbances
4. Drugs (digitalis, quinidine, and procainamide toxicity and toxicity from some general anesthetics used in surgery)

[a] Adapted, with permission, from Samuel Bellet, "Clinical Disorders of the Heart Beat," 3rd ed., Lea & Febiger, Philadelphia, Pa., 1971, p. 119.

compound was effective orally at a lower dose than lidocaine given intravenously and was similar to lidocaine in its potency in restoring ouabain-induced ventricular tachycardia and in correcting postmyocardial infarction arrhythmias in dogs. Protective doses of XVIII were effective 18 and 24 hr after intravenous and oral administrations, respectively. The compound lacks both local anesthetic activity *in vivo* and β-adrenergic blocking properties.

The appearance of several orally effective, long-acting, and less toxic antiarrhythmic agents should be encouraging to the clinician. Many new experimental drugs have been shown in clinical trials to be equally or more efficacious than the currently available choices while exhibiting an encouraging lack of toxic side effects. There has been a great and well-documented need for drugs possessing these properties for prophylactic treatment or prolonged maintenance of high-risk heart patients receiving antiarrhythmic therapy (13, 53, 54).

When considering the treatment of cardiac arrhythmias, choice of the most suitable agent must be based on a thorough knowledge of the basic pathological mechanism causing the disturbance (55, 56). Indeed, an arrhythmia is usually secondary to some primary pathological condition. Bellet (3) divided the factors into three groups: (*a*) local cardiac factors, (*b*) cardiac factors resulting from disturbances in other organs, and (*c*) general factors such as drug toxicity (Table I).

GENESIS OF ARRHYTHMIAS

Electrophysiology of Heart—The complexity of the genesis of arrhythmias becomes simplified somewhat when one considers the problem on a cellular level. This approach became possible in 1950 when the first transmembrane action potential of a single cardiac cell was recorded (57, 58), using a microelectrode developed previously (59). Subsequent studies during the last 20 years have led to a greater understanding of the cellular mechanisms by which arrhythmias are generated. The advances made since these beginnings were compiled and discussed in several excellent books and reviews (60–71), so only a brief introduction will be presented here. With this introduction, the reader will be able to understand better the following discussion on the effect of antiarrhythmic drugs on the transmembrane action potential.

Four inherent properties of cardiac muscle permit its performance as a pump. These properties are automaticity, conductivity, excitability, and contractility. Automaticity enables the heart to generate its own electrical stimulus spontaneously. This stimulus is normally generated in the specialized pacemaker or automatic cells in the sino-atrial node (S-A node). From this focal point, the stimulus is conducted to surrounding cells and other parts of the atria and ventricle by specialized conducting fibers.

Excitation of a cardiac cell may occur spontaneously (self-excitation) as in the automatic cells already described, or it may be the result of an external stimulus, *i.e.*, an artificial pacemaker. The pacemaker provides the spontaneous stimulus which is propagated throughout the heart in the form of an action potential. When the excitatory impulse encounters contractile cardiac cells, the myofibrils of these cells contract and provide the force by which the heart pumps the blood.

The transmembrane potential (difference) observed in all cardiac cells is about −90 mv in quiescent ventricular muscle fibers and Purkinje fibers and from −70 to −80 mv in atrial fibers; the cell interior is negative with respect to the exterior. This potential difference in muscle cells remains constant until excitation occurs; then the stimulus, in the form of a depolarizing current, reduces the potential difference across the membrane. If this potential is reduced from the resting potential (R.P.) of about −90 mv to a critical value (from −65 to −70 mv), called the threshold potential (T.P.), an action potential is produced.

The recorded action potential from canine ventricular muscle is illustrated in Fig. 1D. The curve representing the action potential is divided into five phases (0 through 4). Phase 0 is the rapid depolarization that occurs upon excitation. The difference in membrane potential decreases; during what is termed the overshoot, the inside of the cell actually becomes positive with relation to the outside.

Following depolarization, the cell begins the process of repolarization back to the resting potential (−90 mv). Repolarization in cardiac cells is a slow process, about 500 times longer than nerve cell repolarization. The first phase of repolarization (phase 1) is quite rapid and is then followed by a period of slow repolarization (phase 2 or the plateau). Repolarization speeds up again in phase 3 and completes the process by returning the transmembrane potential back to resting potential. Phase 4 is characterized by an interval of electrical quiescence in nonautomatic

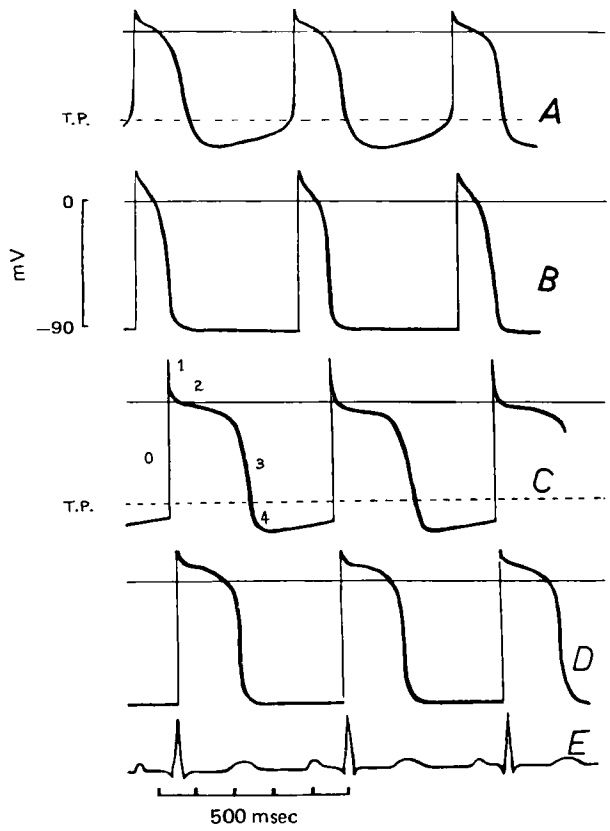


Figure 1—*Transmembrane action potentials recorded from cells of: (A) S-A node, (B) atrial muscle, (C) Purkinje system, and (D) ventricular muscle; on the same time axis is the ECG (E). The five recognized phases of the transmembrane action potential are numbered in the first complex of row C. Note diastolic depolarization and level of threshold potential (T.P.) in rows A and C. The difference in duration and configuration of action potentials from different cell types and the delay in A-V conduction are indicated by the delay in upstroke between B and C. [Reprinted, with permission, from W. Trautwein,* Pharmacol. Rev., *15, 279(1963) (Williams & Wilkins, Baltimore, Md.).]*

cardiac cells, such as ventricular or atrial muscle cells (Fig. 1B).

The action potentials for automatic heart cells are illustrated in Fig. 1. Figure 1A is a typical transmembrane action potential recorded from cells of the S-A node. The maximum diastolic potential reached in S-A nodal cells (−70 mv) is less than in the other types of heart cells. Also, the automatic cells exhibit spontaneous diastolic depolarization observed in the transmembrane action potential as the gradual rise in slope of phase 4. When the gradual decrease in potential difference reaches the threshold potential (about −50 mv in S-A nodal cells), rapid depolarization (phase 0) occurs. By this mechanism, the heart generates its own impulse, giving rise to the property of automaticity.

The automatic cells of the S-A node usually are the true pacemaker of the heart, since they fire at a faster rate than the other automatic cells. Automatic cells also are found in specialized atrial conduction fibers among certain cells in the atrio-ventricular node (A-V node) and in the His–Purkinje fibers. If, for any reason, the firing rate of the S-A nodal cells decreases, then other automatic cells, sometimes called latent pacemaker cells, can take over. However,

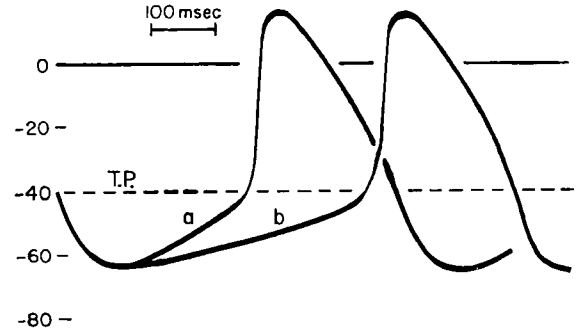


Figure 2—*Illustration of how changes in the slope of phase 4 or the rate of slow diastolic depolarization could be responsible for changes in the firing frequency of cardiac pacemaker cells. (Reprinted, with permission, from B. F. Hoffman and P. F. Cranefield, "Electrophysiology of the Heart," McGraw-Hill, New York, N.Y., 1960, p. 109.)*

under normal conditions, most automatic cardiac cells are excited by a propagated or conducted action potential (wave of depolarizing current) from the pacemaker before the slope of phase 4 reaches threshold potential.

The rate of firing of automatic cells may be altered as a result of a change in the slope of phase 4, a change in the magnitude of the threshold potential, and a change in the magnitude of the maximum diastolic potential (the potential at the conclusion of repolarization) (62). The effect of a change in the slope of phase 4 is illustrated in Fig. 2. The steeper slope (*a*) reaches threshold potential more rapidly than (*b*), resulting in a faster heart rate. On the other hand, a slower heart rate is observed when the slope of phase 4 is decreased.

The body exerts nervous control over the heart by way of the adrenergic (sympathetic) system, which on stimulation results in heart rate increases, and by the cholinergic (parasympathetic) system *via* the vagus nerve, which on stimulation results in a decrease in heart rate. The adrenergic mediators (endogenous and/or exogenous catecholamines) increase the slope of phase 4; the vagal mediator, acetylcholine, decreases the slope of phase 4. Both cause hyperpolarization (increased maximum diastolic potential). Therefore, the knowledge gained from the ability to record transmembrane action potentials has produced greater understanding of the mechanism of adrenergic and vagal control of the heart rate on the cellular level.

The effect of changes in the magnitude of the threshold potential on the rate of pacemaker firing is shown in Fig. 3. In the action potential (*a*), the threshold potential is about −50 mv (T.P.-1); in the action potential (*b*), the threshold potential has been raised to −40 mv (T.P.-2). It can be seen that (*b*) would fire at a slower rate than (*a*). Also, the maximum diastolic potential in the action potential (*c*) has been increased from about −60 mv (*d*) to −70 mv (*e*), resulting in a slowing of the heart rate.

The parameters of the transmembrane action potential that are important in a discussion of the mechanism of action of antiarrhythmic drugs are:

1. Action potential amplitude—the total potential change occurring during phase 0.

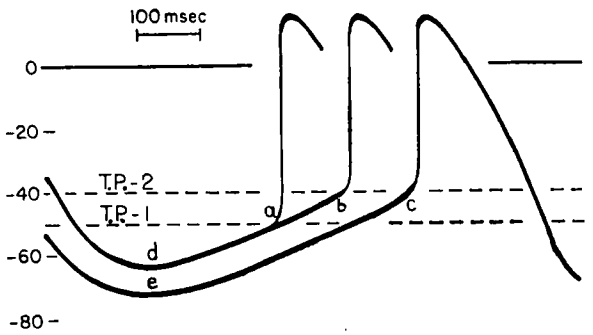


Figure 3—*Illustration of the effect of changes in threshold potential and maximum diastolic potential upon the heart rate. (Reprinted, with permission, from B. F. Hoffman and P. F. Cranefield, "Electrophysiology of the Heart," McGraw-Hill, New York, N.Y., 1960, p. 109.)*

2. Action potential duration—the time period from the start of phase 0 to the end of phase 3. Also, the time required for 50%, 90%, *etc.*, repolarization is sometimes reported as well as the time required to repolarize to some designated voltage.

3. Conduction velocity—the speed at which a stimulus or action potential is propagated.

4. Automaticity—determined by the slope of phase 4 (discussed previously).

5. Maximum upstroke velocity (v/sec)—the steepest slope of the rise of phase 0. This parameter is sometimes reported as average rising velocity.

6. Excitability—dependent upon the level of the threshold potential. For example, if the threshold potential is displaced toward zero potential and the difference between threshold potential and maximum diastolic potential is increased, a greater stimulus is required to effect depolarization.

7. Effective refractory period—period of repolarization during which no normal action potential can be elicited, although a weak, nonpropagated action potential can arise.

8. Absolute refractory period—period of action potential immediately following the start of repolarization during which no response to stimulus is possible. The cell is inexcitable during this period, which usually ends at approximately 50% repolarization.

9. Total refractory period—the resultant of the absolute and effective refractory periods.

10. Membrane responsiveness—the relationship of the maximum upstroke velocity to the level of membrane potential at which the action potential is initiated.

Theory of Arrhythmia Genesis—*Disturbances in Impulse Formation and Conduction*—Several excellent books and reviews are available on the genesis of arrhythmias with relation to changes in electrophysiological and transmembrane properties of the heart (3, 15, 64–69, 71–77).

The currently accepted theory on the mechanisms involved in the genesis of cardiac arrhythmias is that they may result from abnormal impulse formation, abnormal impulse conduction, or a combination of these factors (78). Bigger (79) outlined several factors that may be associated with genesis of arrhythmias (Table II). The disturbances in impulse formation and conduction, and theories as to the origin of the disturbances that cause arrhythmias, have been discussed in detail (64, 66, 68, 73, 74, 76, 77, 79–81).

Table II—Factors Associated with Cardiac Arrhythmias[a]

Disturbances of impulse formation (automaticity)
A. Alterations in normal automaticity
  1. Mechanism
    a. Changes in slope of phase 4 depolarization (ions, autonomic mediators, perfusion, and drugs)
    b. Changes in transmembrane voltage threshold (ions and drugs)
    c. Changes in maximal diastolic transmembrane voltage
    d. Currents flowing from adjacent cells
  2. Site-specialized tissues
    a. S-A node
    b. Atrial specialized fiber tracts
    c. Distal A-V node, bundle of His, bundle branches, and terminal Purkinje fibers
B. Abnormal automatic activity
  1. Mechanism
    a. Changes in repolarization (delayed or abbreviated)
    b. Persistent depolarization
    c. Currents flowing between adjacent cells
    d. After potentials
    e. Oscillatory behavior
  2. Site
    a. Specialized tissues (automatic cells)
    b. "Ordinary" atrial or ventricular myocardium

Disturbances of impulse propagation (conduction)
A. Mechanism
  1. Low transmembrane voltage
    a. Reduced maximal diastolic transmembrane voltage
    b. Transmembrane voltage reduced by spontaneous depolarization during phase 4 (only in specialized tissues)
    c. Incomplete repolarization
  2. Decreased membrane responsiveness
  3. Raised transmembrane voltage threshold
B. Type of conduction alteration
  1. Conduction delay (unidirectional or bidirectional)
    a. With reentrant activity
    b. Without reentrant activity
  2. Conduction failure (unidirectional or bidirectional)
    a. With reentrant activity
    b. Without reentrant activity
C. Site
  1. S-A node and atrium
  2. A-V node
  3. Ventricular muscle and Purkinje fiber junction
  4. Any cardiac tissue

[a] Adapted, with permission, from J. T. Bigger, Jr., in "Cardiac Arrhythmias: the Twenty-fifth Hahnemann Symposium," L. S. Dreifus and W. A. Likoff, Eds., Grune & Stratton, New York, N.Y., 1973, p. 31.

Arrhythmias due to disturbances in impulse formation are thought to be caused by changes in the rate of rise of diastolic depolarization (slope of phase 4). Changes in the slope result in alteration of the heart rate and/or development of new spontaneous ectopic focal discharges in latent pacemaker cells. The normal rate of rise of diastolic depolarization (phase 4) may be altered by an imbalance of the autonomic mediators, acetylcholine and the catecholamines, changes in extracellular ionic concentrations (potassium and calcium ions), hypoxia, changes in the concentration of carbon dioxide, excessive stretch of cardiac tissue, mechanical trauma, and weak electronic currents arising from myocardial ischemia or infarction (66).

Arrhythmias due to disturbances in conduction often are attributed to a phenomenon termed reentry or circus movement (82–86). A model of reentry was

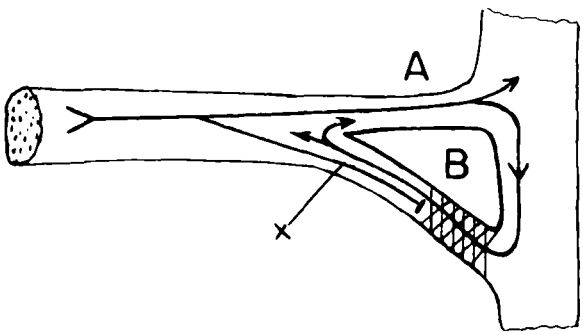


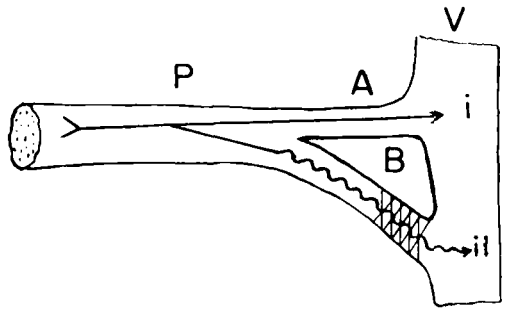
Figure 4—*Diagrammatic representation of arrhythmia due to unidirectional block, giving rise to reentry. This figure represents a peripheral part of the Purkinje system and attached ventricular muscle. The hatched area in branch B represents a unidirectional block to forward conduction. [Reprinted, with permission, from B. F. Hoffman,* Progr. Cardiovasc. Dis., *8, 319(1966) (Grune & Stratton, New York, N.Y.).]*

described by Hoffman (68) and is shown in Fig. 4. As illustrated, branch A possesses normal conduction whereas branch B has a unidirectional block to forward conduction. As shown by the arrows, the normally conducted impulse can enter the muscle fiber and then travel in a retrograde path back through branch B. If the cells that were previously excited by the normally conducted impulse (*i.e.*, at point X) have had time to reach an excitable stage in their action potential, they may be reexcited by the retrograde impulse after the impulse passes through the block area. This wave of reexcitation may then proceed around branch B, branch A, and the ventricular fiber in a circular movement. In this manner, a self-sustaining arrhythmia may arise.

On the other hand, as shown in Fig. 5, the block prevents retrograde conduction, and the conduction of the impulse through branch B is delayed by some mechanism. The impulse traversing branch B may excite the ventricular muscle at a time lapse sufficient for the action potential (i), elicited by the normally propagated impulse through branch A, to have repolarized to enable the delayed impulse to elicit a second action potential (ii).

Disturbances in Fast–Slow Response Relationship—Recently, the two types of electrical activity that have been detected in cardiac fibers and are manifested either in anatomically different tissue or in disease states have been recognized for their important role in the genesis of arrhythmias (72, 80, 81). One type of activity, termed the fast response, is characterized by cardiac fibers with a rapid rate of phase 0 depolarization as a result of a rapid influx of sodium ions. The fast response is found in atrial and ventricular muscle fibers and in fibers of the specialized conducting systems of the atria and ventricles. The rapid influx of sodium ions occurs through specific membrane channels and can be specifically blocked with tetradotoxin (87).

The fast fibers are characterized by a large resting potential (−90 mv), a threshold potential of about −70 mv, a rapid rate of rise of phase 0 of up to 1000 v/sec in Purkinje fibers, and a large amplitude (100–130 mv), all of which result in rapid conduction (0.5–5 m/sec). Such properties confer upon the fast



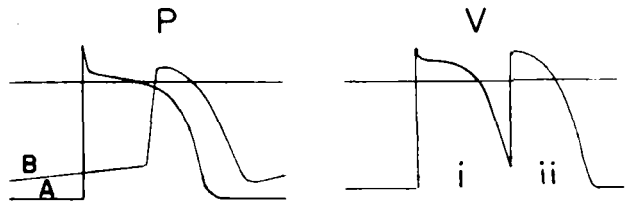


Figure 5—*Diagrammatic representation of arrhythmia due to delayed conduction. The drawing at the top represents a peripheral part of the Purkinje system (P) and attached ventricular muscle (V). In branch A, conduction proceeds at normal velocity and the action potential is shown below by trace A. In branch B, conduction velocity is reduced and unidirectional block is present in the hatched area. The locally recorded action potential is shown by trace B. The action potential in branch A elicits the ventricular action potential number i; the slowly propagating action potential in B initiates the second ventricular action potential, number ii. [Reprinted, with permission, from B. F. Hoffman,* Progr. Cardiovasc. Dis., *8, 319(1966) (Grune & Stratton, New York, N.Y.).]*

response a large safety factor for conduction, so that the minor electrical or anatomical aberrances do not interfere significantly with the spread of the impulse.

The fast fibers also possess a second, slow inward current, probably carried by calcium ions through separate, specific membrane channels not blocked by tetradotoxin. The slow current only becomes activated when the fast sodium-ion depolarizing current has lowered the transmembrane potential to about −55 mv. Since the slow channel consists of a low current and is slowly activated, it does not contribute significantly to phase 0. The slow inward current is also deactivated slowly and persists after rapid depolarization is complete, maintaining the membrane in a depolarized state. For this reason, the slow current is thought to be responsible for the prolonged plateau phase so characteristic of the cardiac action potential.

Fibers that exhibit only the slow response (slow fibers) are anatomically located in the S-A and A-V nodes, the A-V ring fibers, and the mitral and tricuspid valve leaflets. The slow rate of depolarization (1–10 v/sec), low resting potential (from −70 to −60 mv), and low amplitude (35–75 mv) of the transmembrane action potential result in relatively slow conduction (0.01–0.1 m/sec) of the impulse at a low safety factor. Although unaffected by tetradotoxin, the slow membrane channels can be selectively blocked by verapamil and its analog, 5-[(3,4-dimethoxyphenylethyl)methylamino]-2-propyl-2-(3,4,5-trimethoxy-

Table III—Comparison of Properties of Fast and Slow Inward Currents[a]

Electrophysiological Property	Fast Current	Slow Current
Activation plus inactivation kinetics dependent on extra cellular ion concentration of	Fast sodium ions	Slow calcium ions
Abolished by	Tetradotoxin	Verapamil, XIX, Mn, Co, Ni, La
Threshold of activation	−60– −70 mv	−30– −40 mv
Resting membrane potential	−80– −95 mv	−40– −70 mv
Conduction velocity	0.5–3.0 m/sec	0.01–0.1 m/sec
Overshoot	20–35 mv	0–15 mv
dv/dt of phase 0	200–1000 v/sec	1–10 v/sec
Transmembrane action potential amplitude	100–130 mv	35–75 mv
Response to stimulus	All-or-none	Dependent on characteristics of stimulus
Safety factor for conduction	High	Low
Recovery of excitability	Prompt; ends with repolarization	Delayed; outlasts full repolarization

[a] Reprinted, with permission, from D. P. Zipes, H. R. Besch, Jr., and A. M. Watanabe, *Circulation*, **51**, 761 (1975) (American Heart Association).

phenyl)valeronitrile[11] (XIX), and certain metal ions such as manganese (88). A comparison of the electrophysiological properties of fast and slow fibers is shown in Table III.

In addition to the slow and fast fibers, transitional fibers presumably convert the slow response generated by S-A nodal pacemaking cells into a fast response, which can then be safely conducted to the various regions of the heart.

The importance of the slow response in the genesis of arrhythmias was realized when it was discovered that disease states in fast fibers can disrupt the ionic mechanisms giving rise to normal action potentials and can lower the resting membrane potential. Under these conditions, the fast sodium-ion influx becomes partially or wholly inactivated and the slow current becomes predominant. The electrical properties associated with the slow response favor the genesis of arrhythmias since the large safety factor of the fast response is greatly diminished. Indeed, Cranefield (80) stated that "most and maybe all arrhythmias result either from slow conduction or rhythmic activity in a discrete and localized area of cells that show only slow response." Therefore, in the case of the slow response, the genesis of an arrhythmia may be said to arise from both disturbances in impulse formation and conduction.

Although the genesis of arrhythmias has been discussed in terms of changes in automaticity and disturbances of conduction, the actual mechanism probably is more complex, involving a combination of these and other factors which act in concert to disrupt the orderliness of heart rhythm. Mason and Braunwald (89) stated that "central to the perpetuation of arrhythmias is the non-homogeneous nature of myocardial tissue, in which a crucial relationship may exist between the number of impulse wavelets, pathlengths and muscle mass, the duration of the refractory period and the conduction velocity."

Considerations of Rhythms and Arrhythms on Ionic and Molecular Level—The most basic study of the mechanism of arrhythmias is at the biomolecular and ionic level. Every disturbance in heart rhythm, normal or abnormal, can ultimately be traced to changes in the ratios of intracellular to extracellular ionic concentrations, which are mediated by changes in the permeability of the cell membrane. This level of study is of greatest interest to the medicinal chemist, and this relatively new approach will be dealt with in some detail. Several recent reviews and books are available on the subject (60, 61, 63, 74, 79, 90–96).

The electrical activity observed in excitable tissue must have its origin in the movements of ions present in the tissue. Of primary importance in the genesis and maintenance of the electrical activity is the cell membrane separating aqueous solutions of different ionic composition. The most important ions in cardiac tissue are sodium, potassium, and calcium cations and chloride and intracellular organic anions. The membrane of excitable cells is selective in its permeability to ions, *the selectivity being dependent upon the potential across the membrane.*

In addition to the usual physicochemical forces which move ions across semipermeable membranes according to concentration gradients, the cell membrane is equipped with an "active transport" system. This system requires metabolic energy sources and moves or transports ions across the membrane against a concentration gradient (97–99). One active transport system has been termed the sodium–potassium exchange pump or, more simply, the sodium pump.

During the resting phase (phase 4) of excitable cells, the inside of the cell is electronegative relative to the outside. This potential difference is established by the active transport system, which maintains a high potassium-ion concentration inside the cell (37.5 times the extracellular concentration) and a high concentration of sodium ions outside the cell (7.5 times the intracellular concentration). The membrane is relatively impermeable to sodium ions and quite permeable to potassium ions during the resting phase. Therefore, a dynamic equilibrium is attained,

[11] D-600.

Table IV—Alleged Contribution of Various Ionic Channels to Phases of the Cardiac Action Potential[a]

Ion	Direction	Channel	Phase 0, Upstroke	Phase 1, Rapid Repolarization	Phase Notch	Phase 2, Plateau	Phase 3, Final Repolarization	Phase 4, Diastolic Depolarization
Sodium	Inward	i_{Na} (fast)	On	Off	—	—	—	—
		i_{Na} (slow)	—	—	On	Off	—	—
Chloride	Inward	i_{Cl}	—	On	Off	—	—	—
Calcium	Inward	i_{Ca}	On	—	—	—	Off	—
Potassium	Outward	i_{K1}	Off	—	—	—	On	—
		i_{X1}[c]	—	—	—	—	On	Off
		i_{X2}[c]	—	—	—[b]	—[b]	—[b]	—
		i_{Ks}	—	—	—	On	—	Off

[a] Adapted, with permission, from H. A. Fozzard and W. R. Gibbons, *Amer. J. Cardiol.*, 31, 182(1973). [b] Too slow to participate. [c] X_1 and X_2 are additional potassium channels.

which maintains the transmembrane potential at about −90 mv (in atrial and ventricular muscle fibers and Purkinje fibers), and is dependent on the active transport system to bring potassium ions in and carry sodium ions out of the cell.

When a resting cell is stimulated with an impulse large enough to decrease the membrane potential to the threshold potential, rapid depolarization occurs (phase 0). At this point, the permeability to sodium ions increases dramatically (permeability to sodium ions may become 10 times greater than that of potassium ions). The rapid influx of sodium ions normally results in a reversal of the membrane potential. The inside of the cell becomes positive with respect to the outside, as evidenced by an overshoot in the transmembrane action potential of about +30 mv. As a consequence of the influx of sodium ions, a sodium current is produced. This current acts as a depolarizing stimulus to adjacent cells and results in conduction of the impulse from cell to cell.

The slow diastolic depolarization characterized by the gradual rise in phase 4 of automatic cells apparently is due to a steady decrease in the permeability to potassium ions while a small permeability to sodium ions remains constant. The decreased permeability to potassium reduces the efflux of potassium ions out of the cell which, alone, would maintain the negativity of the transmembrane potential; however, the presence of the small steady influx of sodium ions slowly depolarizes the cell. When the slow "sodium leak" reduces the transmembrane potential to the threshold potential, the very rapid influx of sodium ions occurs almost as if a "gate" had been opened (13).

After depolarization, the cell begins the repolarization process to restore the transmembrane potential to its maximal resting value. While rapid depolarization is complete after about 1 msec, repolarization requires up to 500 msec. The mechanisms by which repolarization is accomplished are quite complex, and little was known until a voltage clamp technique was developed (100, 101) for studying cardiac fibers. With this technique, it became possible to differentiate the ion fluxes occurring throughout the action potential (102).

The application of this technique and interpretation of the results must be approached with due caution, as pointed out in an extensive and critical review (103). In spite of the difficulties involved, the procedure has enjoyed rapid growth and has led to an increased understanding of the ionic currents in excitable cardiac cell membranes (104–106).

In 1973, Fozzard and Gibbons (60) indicated that there appeared to be eight separate fluxes that apparently traverse different pores or channels in passing through the cardiac cell membrane. Table IV lists the separate channels and the contribution of each to the various phases of the cardiac action potentials. Figure 6 shows a characteristic cardiac action potential, with the arrows indicating the ionic fluxes asso-

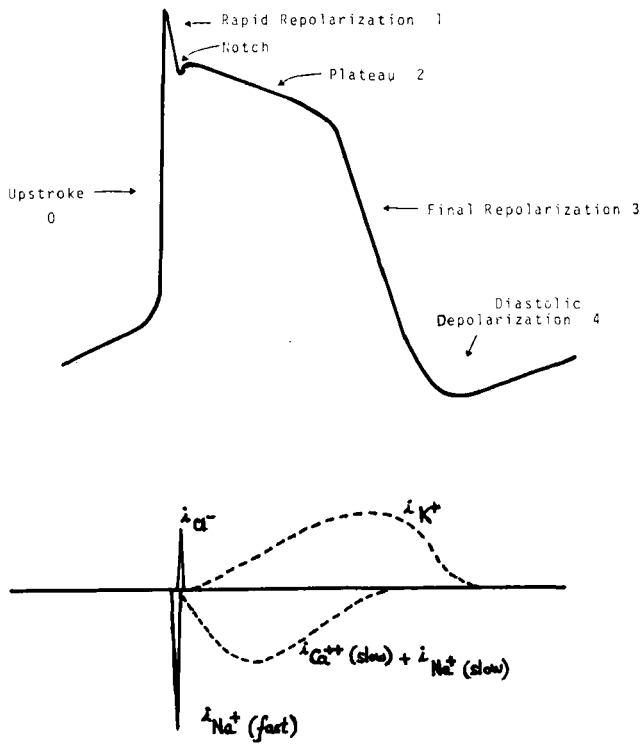


Figure 6—*(Top) Diagrammatic representation of a Purkinje fiber action potential. Each distinctive phase is labeled with the term used in the text where the ionic events related to it are discussed. (Bottom) Corresponding with each phase of the action potential is a diagrammatic representation of the contribution of the time-dependent membrane currents to each phase. The currents shown above the line make the inside of the cell more negative (repolarizing), whereas the currents below the line make the cell interior more positive (depolarizing).*

ciated with the phases of the action potential.

The rapid repolarization (phase 1) appears to result from a decrease in permeability to the influx of sodium ions. At the same time, an increase in permeability to the influx of chloride ions makes the interior of the cell more negative. The notch seen sometimes in Purkinje fibers results from a slow inward sodium flux, a shutting off of the chloride-ion channel, and the influx of calcium ions, the last being necessary for myofibril contraction. Therefore, the repolarization to more negative values is slowed or stopped momentarily.

However, repolarization proceeds slowly during the plateau (phase 2) as a result of the closing of the slow sodium-ion influx and the appearance of a small efflux of potassium. The final and more rapid repolarization (phase 3) seems to involve the shutting down of the inward calcium-ion flux and the efflux of potassium ions through two separate channels. Research on the identification and differentiation of ion channels in membranes is in an early stage, and further study doubtless will require modification of the current concept of ionic channels (60).

An understanding of the macromolecular mechanism for the opening and closing of ionic channels would be most interesting. However, few reports dealing with the problem are available. DeMello (107) presented some hypotheses and drew attention to the importance of membrane phospholipids in maintaining transmembrane potentials. This contention appears to be supported by the fact that electrical excitability can be conferred on a phospholipid bilayer separating two aqueous solutions containing different potassium-ion concentrations (108).

Szekeres and Papp (15, p. 20) reported a theory that postulates the existence of a carrier system of great transport capacity with the ability to accommodate the extremely strong ionic flux seen in phase 0. This carrier system is especially efficient in transporting sodium ions along their concentration gradient into the cell. The proposed system contains carrier molecules, each of which is assumed to contain three or four negatively charged ionic centers. As each carrier molecule binds one sodium ion, two or three negative centers remain free. These free negative ionic centers become electrically associated with the outer surface of the membrane, which is positive at resting potential. However, when the membrane becomes depolarized, the association is broken and each carrier molecule migrates rapidly to the inside of the membrane, carrying one sodium ion into the cell.

The amplitude of phase 0 is greatly dependent upon the value of the transmembrane potential. An increase in the amplitude of phase 0, according to the theory, is a result of more carrier molecules being able to become electrically associated with the outer surface of the membrane when there is a greater positive charge on the outer membrane surface. Conversely, if the resting potential of the membrane is low, fewer carrier molecules associate at the outer membrane surface and the amplitude of the depolarization phase is weaker.

Changeux *et al.* (109) attempted to put the ionic selectivity of the permeability change in excitable membranes on a sounder theoretical basis. They postulated the existence of "ionophores," macromolecular elements of the membrane that recognize the permeative ion at a selective site and transport it along the electrochemical gradient across the membrane. The capacity for selective transport of the particular ionophores involved in the excitation process changes upon excitation or depolarization by means of a structural or conformational change.

Several investigators reported that depolarization causes conformational changes in membrane-bound proteins of excitable cells. Clark and Strickholm (110) offered evidence that a conformational transition involving histidine groups of surface membrane proteins is involved in the action potential and ion permeability regulation in excitable membranes. Tasaki *et al.* (111) collected experimental data which suggest that an ion-dependent conformational change occurs upon excitation. Papakostidis *et al.* (112) reported that in proteins from excitable nerve cell membranes, a relatively large part of the protein occurs as an antiparallel β-structure in the presence of potassium ions. In the presence of sodium and calcium ions, the proteins are no longer in the β-structure but are largely in the helical form.

Although most reported studies were performed on excitable nerve cells rather than excitable cardiac cells, the molecular events probably are quite similar; it is unfortunate that cardiac fibers are more difficult to study than are nerve fibers.

In summary, sufficient evidence has been accumulated to justify theories proposing that the excitatory process in cardiac cells is basically governed by the interaction of membrane components with particular ions. This interaction results in ionic fluxes across the membrane. The maintenance of the resting potential seems to involve a mechanism requiring energy in the form of adenosine triphosphate, since inhibition of the formation or availability of adenosine triphosphate results in a reduction of the transmembrane potential over time (15, p. 315).

The depolarization and repolarization phases appear to depend on conformational changes of the components of the membrane, which open and close gates by allowing simple diffusion or, alternatively, inhibiting the influx or efflux of ions through the membrane. This conformational mobility is dependent upon the changing potential across the cell membrane. This is not surprising when one realizes that changes in potential can disrupt or cause formation of intra- and intermolecular dipole interactions, electrostatic charge interactions, hydrogen bonds, and other intra- and intermolecular associations. Therefore, any extraneous force that acts to: (*a*) disrupt the energy source of the ion pump or (*b*) change the normal ionic concentration of the exo- and/or endoplasm, as well as any agent that interacts with the membrane to cause a change in the proper conformational mobility required for normal action potential formation, may cause a disturbance of the heart rhythm.

MECHANISM OF ACTION OF ANTIARRHYTHMIC DRUGS

Recent attempts to explain the mode of action of antiarrhythmic drugs have been numerous. Complications are quickly evident when one considers the variety of the chemical structures of the drugs used to correct arrhythmias. In addition, most drugs with antiarrhythmic activity have other prominent pharmacological actions. Indeed, nearly all drugs in clinical use as antiarrhythmics were developed and used for some other pharmacological action. Only because of astute clinical observations of their effectiveness in correcting arrhythmias during treatment of the intended disease condition did it become apparent that the drugs were useful as antiarrhythmics. This situation apparently is due to the poor correlation between the activity found in experimental arrhythmias in animals and the therapeutic potencies in human patients (16, 113).

Szekeres and Papp (15, 16) divided antiarrhythmic drugs into two broad classes: specific and nonspecific. Specific antiarrhythmic drugs evoke their action primarily through an indirect mechanism such as altering a specific autonomic nervous response. β-Adrenergic blocking agents belong in this class. The specific antiarrhythmic drugs generally are similar in chemical structure and interact with a stereoselective receptor site.

Nonspecific Action at Myocardial Membrane—The nonspecific antiarrhythmic agents appear to act directly on the myocardial cell membrane, producing a cardiodepressant effect *via* changes in basic electrophysiological properties such as automaticity, excitability, conductivity, and refractoriness[12]. Quinidine (I) is the prototype of this class of agents; consequently, agents exhibiting this type of antiarrhythmic action are said to possess "quinidine-like" properties (16).

Propranolol[13] (VI), a β-adrenergic blocking (specific) agent used clinically as an antiarrhythmic, and other β-blocking compounds have been shown to elicit their beneficial effect primarily from inhibition of adrenergic stimulation; but at higher concentrations, their effect also is from a quinidine-like depression of the myocardium (13). The β-blocking properties are valuable assets to antiarrhythmic therapy, especially when the arrhythmia results from, or is sensitive to, adrenergic stimulation. On the other hand, quinidine and many other nonspecific antiarrhythmic agents have been shown to possess weak β-adrenergic blocking properties (13; 15, p. 301), which, in certain arrhythmias, can be beneficial to their action.

The mechanism by which the drug molecule interacts with the biological system is of primary importance in assaying the mode of action of drugs. Barlow (114) listed three possible mechanisms of interaction: (*a*) a process involving enzymes, (*b*) a process involving receptors, and (*c*) some physicochemical process. In the case of nonspecific antiarrhythmic drugs, most studies have shown that the depression of the myocardial membrane is not directly related to a concomitant suppression of the membrane enzyme, sodium–potassium adenosine triphosphatase, which provides high energy phosphates for operation of the ion transport system (15, p. 296; 65, p. 279; 89, p. 130).

The variety of chemical structures associated with nonspecific antiarrhythmic compounds and the differences observed in the actions of the drugs on electrophysiological parameters indicate that this class of agents probably does not act on specific receptor sites. Additional supportive evidence is that while the antiarrhythmic effect is altered in some ways by differences in stereochemistry, the antiarrhythmic "receptor" is not very stereoselective. For example, the resolution of racemic alprenolol, propranolol, and butidrine into their respecitve enantiomers indicated that only the *levo*-isomers are potent β-adrenergic blocking agents whereas both the *dextro*- and *levo*-isomers possess local anesthetic and antiarrhythmic activity (115–119). The differences in potency seen in closely related chemical structures, or in isomers of the same compounds, may be the result of greater bioavailability and specificity for cardiac tissue of one structure or isomer and not the result of stereoselective receptors (120, 121).

The consensus is that nonspecific or quinidine-like antiarrhythmic drugs act by a physicochemical process. Evidence has been obtained with studies on the interaction of local anesthetics (most antiarrhythmic drugs possess local anesthetic activity) with monomolecular films of membrane lipids extracted from nerve cells (94). These experiments indicated that the local anesthetic drugs penetrate the monolayer and increase the surface pressure, as if the drug molecules had penetrated the monolayer and caused it to expand. Also, the magnitude of the increase in surface pressure exactly paralleled the potency of the drugs in causing nerve block.

The results of this and other similar studies prompted Shanes (94) to suggest that local anesthetic drugs block conduction by penetrating the cell membrane between the pores of channels through which sodium ions pass across the membrane. Following penetration and occupation of the membrane, the drugs would tend to compress the channels and hinder their enlargement at times when an increased permeability is required. Shanes termed this type of drug action membrane stabilization. Subsequently, the phenothiazine tranquilizers, antihistamines, steroids, antiarrhythmic agents, and other drugs were found to decrease membrane permeability to sodium ions (122, 123).

Shanes strengthened his theory by finding that destabilizing or labilizing drugs (the veratrum alkaloids), which increase the membrane permeability to sodium, cause a gradual decrease in surface pressure of the monolayer. The change in pressure can be blocked by the same procedures used to block the veratrum alkaloid effect on nerve membranes: (*a*) addition of calcium, (*b*) lowering the pH, and (*c*) treatment with a local anesthetic drug (a membrane stabilizer) (94).

[12] The terms nonspecific, quinidine-like and Class I action, and cardiac membrane stabilization and myocardial depression are used interchangeably throughout this review.

[13] Inderal.

The nonspecific membrane-stabilizing effects of a series of β-adrenergic blocking agents were investigated using isolated nerve and myocardial tissue and erythrocyte ghosts and blood platelets (124–127). The local anesthetic properties, changes in myocardial conduction velocity, protection of human erythrocytes against hypotonic hemolysis, and inhibition of the active transport of serotonin across the blood platelet membrane were studied. In all cases, the results indicated that apart from the β-adrenergic blocking properties, these agents possess striking membrane-stabilizing properties at the concentrations studied. Also, evidence was obtained from morphological studies and from experiments using a fluorescent probe that the underlying mechanism of the membrane stabilization is a change in membrane protein conformation induced by adsorption to or absorption in the membrane by the drug molecules resulting in alterations in permeability.

A membrane expansion theory of anesthesia was proposed recently in which the anesthetic and other nonspecific nerve blocking drugs are said to adsorb to hydrophobic regions of membrane proteins, evoking conformational changes in the proteins and thus partially or wholly blocking the ionic conductance channels necessary for action potential production (128).

Other studies showed that membrane-stabilizing drugs inhibit the permeation of sodium ions through the membrane by complexing with a membrane phospholipid, which seems to be involved in the movement of ions across the membrane (94, 107).

Regardless of the specific macromolecular element of the membrane with which the stabilizing drug interacts, these drugs probably invade the cell membrane and alter ionic permeability by a physicochemical process. The physical properties of the drug that seem to be necessary include a pKa around 8.0–9.0, adequate lipid solubility, and appropriate chemical moieties. The molecular structure of most nonspecific antiarrhythmic drugs consists of three moieties, which presumably are necessary for activity: (*a*) a benzene ring or condensed aromatic portion connected to (*b*) a basic amino group, usually tertiary or secondary but in some cases primary, by way of (*c*) an ester, ether, amide, or hydroxyalkyl group capable of becoming involved in hydrogen bonding. These structural features are almost identical to those generally considered necessary for local anesthetic drugs (129).

Indeed, with very few exceptions, all nonspecific antiarrhythmic drugs and most β-adrenergic blocking drugs used to control rhythm disturbances are membrane-stabilizing agents and many possess local anesthetic activity (115–119, 130, 131). The strong connection between local anesthetic activity and antiarrhythmic activity undoubtedly stems from the membrane-stabilization properties of both classes.

Figure 7 depicts an oversimplified representation of the interaction of nonspecific, membrane-stabilizing antiarrhythmic drugs with a model membrane (132). It can be seen that incorporation of sufficient numbers of membrane-stabilizing molecules into the membrane obviously alters its function.

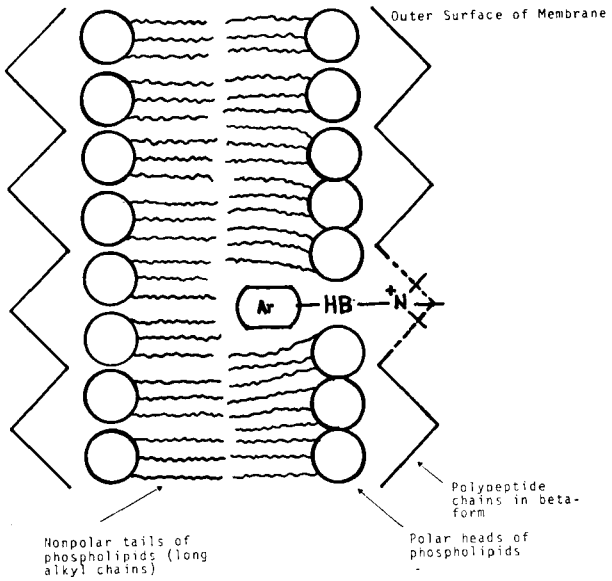


Figure 7—*Schematic illustration indicating possible molecular interaction of antiarrhythmic agents (or other membrane-stabilizing drugs) with a cell membrane. The portion of the drug molecule labeled Ar represents the aromatic ring usually contained in antiarrhythmics, while HB indicates the group that may become involved in hydrogen bonding. In this model interaction, it can be seen that the drug may alter the structure of both the outer protein layer and the phospholipid layer.*

It has been suggested that in addition to disturbances of the cardiac membrane conformation caused by the binding of antiarrhythmic drugs, the essential amino group may also play an important role (133, 134). This basic center has a sufficiently high pKa in all antiarrhythmic drugs (except phenytoin, which is weakly acidic) to cause it to be ionized significantly at physiological pH. The positioning of such a cation at the outer surface of the membrane may impede ionic transport as a result of its possible hydration and/or repellency of sodium ions and other cations (135).

In summary, there appears to be sufficient evidence to explain the action of nonspecific antiarrhythmic drugs on the basis of a *physical membrane occupancy theory*. This theory depends upon the ability of the drug to: (*a*) bind at cardiac membranes, (*b*) induce a change in the conformation of the membrane that will ultimately give the desired effects, and (*c*) present a charged amino group at or near the surface of the membrane.

Electrophysiological Effects on Transmembrane Action Potential—The effect of membrane-active agents on the permeability of ions can be observed by changes in parameters of the transmembrane action potential. Since the development of the technique for recording the transmembrane action potential of cardiac cells, many studies have elucidated the effects of antiarrhythmic drugs on these parameters. Numerous reviews of the subject have appeared (15–17, 23, 61, 65, 69–74, 76, 89, 94, 136–142).

In assessing the effect of antiarrhythmic drugs on the transmembrane action potential of isolated cardiac tissues, one must exercise due caution. The parameters of the transmembrane action potential are de-

Table V—Effects of Antiarrhythmic Agents on the Transmembrane Action Potential of Isolated Cardiac Tissue[a]

Agent	Type of Tissue[b]	Resting Potential	Amplitude	*dv/dt*	Membrane Responsiveness	Conduction Velocity	Duration	Refractory Period	Automaticity	Reference
Quinidine	Canine P.F.	0	↓	↓	↓	↓	↑	↑	↓	137, 148 149
Procainamide	Canine P.F.	0	↓	↓	↓	↓	↑	↑	↓	137, 148 149
Lidocaine	Canine P.F.	0	↓	↓	↓	↓	↓	↓	↓	150
Propranolol	Canine P.F.	0	↓	↓	↓	↓	↓	↓	↓	137, 148 149
Phenytoin	Canine P.F.	0	0	0, ↓[c]	↓[c], 0, ↑[d]	0, ↓[c]	↓	↓	↓	137, 148 149
Phenytoin	Rabbit A.M. and V.M.	0	0	↓	↓	↓	0	?	↓	151
Disopyramide	Canine P.F.	0	0	↓	↓	↓	↑	↑	↓	152, 153
Ajmaline	Canine P.F., A.M., and V.M.	0	↓	↓	↓	↓	↑[e], ↓[f]	?	↓	154
Mexiletine	Rabbit A.M. and V.M.	0	↓	↓	↓	↓	0	↑	0	155
Aprindine	Canine P.F.	↓	↓	↓	↓	↓	↓	↑	↓	40, 156
Verapamil	Canine P.F.	0	0	0	0, ↓	?	0, ↑[c]	0, ↑[c]	↓	28
Amiodarone[g]	Rabbit A.M. and V.M.	0	0	0	0	0	↑	↑	↓	157
Dimethyl quaternary propranolol[h]	Canine P.F.	0	↓	↓	↓	↓	↓	↓	↓	158
Bretylium	Rat A.M. and V.M.	0	↓	↓	↓	?	↑	↑	?	159

[a] 0 = no effect, ? = not reported, ↓ = decrease, ↑ = increase; and ↓ = questionable or slight effect. [b] P.F. = Purkinje fiber, A.M. = atrial muscle, and V.M. = ventricular muscle. [c] At high concentration only. [d] In acutely depressed fibers. [e] Atrial muscle and ventricular muscle. [f] Purkinje fiber. [g] After 6 weeks of treatment of whole animal. [h] UM-272.

pendent upon the ionic concentration of the medium or perfusate, especially the potassium concentration (23, 140, 143). Considerable confusion has resulted from studies on the effects of drugs when lower than normal physiological potassium concentrations have been used. Agreement over the interpretation of observed electrophysiological actions of drugs studied in isolated tissue and correlation to the clinical situation is complicated by several factors (144):

1. Disagreement exists over which dose of drug *in vitro* is comparable to the effective plasma concentration in humans.
2. Information is lacking on the effective drug content in myocardial tissue.
3. Fibers from different parts of the heart respond differently to comparable drug concentrations.
4. Abnormal or diseased tissues respond differently than normal tissue.
5. Small changes in ionic concentrations and pH can markedly influence the transmembrane action potential.
6. Important actions of the drug may be absent or overlooked in the experimental models.

In an attempt to remedy some of these problems, a technique was developed whereby isolated cardiac tissue is perfused with arterial blood from a donor animal and the effects of the drug on the whole animal and the isolated tissue are determined simultaneously (145, 146). Isolated diseased human cardiac tissues have been used in studies of the effects of drugs on the transmembrane action potential (147).

The effects of several antiarrhythmic drugs on various parameters of the transmembrane action potential of isolated cardiac tissue are given in Table V. There is still disagreement between some investigators over the effects listed for certain compounds, but the reviewers have attempted to extract the data from the most recent reviews and experimental studies. Vaughan Williams (23) reported that quinidine, procainamide, lidocaine, and phenytoin apparently elicit their action on the myocardium by depressing the maximum rate of depolarization, also called maximum upstroke velocity, represented by phase 0 in the transmembrane action potential. Lidocaine and phenytoin were previously thought to have no effect on the maximum rate of depolarization at therapeutic concentrations (160, 161). However, reinvestigation of these two drugs in a medium containing potassium concentrations more closely approaching physiological levels indicated that these drugs did indeed depress the maximum rate of depolarization at concentrations thought to correspond to therapeutic blood levels (23, 151, 162).

In addition to decreasing the rate of rise of the action potential, most of the quinidine-like group of drugs reduce heart rate and excitability of the myocardium without changing the resting potential (16). Also, conduction velocity is decreased and the effective refractory period is increased (61).

Apparently, the effects of these drugs result from their effect on sodium permeability. Upon excitation by an impulse, a less than normal increase in sodium permeability is observed, as though the gate that opens to allow the inrush of sodium is inhibited from opening fully (23). Therefore, the action potential rises less rapidly and there is less overshoot. This situation leads to a decrease in conduction velocity, since this parameter is dependent on the rate of rise, the overshoot, and the amplitude of phase 0.

After an action potential is initiated by the rapid

influx of sodium ions (phase 0), repolarization must proceed to a certain negative potential before the gate can reopen and allow the influx of sodium ions for production of a second action potential. The effective refractory period may be thought of as that point at which the repolarization has proceeded sufficiently for the rate of rise of a second excitation to be rapid enough to permit propagation of the impulse. Since quinidine and quinidine-like drugs inhibit the entry of sodium ions, repolarization must proceed further before the influx of sodium can become great enough to allow the minimum rate of rise for a propagated action potential (23). This is observed as an increase in the effective refractory period, an important property of antiarrhythmic drugs.

All quinidine-like drugs decrease the slope of phase 4 or the slow diastolic depolarization of automatic cells. This decrease is manifested by a decrease in automaticity. Additionally, the automaticity of cells responsible for the formation of ectopic impulses is depressed more than the automaticity of the S-A pacemaker, so the dominance of the normal cardiac pacemaker usually results (16).

From the preceding discussion, it appears that the effects of quinidine and quinidine-like drugs, at least on the electrical activity of fibers of isolated tissue, are due to induced changes in membrane permeability, particularly depression of sodium flux into the cell.

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RESEARCH ARTICLES

Evaluation of Mannich Bases and Related Compounds as Inhibitors of Mitochondrial Function in Yeast and Inhibition of Blood Platelet Aggregation, Blood Clotting, and *In Vitro* Metabolism of 5-Dimethylamino-1-phenyl-1-penten-3-one Hydrochloride

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Abstract □ 5-Dimethylamino-1-phenyl-1-penten-3-one hydrochloride (Ia) and 32 analogs were tested for inhibition of respiratory-dependent growth in *Saccharomyces cerevisiae*. Thirteen of the 33 compounds tested appeared to affect mitochondrial function, since the inhibition of respiratory-dependent growth was statistically greater than the inhibition of growth on fermentable energy sources. Inhibition of mitochondrial function in yeast and growth inhibition of an *in vitro* culture of human epidermoid carcinoma (KB) were positively correlated since 83% of the compounds tested either had mitochondrial-inhibiting properties and significant activity in the KB test or were inactive in both tests. Similarly, 78% of compounds tested showed murine toxicity and mitochondrial inhibition or had no effect on murine toxicity and yeast mitochondrial function. Injection of Ia into rats resulted in the appearance of blood in the urine and feces. Compound Ia inhibited adenosine diphosphate and collagen-induced aggregation of rat platelets but had no effect on blood clotting. TLC, following incubation of Ia with a rat liver extract, showed that the structure of Ia was not enzymatically modified and indicated activity *per se* on platelet aggregation and mitochondrial function.

Keyphrases □ Mannich bases—effect on mitochondrial function in yeast, human epidermoid carcinoma cultures, blood platelet aggregation, blood clotting, rats □ Mitochondrial activity—effect of Mannich bases and related compounds, yeast □ Blood platelet aggregation—effect of Mannich bases and related compounds, rats □ Coagulation, blood—effect of Mannich bases and related compounds, rats □ Structure-activity relationships—effect of Mannich bases and related compounds on mitochondrial function in yeast, human epidermoid carcinoma cultures, blood platelet aggregation and blood clotting, rats

Mannich bases have a wide range of biological activity including antineoplastic properties (1, 2), antimicrobial effects (3–5), analgesic activity (6), local anesthetic properties (7, 8), and psychotropic effects (9). To pursue a continuing interest in Mannich reactions (10–12) and α,β-unsaturated ketones (13, 14), several properties of a simple Mannich base, 5-dimethylamino-1-phenyl-1-penten-3-one (Ia), derived