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Ionic Mechanisms in Heart Muscle in Relation to the Genesis and the Pharmacological Control of Cardiac Arrhythmias[1]

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I. Introduction

BECAUSE of the increasing relevance of the knowledge of fundamental mechanisms of action of antiarrhythmic drugs to therapeutic practice, the progressive refinements during the last several decades of techniques to study the effects of drugs and hormones on the electrical activity of the heart have attracted much attention (22, 77, 78, 168, 296). Before 1950 much of the understanding of the drug effects on the excitability of the heart was derived from studies involving surface recordings of the activation sequence (30). The Ling-Gerard microelectrode was introduced in 1949 (176) and was applied promptly to the study of electrophysiological and electropharmacological phenomena in cardiac muscle in the 1950's and early 1960's (139, 307, 310). Data from such microelectrode studies have led to the development of inferential links between basic membrane theory and cardiac arrhythmias in terms of changes in impulse propagation and automaticity (115, 139, 140); they have also provided a framework for the interpretation of the mode of action of antiarrhythmic drugs from their effects on the transmembrane potentials from different parts of the heart (218, 253, 262, 263, 301, 302, 308, 309).

Over the last 10 years, further advances in cardiac electrophysiology have occurred (47, 150, 210, 284), due to, in large measure, the application of voltage clamp in heart muscle and the technique is now being used increasingly to investigate mechanisms of action of cardioactive drugs (87, 97, 165, 169, 170, 212, 279, 286, 294–297, 308, 309). It must, however, be emphasized that to date not all available antiarrhythmic drugs have been investigated under voltage clamp conditions. For the agents which have been so studied, information is still limited with respect to the correlation of results from voltage clamp experiments in isolated heart muscle and the mode of action of these compounds in intact animals and in man. This report will consider the initial results which have been obtained by voltage clamp in heart muscle and their relevance to the understanding of membrane actions of antiarrhythmic drugs in relation to the genesis of cardiac arrhythmias. However, only those aspects of the cable properties and excitation phenomena in the heart necessary for the understanding of the new findings of drug effects on cardiac membrane will be discussed. The theoretic background of cable analysis will not be exhaustive and will be confined to the features of particular relevance to the elucidation of the drug actions on the excitability and the passive electrical properties of the cardiac membrane. The mathematical deductions of equations are therefore largely omitted and attention is drawn to the original publications (70, 129, 130, 132, 137, 208), which may be helpful for a more detailed understanding of the subject. This review is divided into three parts: the first, dealing with the current concepts of normal myocardial electrophysiology; the second, with the possible mechanisms underlying the derangements in electrical activity which produce cardiac arrhythmias; and the third, with

the electrophysiological effects of antiarrhythmic agents used in the control of such disorders of rhythm and conduction.

II. Myocardial Electrophysiology

The myocardial cell may be considered a cable-like structure with a well-conducting core and a thin rather effective insulating membrane, the electrical circuit of which may be assumed to consist of a capacitance in parallel with a resistance. Although there are limitations of this concept in cardiac muscle in contrast to that in nerve, it is nevertheless useful to imagine cardiac fibers connected to each other by low resistant pathways forming muscle bundles which may function as simple cables. However, the well-known structural complexity of cardiac muscle cannot be ignored and the applicability of simple cable analysis in this tissue therefore needs to be examined critically (see below).

The intracellular fluid of the myocardial cell contains 150 mM potassium and approximately 10 to 14 mM sodium. In contrast, the extracellular concentrations of potassium and sodium are about 5 mM and 140 mM respectively. From this unequal distribution of ions, diffusion potentials are generated and their equilibria are given by Nernst's equation:

$$E_{ion} = \frac{R \cdot T}{z.F} \cdot ln \frac{C_2}{C_1} \qquad (1)$$

where z is the valency of the particular ion, C_1 and C_2, the concentrations of the ion inside and outside of the membrane and R, T, and F have their usual meanings. Rearranging for $\log_{10}$ and 37°C one obtains:

$$E_{ion} = -61.5 \cdot log \frac{C_1}{C_2} \qquad (2)$$

Thus, from the knowledge of the transmembrane ionic concentrations the equilibrium potentials of potassium and sodium ions may be calculated. They are of the order of −90 mV and +60 mV respectively.

Since the relative permeability (P_{ion}) for potassium under resting conditions is much higher than that for sodium, the measured membrane resting potential is in the range of −80 mV, *i.e.*, close to the potassium equilibrium potential, E_K. One may therefore extend equation (1) according to Goldman (93) and Hodgkin and Katz (136) as follows:[4]

$$V_r = \frac{R \cdot T}{F} \cdot \log \frac{K_i \cdot P_K + Na_i \cdot P_{Na} + Cl_o \cdot P_{Cl}}{K_o \cdot P_K + Na_o \cdot P_{Na} + Cl_i \cdot P_{Cl}} \qquad (3)$$

P_{ion}, the relative permeability of an ion, is defined as the ease with which the ion is allowed to penetrate the cell membrane and can be expressed in mathematical terms:

$$P_{ion} = u_{ion} \cdot \beta_{ion} \cdot \frac{R \cdot T}{a \cdot F} \qquad (4)$$

where a is the thickness of the membrane, u is the mobility of the ion, and β the partition coefficient with the dimension cm/sec relating the concentration of the ion at the outer surface of the membrane to the concentration in the external solution (35, 96, 138).

A. Cable Properties

A small current applied with an intracellular microelectrode at one point of a cable causes an electrotonic potential which does not reach threshold and whose steady state value follows an exponential decline with distance (fig. 1).

The current flowing in the longitudinal direction, i_a, can be described as

$$i_a = \frac{dV}{dx} \cdot \frac{1}{r_a} \qquad (5)$$

where r_a is the internal resistivity, x, the distance along the cable and V the transmembrane potential expressed as the deviation from the quiescent potential in mV. The membrane current, i_m, is related to the axial current i_a in the following way:

$$i_m = \frac{di_a}{dx} \qquad (6)$$

From equations (5) and (6) it follows that

[4] For definitions of abbreviations, see Appendix I.

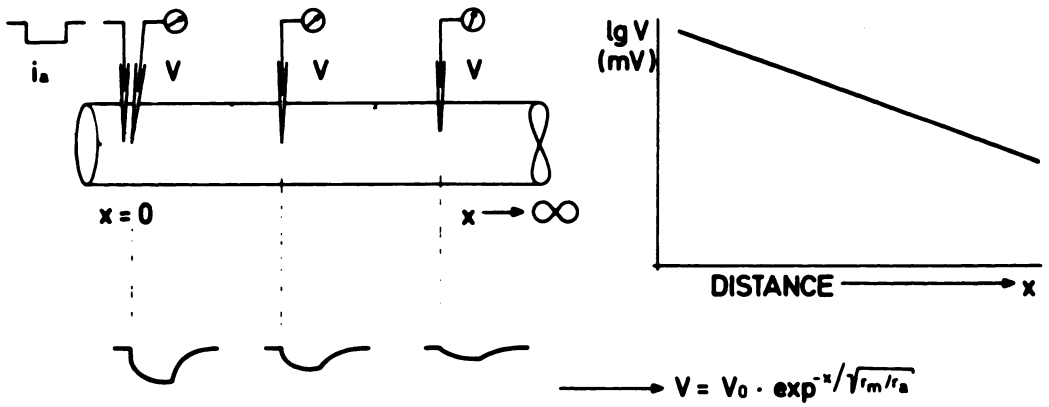


FIG. 1. Spatial decay of electrotonic potential in an infinite cable: axial current i_a is injected by means of a microelectrode at one point; the distribution of the membrane current along the fiber is measured with a second intracellular microelectrode. Under these conditions, the spatial decay of the electrotonic potential can be expressed by the equation

$$V = V_0 \cdot e^{-x/\sqrt{r_m/r_a}}$$

where V is the electrotonic potential measured at various distances along the fiber and V_0 is the potential near the polarizing microelectrode.

$$i_m = \frac{d^2V}{dx^2} \cdot \frac{1}{r_a} \tag{7}$$

Assuming that the electrical network of the fiber can be represented by a simple RC-circuit the membrane current consists of two components:

$$i_m = i_c + i_i \tag{8}$$

or

$$i_m = c_m \cdot \frac{dV}{dt} + i_i \tag{9}$$

where c_m is the membrane capacitance, i_m, the membrane current, i_c, the capacity and i_i, the ionic current. Combining equations (7) and (9) one obtains:

$$\frac{1}{r_a} \cdot \frac{d^2V}{dx^2} = c_m \cdot \frac{dV}{dt} + i_i \tag{10}$$

or

$$\frac{1}{2R_i} \cdot \frac{d^2V}{dx^2} = c_m \cdot \frac{dV}{dt} + I_i \tag{11}$$

This is the general cable equation; since

$$x = \Theta \cdot t \tag{12}$$

equation (11) may be rewritten:

$$\frac{1}{2R_i \cdot \Theta^2} \cdot \frac{d^2V}{dt^2} = C_m \cdot \frac{dV}{dt} + I_i \tag{13}$$

where Θ is the conduction velocity. Equation (13) describes a conducted action potential provided the membrane voltage exceeds the threshold potential. In this case, I_i is time and voltage dependent and may be formulated by Hodgkin-Huxley equations (see below).

The velocity of conduction of an action potential is:

$$\Theta = \sqrt{\frac{a \cdot K}{2R_i \cdot C_m}} \tag{14}$$

where a is the radius of the fiber, K is a constant proportional to the current flowing during excitation, and R_i is the specific internal resistivity in $\Omega \cdot$cm (127, 132, 150).

B. Decline of Potential in the Steady State

We shall consider that a constant current is applied to the interior of a cable at one point ($x = 0$) for a longer period of time. Current will flow along the axon and also across the cell membrane. Initially, there will be a substantial capacity current and the voltage will rise steeply. However, as

the membrane capacity becomes charged up, the capacity current and dV/dt will both decline toward zero. Then equation (10) will simplify to:

$$\frac{1}{r_a} \cdot \frac{d^2V}{dx^2} = \frac{V}{r_m} \tag{15}$$

Provided the cable is infinitely long, the solution to this equation is:

$$V = V_0 \cdot e^{-x/\lambda} \tag{16}$$

where $\lambda = \sqrt{r_{m/r_i}}$, *i.e.*, the voltage declines exponentially from its initial value V_0.

The ratio r_m/r_i determines the extent of the spatial spread of the voltage. The constant λ is therefore known as the space constant. This distance is usually of the order of 2 mm (307). Hence, if $x = \lambda$,

$$V = V_0 \cdot \frac{1}{e} \tag{17}$$

If the cable is shorter than about three space constants, the current flowing in the longitudinal direction will be reflected provided the cut ends are sealed. In heart muscle this obtains only when calcium is present in the bathing solution (57). The reflected current is itself exponentially declining and superimposes on the current which would flow in an infinitely long cable. Thus, the spatial decay of potential in a short cable is less steep and will be almost negligible when the cable is less than one space constant. On the other hand, in a low calcium medium (low resistance of the cut ends) the electrotonic potential is sharper, the shorter the cable (150, 307).

C. Response of the Membrane to Uniform Current

Hodgkin and Huxley (129) succeeded in inserting a metal electrode in the longitudinal direction into a giant axon of a squid, *Loligo*. By this procedure the internal resistivity is effectively short-circuited so that the current flow through the membrane is virtually uniform. Since r_a is now negligible the left side of equation (11) becomes zero; hence, the latter simplifies to:

$$\frac{V}{r_m} + c_m \frac{dV}{dt} = 0 \tag{18}$$

The solution to this equation for the case of a current which is suddenly applied at $t = 0$ is

$$V = V_\infty (1 - e^{-t/\tau}) \tag{19}$$

$\tau = r_m \cdot c_m$; this is known as the time constant of the membrane and determines the time taken for the voltage to rise to $1 - 1/e$, *i.e.*, to about two-thirds of the infinity value V_∞; when $V = V_\infty$, the voltage is given by

$$V_\infty = I_0 \cdot r_m \tag{20}$$

Hence r_m may be determined. Its value depends greatly on the size of the axon. When this factor is taken into account in calculating R_m, the values range between 1,000 and 10,000 $\Omega \cdot cm^2$. From this value and from the time constant the membrane capacitance may be calculated. This is usually of the order of 1 to 10 $\mu F/cm^2$.

The nerve value probably represents the true "membrane" capacity since the membrane in these preparations is a simple cylindrical surface, if surface unfoldings are ignored. However, it must be appreciated that in skeletal and cardiac muscle the membranes are arranged in a more complex fashion (70, 76, 82, 191, 265).

In general, the procedure for calculating the passive electrical parameters of a cable is relatively simple. The parameters which have to be determined are the input resistance (V_0/I_0), the space constant, the time constant, and the diameter of the cable. From these values, the electrical constants are calculated in the following way:

$$V_0/I_0 = r_i \cdot \lambda \tag{21}$$

and

$$\lambda^2 = r_m \cdot r_i \tag{22}$$

Since r_m and r_i are now known, R_m and R_i can be obtained:

$$R_m = r_m \cdot 2a\pi \tag{23}$$

and

$$R_i = r_i \cdot a^2\pi \tag{24}$$

The membrane capacitance is then obtained from

$$\tau = R_m \cdot C_m \tag{25}$$

where

$$C_m = c/2a\pi \tag{26}$$

It should be noted, however, that in a long fiber polarized at one point (which is the most probable situation cardiac electrophysiologists may be faced with) the time constant is not measured at 63% of V_∞ but at 84% (137, 307).

D. The Strength-Duration Curve

The constant current needs to be maintained only long enough for V_r to reach the threshold potential, V_{th}, in order to excite. The duration t_i required by a current of strength i_m will be

$$i_m = \frac{V_{th}}{R_m\,(1 - e^{-t_i/\tau})} \tag{27}$$

V_{th}/R_m is the steady state current which is required to take V_r to V_{th}. This current, *i.e.*, the current which succeeds in exciting when held on for a long period of time, is called the rheobasic current, i_{rh}. Hence

$$i_m = \frac{i_{rh}}{(1 - e^{-t_i/\tau})} \tag{28}$$

In general, it can be shown that for very small values of t_i

$$i_m \cdot t_i = i_{rh} \cdot \pi = Q_{th} = constant \tag{29}$$

or, in other words, a constant charge Q_{th} has to be applied to excite the cell. Since under these conditions the current necessary to excite will be considerably larger than the rheobasic current (*i.e.*, $i_m \gg i_{rh}$) the voltage changes will be determined by the capacity current alone (211).

E. The Hodgkin-Huxley Concept: Mechanisms of Excitation

When the electrotonic potential exceeds the threshold potential, the membrane becomes highly permeable to sodium ions. Thus, positively charged particles enter the cell according to their "driving force" and thereby shift the membrane voltage close to the sodium equilibrium potential, E_{Na}. Once the membrane potential has been depolarized beyond the threshold, the explosive increase in conductance becomes a "self-boosting" event; the sodium current is increased and shifts the membrane voltage toward more positive potentials, leading to a further increase in sodium conductance. However, this high sodium conductance is rapidly inactivated. Moreover, in response to depolarization, a time-dependent potassium current switches on. Positive K ions flow through the membrane in an outward direction leaving a negative charge behind so that the negativity inside the cell increases and repolarization occurs (fig. 2).

If this sequence of events occurs in nerve or muscle fibers, the impulse is conducted by amplifying suprathreshold depolarization of say 20 mV to a full action potential of 120 mV in amplitude. Thus, unlike electrotonic spread, such an impulse travels over long distances without any attenuation. The experimental evidence for this was derived largely from studies in nerve by Hodgkin and Rushton (137) and Hodgkin *et al.* (135) in Cambridge and by Cole (43) in the United States.

In the late forties, it became obvious that the currents underlying an action potential were *voltage-* (not current-) dependent besides varying with time. However, from equation (10) it can be seen that in a cable the current does not depend solely on voltage and time but it also may vary with distance. Therefore, in order to analyze the time dependence of currents, techniques had to be developed which, under experimental conditions, first, would eliminate the variation of currents with distance by preventing the flow of longitudinal current

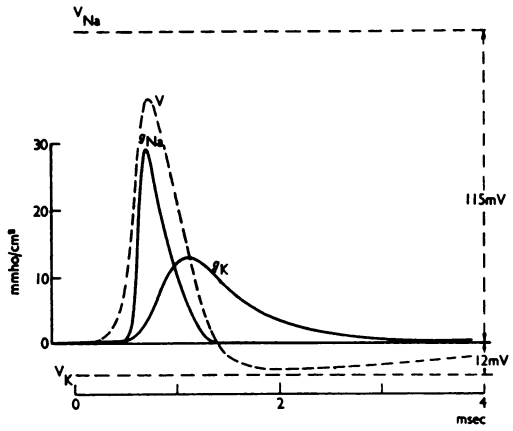


FIG. 2. Action potential (dashed line) and conductances (solid line) as computed by Hodgkin and Huxley (133) on the basis of "voltage clamp" experiments (see below). [From Hodgkin (128) with permission of the author and of the Liverpool University Press.]

and, second, would allow the membrane voltage to be chosen arbitrarily. Uniform polarization was obtained by Cole (43) and Hodgkin *et al.* (134) when they inserted two longitudinal electrodes into a squid giant axon. When this is done, the left side of equation (10) becomes zero since the internal resistivity is shunted out and no longitudinal current flows:

$$c_m \frac{dV}{dt} + i_i = 0 \qquad (30)$$

Furthermore, these authors were the first to introduce the technique of "voltage clamp" which made use of electronic feedback allowing the membrane voltage to be held at predetermined levels while the current necessary to achieve it could be measured. Using this method, Hodgkin and Huxley (130–133) analyzed the time and voltage dependence of sodium and potassium currents flowing at the membrane during excitation (fig. 3). Under these conditions, the ionic current is given by:

$$i_i = i_{Na} + i_K \qquad (31)$$

where

$$i_{Na} = g_{Na} \cdot (V_m - E_{Na}) \qquad (32)$$

and

$$i_K = g_K \cdot (V_m - E_K) \qquad (33)$$

g_{Na} and g_K are the conductances of sodium and potassium respectively. Thus, measuring the membrane currents and knowing the values of the equilibrium potentials (which can also be determined experimentally) one may calculate the conductances of different ionic current systems at any given instant (fig. 4).

In addition, Hodgkin and Huxley (133) formulated equations with which they could reconstruct not only the shape of the action potential but also the most important physiological parameters such as threshold of excitability and the refractory period. Imagine a process which may run between A and B in either direction:

$$A \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} B$$

A and B are two different stages and α and β are the rate constants of the forward and

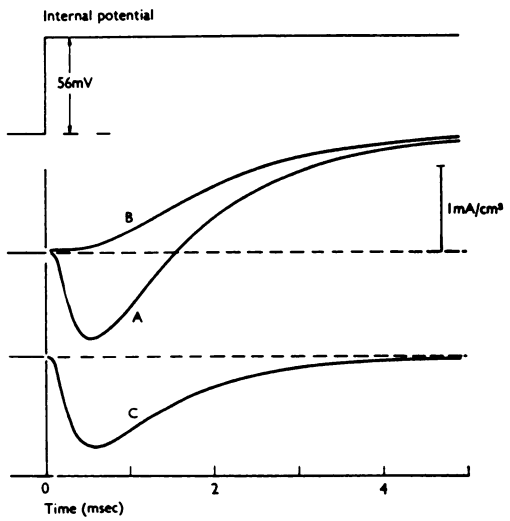


FIG. 3. Separation of membrane current into components carried by Na and K; outward current upwards. A, current with axon in sea water = $I_{Na} + I_K$. B, current with most of external Na replaced by choline = I_K. C, difference between A and B = i_{Na}. [From Hodgkin and Huxley (130) and Hodgkin (128), with permission of the authors and of the Liverpool University Press.]

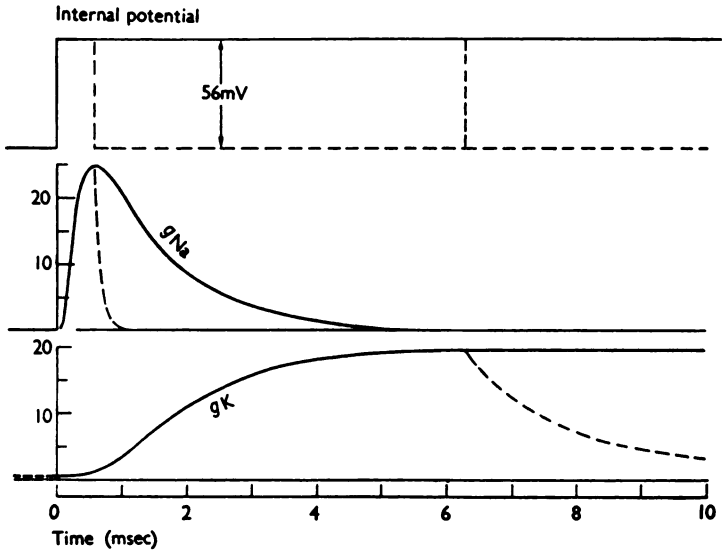


FIG. 4. Time course of sodium conductance (g_{Na}) and potassium conductance (g_K) associated with depolarization of 56 mV; the continuous curves, which are derived from those in figure 3, are for a maintained depolarization; broken curves give the effect of repolarizing the membrane after 0.6 or 6.3 msec. [From Hodgkin (128) based on Hodgkin and Huxley (130, 131), with permission of the authors and of the Liverpool University Press.]

backward reactions. The change in B with time may be described in the following way:

$$\frac{dB}{dt} = \alpha A - \beta B \tag{34}$$

Since

$$A + B = 1 \tag{35}$$

equation (34) may be rearranged:

$$\frac{dB}{dt} = \alpha(1 - B) - \beta B \tag{36}$$

If the system is in the steady state, *i.e.*, $dB/dt = 0$ then

$$0 = \alpha - (\alpha + \beta) \cdot B_\infty \tag{37}$$

Hence

$$B_\infty = \frac{\alpha}{\alpha + \beta} \tag{38}$$

The rate of change in B with time (which is the reciprocal of the time constant) will be obtained by adding the forward and backward reaction rates:

$$\tau^{-1} = \alpha + \beta \tag{39}$$

The sodium conductance is described as

$$\overline{g_{Na}} = g_{Na} \cdot m^3 \cdot h \tag{40}$$

where $\overline{g_{Na}}$ is a constant; m and h are dimensionless variables which are voltage and time dependent, behaving in a similar manner to B and controlling the degree of activation of a particular current system, *e.g.*, i_{Na}; m_∞ and h_∞ are the steady state degrees of activation of m and h.

The α's and β's are the rate constants of the dimension sec^{-1} which are voltage dependent only. Thus,

$$\frac{dm}{dt} = \alpha_m \cdot (1 - m) - \beta_m \cdot m \tag{41}$$

and

$$\frac{dh}{dt} = \alpha_h \cdot (1 - h) - \beta_h \cdot h \tag{42}$$

When $dm = dh = 0$ then

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m} \tag{43}$$

and

$$h_\infty = \frac{\alpha_h}{\alpha_h = \beta_h} \quad (44)$$

According to equation (39)

$$\tau_m^{-1} = \alpha_m + \beta_m \quad (45)$$

and

$$\tau_h^{-1} = \alpha_h + \beta_h \quad (46)$$

Similarly, the time and voltage dependence of the potassium conductance can be described:

$$g_K = \overline{g_K} \cdot n^4 \quad (47)$$

where $\overline{g_K}$ is a constant and n follows first order kinetics similar to B (see above). The power function is necessary to describe the S-shaped time course of the recorded potassium current (133).

The mathematical description as presented here is the simplest one of various possibilities but it does have the advantage that only first order differential equations are used. However, other models which also have been suggested contain partially second order equations representing in part an entirely different approach (73, 74, 143, 144, 151, 153, 199). Hodgkin and Huxley themselves deliberately avoided explaining the precise meaning of these parameters in physicochemical terms for which their classical concept has been challenged by different investigators, in particular Tasaki (280). Hodgkin and Huxley cautiously alluded to "sites" which had to be activated during depolarization. As yet, it must be emphasized that it is not known how conductance changes in the membrane are brought about although considerable advances have recently been made (7, 8, 122–126).

One of the attractive features of the Hodgkin-Huxley model lies in the fact that each of the parameters can actually be derived from experimental data (127, 128) and they can be influenced discretely by drugs with relatively specific electrophysiological actions. We may allude to "channels" which allow ions to traverse the membrane and which may be controlled by "gates." Such gates open and close continuously and the variables (for instance m) then determine how many m-gates are in the open position at a given moment (*cf.* equation 40). On the other hand, (1-h) indicates the number of m-gates that are in the closed position. In contrast $\overline{g_{Na}}$ is proportional to the number of sodium channels. In very simple terms, the sodium current can be influenced by plugging the sodium channels in all-or-nothing fashion or by changing the electrical field at the membrane, which results in a shift of the kinetics along the voltage axis. These mechanisms, either alone or in combination, appear to constitute the basis of action of the major antiarrhythmic drugs which have local anesthetic properties on nerve (see below). If it is assumed that there is a single sodium channel, equation 40 may be interpreted as implying that each such channel has three m-gates which open during depolarization and an h-gate which closes when the cell is depolarized [compare Noble (208) and fig. 5]. In the resting state the m-gates are closed whereas the h-gates are open. When the threshold is exceeded, the fraction of the open m-gates increases with a time constant of about 0.1 msec whereas it takes about 1 msec until the statistical distribution of open h-gates decreases significantly. Thus, for about an msec or so, both m- and h-gates are in the open position allowing the maximum rate of transfer of sodium ions into the cell. Thereafter, the h-gates close, switching off the excitatory sodium current. This process is known as *inactivation*. However, when depolarization beyond the threshold is brought about somewhat slowly, the threshold voltage is shifted in the positive direction. This event is due to two factors: 1) a diminution of the value of h, and 2) a rise in the value of n resulting in a "switch off" of the fast sodium current and a "switch on" of the potassium current. This sequence of events is known as *accommodation* (208). When the cell repolarizes, h regains higher values, that is, more h-gates

are open and the cell becomes excitable again. This is designated as *recovery from inactivation* and the time from the upstroke of the action potential until this occurs is known as the *refractory period* (fig. 6).

The *threshold potential* is determined by the "foot" of the s-shaped m_∞-curve provided that depolarization beyond the threshold takes place somewhat rapidly (see above). Hence, the variables m and h control the important parameters of an excitable cell: threshold and refractory period (4). The concept of separate activation (m) and inactivation (h) gates has recently gained strong support from the work of Armstrong *et al.* (8), who showed that the process controlling inactivation (h) can be destroyed by an enzyme, pronase, without effect on the activation (m) of the sodium current.

It is important to note that if a cable is polarized by means of an intracellular microelectrode at one point, the threshold potential is somewhat positive in comparison with a uniformly polarized fiber, since in a long cable the membrane potential varies with distance (fig. 1, *cf.* equation 16) and a certain "liminal length" of the fiber has to be depolarized in order to elicit a conducted response (158, 208, 211, 240). However, in comparison with the squid axon, the situation in heart muscle is much more complex. Anatomically, the cardiac membrane is not a pure cylindrical surface; instead, it covers fibers which are interconnected by low resistance pathways. In fact, the membranes of these cells are closely attached to each other forming narrow clefts in the depths of Purkinje fibers or of the cardiac muscle bundle. Because of this structural complexity, it is much more difficult to obtain a reasonably uniform polarization in these fibers. Furthermore, cardiac fibers are rather small so that no internal electrodes can be placed inside them in the longitudinal direction. Hence to be applicable in cardiac muscle, the original voltage

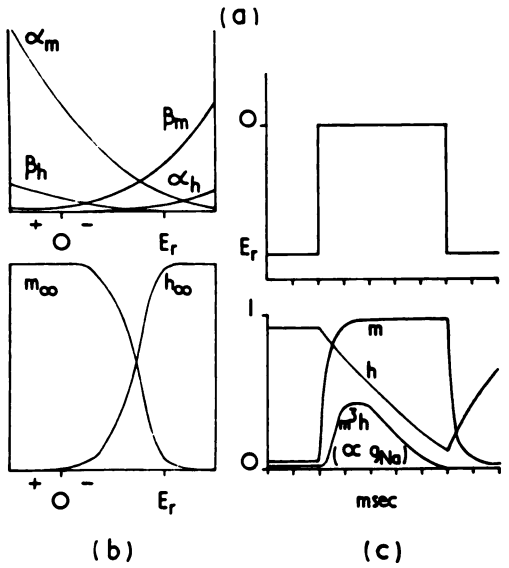


FIG. 6. Left, a, variations of rate constants with membrane potential. Left, b, variations of m_∞ and h_∞ with E_m. Right, c, response of m, h, and g_{Na} to sudden depolarization of membrane. [From Noble (208) with the permission of the author and *Physiological Reviews.*]

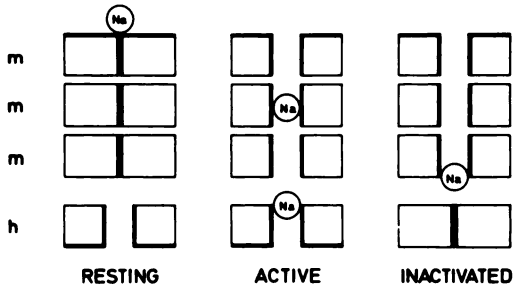


FIG. 5. Illustration of the Hodgkin-Huxley model of the sodium conductance showing a single sodium channel in three different states: resting, active and inactivated. According to the formulation $g_{Na} = \bar{g}_{Na} \cdot m^3 \cdot h$, there are three m-gates and one h-gate. During depolarization, the m-gates open with a time constant of about 0.1 msec and the h-gate closes with a time constant of about 1 msec. Note, that in this model *in*activation and *re*activation have to occur with identical time constants at a given voltage. In the illustration, m and h indicate the appropriate gates whereas in the equation above m and h are dimensionless variables which specify the fraction of the open gates. A single channel opens and closes within a time considerably shorter than the time constants mentioned. However, if h were to be 0.8, it signifies that 80% of the h-gates are in the open position whereas 20% are closed. [From Antoni (4) with permission of the author. F. K. Schattner Verlag G.m.b.H. Stuttgart and New York.]

clamp technique had to be modified in a number of important respects.

A spatial decay of the membrane potential may be avoided by limiting the length of the test preparation (*cf.* equation 18) as might be done by cutting Purkinje fibers into short cables of less than a space constant. Under these circumstances, close to uniform polarization can be obtained by applying current through an intracellular microelectrode at one point (56). However, using this arrangement, the excitatory sodium current cannot be measured accurately since membrane resistance is decreased to about 1/100th of its resting value during the upstroke of the action potential or during the initial phase of a depolarizing voltage clamp (310). Hence, the space constant ($\lambda = \sqrt{r_m/r_i}$) is decreased to about 1/10th. As a consequence, during the surge of the fast sodium current, about five space constants are clamped on either side of the microelectrode, which does not, of course, yield a uniform clamp. Moreover, microelectrodes usually have a very small tip diameter with a high resistance limiting the amount of current which can be injected into the fibers. However, it is noteworthy that under the assumption that the Purkinje fiber is a simple cable, Weidmann (307) calculated the resting membrane resistance (R_m) to be about 2000 $\Omega \cdot cm^2$, whereas the membrane capacitance (C_m) was found close to 12 $\mu F/cm^2$. Nevertheless, Weidmann was aware that the membrane area may have been underestimated and recent findings by Mobley and Page (191) show that in Purkinje fibers, the membrane area is about 10 times larger than might be expected in a simple cable. Therefore, they concluded that in Purkinje fibers R_m is about 20,000 $\Omega \cdot cm^2$ and C_m is only 1 $\mu F/cm^2$. Sommer and Johnson (265) have investigated Purkinje fibers by means of electron microscopy and they found that the clefts between the cells constituted a large series resistance and that R_m had to be at least 10,000 $\Omega \cdot cm^2$ in order to obtain a uniform polarization of the membrane. From their data, it may be safely concluded that the records of slower current changes are not seriously distorted.

A somewhat different approach was adopted in atrial and ventricular muscle by other investigators. In these preparations, an attempt was made to get an improved voltage control by insulating two sections of a muscle strip by means of sucrose (22, 33, 90, 98, 239) and feeding current through extracellular electrodes. The voltage is measured either with a microelectrode impaled close to the partition (single gap) or by means of a second partition (double gap). Using this "sucrose gap technique," it was originally hoped that the fast sodium current could be adequately measured (fig. 7). However, as Sommer and Johnson (265) and Johnson and Lieberman (156) have shown, the clefts between the cells do form a rather large series resistance across which there is considerable voltage drop during the attempt to control the membrane voltage. Beeler and Reuter (21), McGuigan (183), Léoty and Poindessault (174) and Connor *et al.* (45) have all shown that this series resistance may let the voltage run

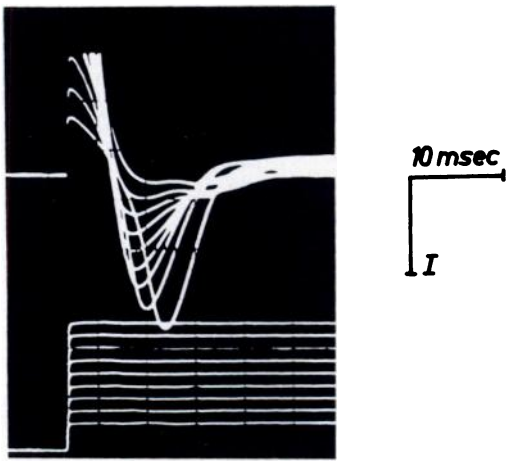


FIG. 7. Family of inward currents (upper traces) associated with step depolarizations (lower traces) ranging from 20 to 100 mV (10 mV steps). Holding potential = −60 mV. Maximum Na current occurs at −40 mV. Peak inward current and membrane potential are almost linearly correlated. The turn on of Na current is to some extent distorted by the capacity current (possibly also leakage current) related to the onset of the clamp. [From Haas, Kern, Einwächter, and Tarr (98) with permission of the authors.]

out of control during the surge of the fast sodium inward current. This series resistance increases during the course of the experiment when the sucrose is accumulating in the clefts, thereby also increasing R_i of the bundle. Although it appeared to be a matter of debate until relatively recently as to how good the voltage control in various cardiac preparations could be, during the last few years evidence has accumulated to indicate (45, 156, 183, 278) that the fast sodium current recorded under voltage clamp conditions in cardiac muscle can be measured but not with fine precision. It is therefore possible to perform neither a very detailed analysis of the sodium kinetics under control conditions nor to analyze relatively small changes under pharmacological conditions. In addition, Connor *et al.* (45), Jacobson *et al.* (152), and Atwell and Cohen (17) have shown convincingly that during the surge of the fast inward sodium current there is not only longitudinal but also radial nonuniformity. In other words, cells at the surface of the bundle may be relatively well clamped whereas those in the center of the bundle may function independently of "clamp." However, many of the data under these conditions are still likely to be real, at least in a qualitative respect. For instance, several authors (88, 98, 167) showed that the time constant of reactivation was much slower than inactivation of the fast sodium current. Although this relationship cannot be maintained strictly, it seems very likely that in cardiac muscle, *re*activation is a much slower process than inactivation (see below). However, it should be emphasized that results reported by Haas *et al.* (98) were obtained at rather low temperatures (6°C). It cannot of course be distinguished under these circumstances whether reactivation shows a single, double, or even a multiexponential time course. In this respect, the investigations of Dudel *et al.* (62) and Dudel and Rüdel (65) are technically interesting, although they do not contribute much to our present knowledge of the kinetics of the fast sodium current. Dudel *et al.* (62) studied the time dependence of the current records from which the parameters necessary to describe a current system in terms of the Hodgkin-Huxley theory cannot be extracted. Dudel and Rüdel (65), on the other hand, analyzed the kinetics of the fast sodium current in Purkinje fibers at low temperatures, thereby showing slowing down of the rapid kinetics of i_{Na}. Although the analysis is very detailed and elegant, it is not possible to extrapolate their findings to normal temperatures since the kinetics are not only slow but also shifted in the hyperpolarizing direction to a considerable extent. The 0.5 value of h_∞, for instance, is located at −140 mV and the threshold of i_{Na} (foot of m_∞) was found at −85 mV (See fig. 3 and 7).

The authors of this review do not agree with the view of Johnson and Lieberman (156) that virtually all the voltage clamp data are more or less artifactual, largely on the grounds of the arguments presented by Sommer and Johnson (265) themselves (see their fig. 48). It is our opinion nevertheless that apart from the fast sodium current, most of the voltage clamp results so far available from cardiac muscle are also scarcely beyond criticism but they do appear to be of sufficient validity to permit the analysis of voltage and time dependence of slower ionic currents flowing during the cardiac cycle. We do, however, agree that it is necessary to further improve the voltage clamp technique as applied to cardiac muscle in order to minimize the differences between the experimental tracings and the actual currents flowing at the surface membrane (see also ref. 78). In this context, it is noteworthy that Colatsky and Tsien (42), by using rabbit Purkinje fibers, have considerably improved on the existing techniques of clamping the fast sodium current in this tissue. It is of interest that the modified voltage clamp technique as used by Weidmann (308) obviates to a great extent many of the observed difficulties. He controlled a small area of the surface membrane in Purkinje fibers and measured the upstroke velocity (dV/dt_{max}), which, as might be expected from cable equations,

was proportional to the amount of the fast sodium current flowing inward. Clamping to different potentials and initiating action potentials from various levels, Weidmann measured for the first time an h_∞ curve in heart muscle. Since then this technique has been used commonly, having been modified by different investigators (27, 28, 119, 292) (fig. 8).

F. Modification of the Hodgkin-Huxley Model

According to the original HH-theory, at a given membrane potential in nerve, *in*activation and *re*activation are expected to occur with identical time constants. In contrast, in heart muscle such as frog atrial muscle (97, 98, 279), Purkinje fibers (88), and ventricular muscle (87, 88, 166), such is not the case. In these tissues it has recently been shown that *re*activation is a very much slower process than *in*activation (fig. 9).

Haas *et al.* (98) interpreted this finding by assuming that inactivation and reactivation were controlled by two different gates, designated p and q, both of which follow first order kinetics. In this case we may formulate the sodium conductance by replacing h:

$$g_{Na} = \overline{g_{Na}} \cdot m^3 \cdot p \cdot q \qquad (48)$$

where

$$\frac{dp}{dt} = \alpha_p \cdot (1 - p) - \beta_p \cdot p \qquad (49)$$

and

$$\frac{dq}{dt} = \alpha_q \cdot (1 - q) - \beta q \cdot q \qquad (50)$$

p has a short time constant (1–3 msec), whereas the q-gates are controlled by kinetics whose time constant is about 50 msec. Thus, during depolarization the statistical distribution of the open p-gates decreases quite rapidly; in contrast, after repolarization it takes a much longer time until the fraction of the open q-gates increases appreciably and the fast sodium current becomes available again (fig. 10).

Another important difference between heart muscle and nerve is the much longer duration of the cardiac action potential and the extraordinary variety and complexity of current components flowing during repolarization. For example, in cardiac Purkinje fibers, there are at least two components of pure potassium current labelled i_{K_1} and i_{K_2}; other current systems activated in the plateau range of potentials, which have been called i_{x_1} and i_{x_2}, are partially but not exclusively carried by potassium ions. Except for i_{x_2}, which is linear, all these out-

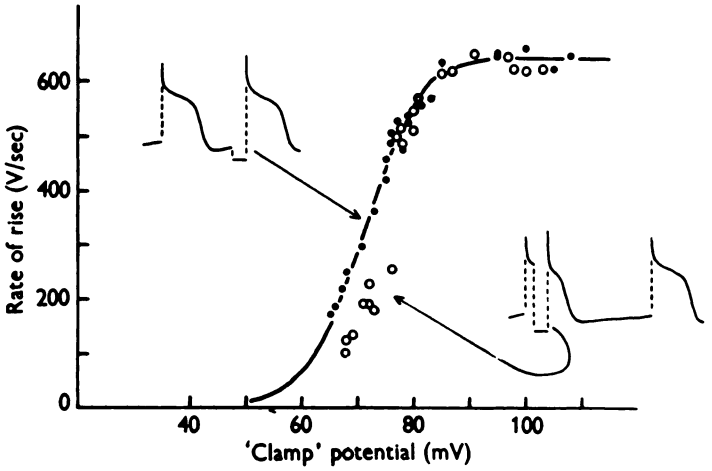


FIG. 8. Relationship between "clamp" potential and maximal rate of rise of action potential. Closed circles, values obtained with "clamp" in diastole. Open circles, values obtained with "clamp" during systole. [From Weidmann (308) with permission of the author and *Journal of Physiology.*]

ward current components show strong inward going rectification, i_{K_2} even with a marked negative slope (111, 180, 208, 212–214; see also 1). However, i_{x_2} does not appear to play a significant role during the course of the action potential since its time constant is too sluggish.

Current systems similar to i_{x_1} and i_{x_2} have also been described in frog atrial fibers (31) and in mammalian ventricular muscle (182). In the brief communication by McGuigan (182), the slow outward current was interpreted as a mixture of two currents x_1 and x_2 similar to those described for Purkinje or atrial fibers. A more detailed analysis showed that it was not possible to separate the tails at potentials negative to the resting potential into the sum of two exponentials (186). However, both in atrial and ventricular muscle the current components underlying the pacemaker activity in Purkinje fibers (i_{K_2}) appear to be absent (33, 182). From the work of Hoffman and Cranefield (139) it is known that neither atrial nor ventricular fibers normally generate pacemaker potentials. However, Engstfeld (69b) has shown that barium ions induce pacemaker activity in ventricular fibers. Hence, it may be asked whether a pacemaker system similar to that in Purkinje fibers does exist at all in these fibers or whether the activation range of a possibly existing pacemaker current component is usually so negative in these fibers that potentials necessary for the activation of this component are not reached during a normal cardiac cycle.

Dudel *et al.* (64) described a so-called "dynamic current" which was thought to be carried at least partially by chloride ions and which is of little importance in the inscription of the plateau other than occasionally producing a "notch" (86, 110, 180, 214). The reason for the relative insignificance of the i_{dyn} is that the latter is inactivated with a time constant of about 50 to 80 msec, which is somewhat short in relation to the total duration of the plateau of the normal Purkinje fiber. In addition, the time constant of *re*activation of i_{dyn} is very long (of the order of seconds) so that during the normal activity of the heart this current is always inactivated (222). This interpretation was challenged by Peper and Trautwein (220), who suggested that inactivation of the dynamic current provides the major source of outward current terminating the plateau. A very detailed analysis of the dynamic chloride current was recently published by Fozzard and Hiraoka (79). Haus-

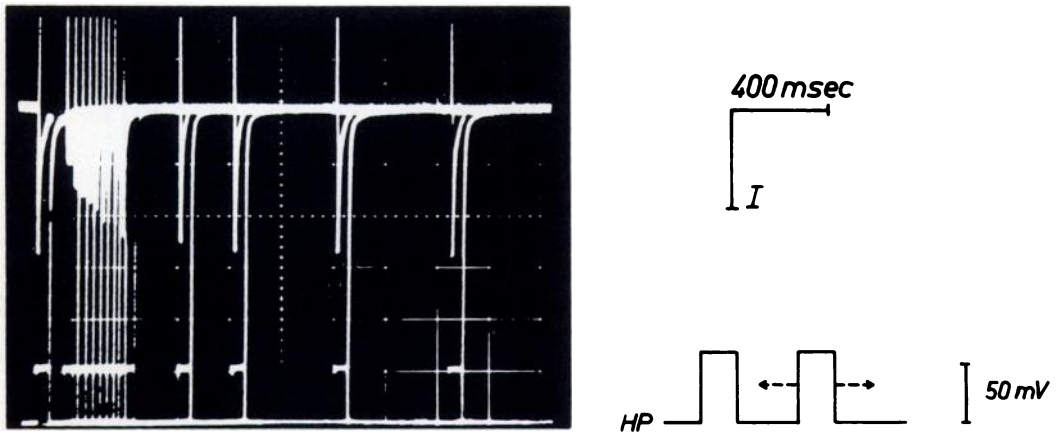


FIG. 9. Removal of Na inactivation after repolarization to the holding level, determined with two consecutive depolarizing pulses of 50 mV amplitude and 52 msec duration. Superimposed traces of membrane current (upper beam) and voltage (lower beam). Holding potential −70 mV. The conditioning pulse is shown at extreme left. The test pulse is initiated at various times after the end of the conditioning pulse. The vertical bars reaching the upper and lower edges of the screen are the capacity currents related to make and break of each pulse. Fast inward current is a short spike. [From Haas, Kern, Einwächter, and Tarr (98) with permission of the authors.]

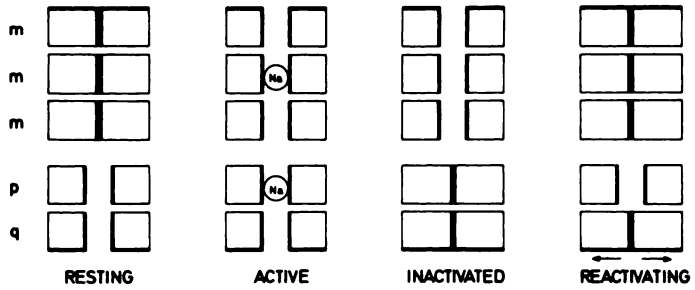


FIG. 10. Illustration of the model of the sodium conductance according to Haas, Kern, Einwächter, and Tarr (98). In frog atrial muscle, *in*activation and *re*activation occur with different time constants; thus, in this model, h was replaced by two variables, p and q, which represent two entirely different gating mechanisms. In the equation $g_{Na} = \overline{g_{Na}} \cdot m^3 \cdot p \cdot q$, both p and q are decreasing (closing) during depolarization. p has a time constant of about 1 to 3 msec, τ_q may be up to 50 msec or more, *i.e.*, during depolarization and shortly thereafter respectively, the p-gates close about 50 times as quickly as the q-gates do. After termination of the plateau and full recovery of the normal resting potential, the p-gates open, of course, rather quickly; the q-gates, however, take somewhat longer until a larger fraction of them is in the open position. Hence, the "effective refractory period" may considerably outlast the duration of the action potential.

wirth *et al.* (110) and Noble and Tsien (215), on the other hand, showed that the dynamic chloride current cannot be responsible for the maintenance or termination of the plateau and the generation of the "notch" at the same time or during the same action potential. However, the precise functional significance of the dynamic chloride current is still unclear and merits further experimental investigation. Siegelbaum *et al.* (251) recently showed that some of the time and voltage dependence of the "dynamic current" (i_{qr}) arises from the same mechanisms underlying i_{si} as well as contraction. These findings have two important consequences: first, the ionic basis of the transient outward current still remains uncertain; and second, the apparent dependence of i_{qr} on the intracellular calcium raises fundamental difficulties for the analysis of the slow inward current in Purkinje fibers.

Another current component is the so-called second slow inward current which has become increasingly important during the last few years and which is thought to be largely carried by calcium ions (20, 22, 67, 168–170, 185, 205, 206, 217, 221–223, 227, 238, 277, 287, 288, 293, 304). This current system shows activation and inactivation kinetics similar to those of the fast sodium current by having very much slower characteristics. According to the HH-formulation, this current has been described in mathematical terms:

$$i_{si} = \bar{i}_{si} \cdot d \cdot f \qquad (51)$$

where i_{si} is the fully activated current-voltage relationship of i_{si}; d and f are dimensionless variables analogous to m and h which control the degree of activation and which likewise follow first order kinetics. This current component is involved in the slow conduction of impulses which are travelling around anatomical loops in some cases of experimentally-induced arrhythmias (320, 321) despite the fact that the fast sodium current is completely inactivated. In these cases, the conduction velocity may be as low as 1/100th of the normal value.

Recently, Lederer and Tsien (173) described an entirely new current system which they called "transient inward current" (TI). This current component is induced by cardiac glycosides or high external calcium concentrations and is evoked by repolarization following relatively long lasting depolarizations to the plateau level. This current system causes a so-called "transient depolarization" (TD) described by Ferrier and Moe (71), Hashimoto and Moe (103), and Saunders *et al.* (243). Although this current is time-dependent (160, 173) it does not show typical HH-kinetics.

The TI is sensitive to external calcium and inhibited by manganese ions. This is consistent with the belief that the TI represents a transient calcium influx (71) but sodium, potassium, chloride, and hydrogen ions have been excluded as charge carriers of the TI (160). Low sodium or high external calcium yielded large TI's in the absence of cardiac glycosides. No information is available yet whether the TI may depend upon elevated internal calcium levels. Moreover, it is not entirely clear whether TI and i_{si} pass through separate or identical channels. Although neither possibility could be definitely ruled out, it seems rather unlikely that the TI is carried by the channels of the slow calcium inward current since the latter behaves differently in many respects: i_{si} is activated during *de*polarization, TI is triggered following *re*polarization; replacement of calcium ions by strontium enhances i_{si} but reduces TI. In addition, tetrodotoxin (TTX) blocks TI in contrast to i_{si} (160). Likewise, the onset and recovery of blockade of both currents by manganese ions show different time constants (160).

The TI appears to be the current which would be needed to depolarize the cardiac fiber beyond the threshold shortly after termination of an action potential. Müller (200) has shown that cardiac glycosides may induce spontaneous activity and low voltage oscillations in Purkinje fibers; however, in ventricular fibers, they only cause a slight shortening of the action potential. Since ventricular extrasystoles are usually triggered by the Purkinje system (200, 201) it is very likely that the TI is responsible for the ventricular extrasystoles following each normal beat (pulsus bigeminus) which are often seen in digitalis intoxication (see below).

It is not our aim to review exhaustively all the current components believed to be flowing during a cardiac cycle. This has been reviewed elsewhere (180, 209, 210, 287). As an example of one of the K-currents which is of particular significance, we shall deal with the current underlying pacemaker activity in Purkinje fibers which was labelled i_{K_2} by Noble and Tsien (212):

$$i_{K_2} = \overline{i_{K_2}} \cdot s \tag{52}$$

where $\overline{i_{K_2}}$ is a function of voltage only and s is a variable which follows first order kinetics:

$$\frac{ds}{dt} = \alpha_s \cdot (1 - s) - \beta_s \cdot s \tag{53}$$

G. The Mechanism of the Pacemaker Potential

The events underlying the pacemaker potential, at least in the Purkinje fiber, are much simpler than the rather complicated mechanism on which the kinetics of the fast sodium current are based. Unlike the latter, the pacemaker current is only controlled by a single process which is activated during depolarization and which is deactivated when repolarization takes place. Expressed very simply, the pacemaker current is fully switched on when the fiber repolarizes and reaches the maximal diastolic potential. At this level, however, the steady state degree of activation of i_{K_2} (S_∞) is almost zero (fig. 11).

In order to approach the steady state value, i_{K_2} deactivates (*i.e.*, the fraction of the open s-gates decreases) with a time constant of about 1 to 2 sec. After about 1.6 sec, s crosses s_∞ and thereafter s has to rise again since s_∞ now has a larger value than s (212) (fig. 12).

However, because of the negative slope of i_{K_2} (34, 101, 111, 212, 296, 297) the absolute value of the pacemaker current is further diminished despite the fact that the degree of its activation now *in*creases. Thus, the membrane potential eventually reaches the threshold (299) or, if there is time enough for sufficient outward current to be activated, it undergoes damped oscillations (311).

To test the validity of the above concept, one may scrutinize the experimental records of Weidmann (306). During the course of the pacemaker potential, he injected

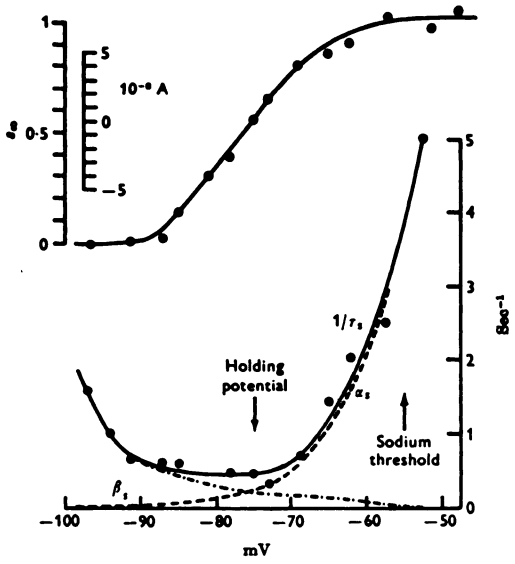


FIG. 11. Voltage dependence of kinetics of i_{K_2}. Top, voltage dependence of fractional activation (S_∞) in the steady state measured as the peak current change from background on return to holding potential (−75 mV). Ordinates: peak current and s. Abscissae: membrane potential (as in bottom curves). Bottom, points show measured values of τ_s^{-1}. Interrupted lines show α_s (dashed line) and β_s (dashed-dotted line) calculated from $\tau_s^{-1} = \alpha_s + \beta_s$ and $s_\infty = \alpha_s/\alpha_s + \beta_s'$ using continuous curves for s_∞ and τ_s drawn by eye through points. Arrows show position of sodium threshold and of holding potential. Temperature 36°C $[K]_o$ = 4 M. [From Noble and Tsien (212) with permission of the authors and *Journal of Physiology*.]

small current pulses into the fiber and recorded the appropriate voltage change with a second intracellular microelectrode. Terminating a depolarizing pulse, the diastolic depolarization was less steep; following a hyperpolarizing pulse, the steepness of the pacemaker potential increased. Weidmann's (306) results are in close agreement with the predictions of the model described above. Recently, it has been possible to show that the chronotropic effect of small current pulses could be reconstructed (106) using a mathematical model (106, 180) including equations (52) and (53).

On the general subject of pacemaker phenomena in cardiac tissues, it should be appreciated that while the normal pacemaker potential of Purkinje fiber has been best studied (210), increasing evidence points to the possibility that pacemaker activity in the sinoatrial node or pacemaker phenomena in cardiac arrhythmias may have distinctly different ionic mechanisms (9, 109, 269). Although a technique permitting voltage clamp experiments in the sinus node has recently been described (216), most of the currently available information on the ionic mechanisms underlying phase 4 depolarization in sinus node cells is still inferential however, being derived from voltage clamp experiments performed on isolated atrial trabeculae from the frog heart (31, 33); the data suggest that the decay of i_{K_2} is an unlikely mechanism for pacemaker

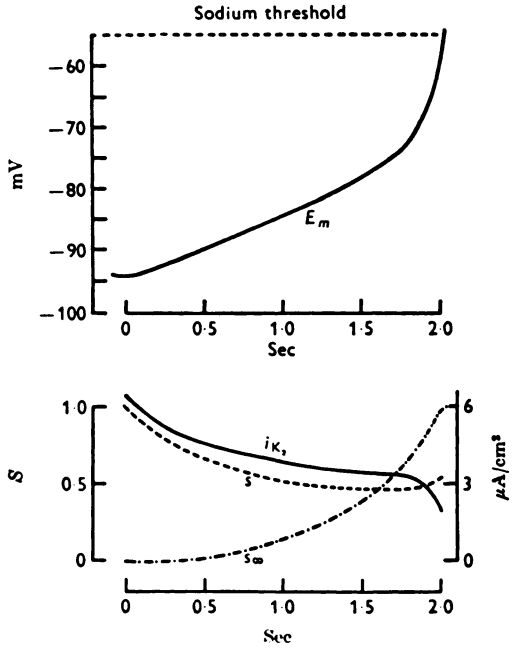


FIG. 12. Mechanism of the pacemaker potential based on the kinetics of i_{K_2}. Top, variation in membrane potential during pacemaker activity, replotted from Vassalle (299, fig. 1). Bottom, the steady state degree of activation (s_∞ in fig. 11) was "translated" from its voltage dependence into time dependence using Vassalle's (299) pacemaker potential; the time course of s and i_{K_2} was calculated using a numerical approximation of equation 31 and the rectifier function for 2.7 mM shown in figure 19. Note, that although s does not fall below a certain value and actually increases toward the end of the pacemaker potential, i_{K_2} falls continuously. This is a consequence of the negative slope in the rectifier function. [From Noble and Tsien (212) with permission of the authors and the *Journal of Physiology*.]

potential in the sinoatrial node (109, 269). For example, the voltage range over which phase 4 depolarization is found in sinoatrial nodal cells is one where pacemaker current in Purkinje fiber (i_{K_2}) is fully activated. In the absence of a voltage shift in the activation curve, this current could not thus generate diastolic depolarization in the sinoatrial node (31, 32). Also, the slope of phase 4 in sinoatrial nodal cells is more resistant to the depressant effect of enhanced extracellular potassium concentration when compared to Purkinje fibers (139, 283). Furthermore, although it appears that much of the background inward current is carried essentially by sodium in Purkinje fibers as indicated by the reduction in the slope of phase 4 depolarization in low sodium media (59), in the sinoatrial node, a decrease in extracellular sodium produces little effect on the slope of phase 4 depolarization (139). Finally, the demonstration that Mn^{++} can block pacemaker activity in depolarized frog atrial fibers suggests that the second inward current (i_{si}) may play a significant role in the generation of pacemaker potentials (269). Such a mechanism may also mediate the genesis of certain types of abnormal automatic rhythms under pathological conditions (see below), an understanding of which may be crucial in their control by pharmacological interventions.

H. Mechanisms Underlying Repolarization

The mechanisms of repolarization in cardiac muscle and in Purkinje fibers have recently been reviewed by Noble and Tsien (215), McAllister *et al.* (180), Noble (210), and Trautwein (287). There is general agreement as to the current components contributing to the plateau of Purkinje fibers, perhaps with the exception of the dynamic chloride current, which is not considered by Noble and Tsien (215) as a current source of major importance to the plateau.

A slowly inactivated inward current was investigated by Reuter (221) and by Vitek and Trautwein (304). Reuter (221) found in sodium-free solution a calcium current which was activated in the plateau range of potentials and in Tyrode solution an inward current which was partially and slowly inactivated and partially maintained. The existence of this current component was subsequently confirmed by Vitek and Trautwein (304), who demonstrated that the latter is not a slowly inactivated component of the fast sodium transient; rather, it is a distinct second inward current.

Although it is not yet clear which ionic species are carrying this current, experimental results of Reuter (221) and Vitek and Trautwein (304) indicate that this current system contains sodium and calcium ions. This would be consistent with the experimental findings that the plateau is considerably shortened in low sodium solutions and that the height of the plateau is dependent on the external calcium concentration (221). The other basis of repolarizing currents is an outward current, carried largely but not exclusively by potassium ions, which is activated in the plateau range of potentials with a time constant of about 1 sec. This current system shows marked inward going rectification and has been designated i_{x_1} by Noble and Tsien (213, 214).

In Purkinje fibers, the second slow inward current is inactivated with a time constant of about 100 msec during the beginning of the plateau (304). In ventricular muscle, inactivation takes place with a time constant of about 40 to 60 msec at 0 mV (170, 205, 206, 288, 291). At more positive potentials, (−40 mV) inactivation is slowed to about 280 msec (205, 206). It should be emphasized that the contribution of different current components to the plateau varies between, for instance, Purkinje and ventricular fibers (205, 215, 287). However, there is still controversy regarding the relative contribution of these currents to the plateau of Purkinje fibers (110, 180, 214, 220, 288, 304).

Trautwein *et al.* (291) believe that inactivation of the second slow inward current provides the larger part of repolarizing current whereas Noble and Tsien (215), Noble (210), and Hauswirth *et al.* (110) attribute the net outward current terminating the plateau largely to the activation of the outward plateau current, i_{x_1}. For details of the arguments, see Noble and Tsien (215), McAllister *et al.* (180), Noble (210), and Trautwein (288). However, it should also be remembered that in different Purkinje fibers the duration of the action potential varies greatly and hence the relative contribution of the different current components to long and to short plateaus may also differ considerably. The results reported by Vitek and Trautwein (304) show that inactivation of the slow inward current plays a major role at the beginning of repolarization with a short plateau of about 300 msec since inactivation is a relatively long lasting process in comparison to the phase of repolarization. In these fibers it is possible that the slow inward current could provide the major source of the time-dependent current changes during the plateau (304). The relatively short inactivation time constant of this current system (about 100 msec at 0 mV and about 90 msec at −25 mV) would make it rather unlikely that this process could be the only time-dependent current change during long lasting action potentials of about 500 to 900 msec. In these cases repolarization is caused by the activation of an outward current (i_{x_1}) whose time constant in the plateau range of potentials is about 1 sec (110, 180, 210, 213, 214). In ventricular fibers, however, inactivation of the second slow inward current may be of greater importance than in Purkinje fibers.

In figure 13, the voltage changes are summarized with respect to the flow of various current components during the course of the normal Purkinje fiber action potential. The upstroke is generated by rapid activation of i_{Na} followed by inactivation occurring near the peak of the overshoot potential. This event is followed by the activation and inactivation of i_{qr} and i_{si}, which, over a relatively large voltage range, overlap with each other. i_{qr} does not play a significant role in the repolarization phase of the action potential and its true significance remains unclear. However, the inactivation of the second slow inward current (i_{si}) provides sufficient movement of positive charge in the outward direction so that it may be considered to be the major source of repolarizing current during the first 100 to 200 msec after the onset of repolarization. Thereafter, i_{x_1} acquires sufficient activation to provide the source of outward current to complete the repolarization process and to terminate the plateau. After repolarization,

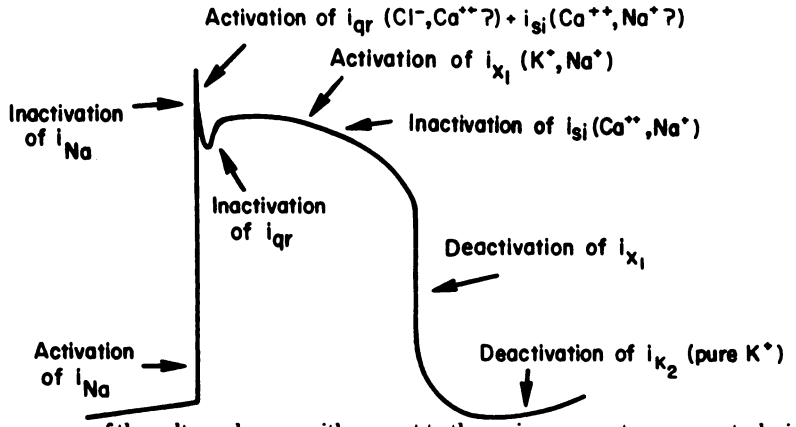


FIG. 13. A summary of the voltage changes with respect to the various current components during the course of a normal Purkinje fiber action potential. The arrows indicate the potentials and the tissues at which the current components described above switch on and off to inscribe the normal action potential (see text).

i_{x_1} deactivates as does the pacemaker current (i_{K_2}) allowing the background inward (?sodium) current to depolarize the fiber.

III. Membrane Factors in Arrhythmogenesis

Since the early discussions of Mines (190) and Schmidt and Erlanger (247), electrophysiological factors relative to alterations in impulse propagation and automaticity in the genesis of clinical and experimental arrhythmias have successively been reviewed by different investigators (3, 30, 138, 192, 194, 210, 231, 244, 270, 271, 273, 274, 285, 286, 311, 312). The literature on the subject continues to grow almost exponentially with the recent emphasis on attempts to delineate ionic mechanisms underlying the genesis of various forms of cardiac arrhythmias (9).

It is widely appreciated that the normal cardiac rhythmicity is maintained by 1) the dominance of a single pacemaker discharging with the highest frequency, 2) fast and generally uniform conduction in predetermined pathways of impulse transmission, and 3) long and uniform duration of the action potential and of the refractory period of the fiber as well as the fact that the duration of the Purkinje fiber action potential normally outlasts that of the ventricular action potential thus providing the safety factor for the orderly conduction of the depolarizing impulse. Clearly, unusual shortening of the action potential duration and of the refractory period, excessive slowing of the conduction velocity or marked dispersion in the recovery of the refractory period and thus of excitability as indicated by varying rates of repolarization in subjacent ventricular fibers, are likely to be proarrhythmic. It has become customary (25, 51, 141, 322–324) to consider the problem of arrhythmogenesis under categories of altered impulse formation (*i.e.*, arrhythmias due to enhanced automaticity) and of impulse propagation (*i.e.*, arrhythmias due to reentry). Evidence, however, is accumulating to indicate that altered cardiac excitability does not readily fit into this simplistic scheme and it may constitute a discrete subdivision of arrhythmogenic mechanisms (11–13, 58, 80, 100, 275). The knowledge about the changes in membrane currents and ionic conductances underlying these different arrhythmogenic processes—automaticity, reentry and altered excitability—is still limited but is clearly relevant to the control of these electrophysiological derangements by pharmacological means.

A. Focal Activity

The tempting simplicity of an ectopic focus as an arrhythmogenic mechanism stems from the fact that typical voltage tracings from intracellular recordings such as oscillations found in the pacemaker region of the heart as well as in the plateau range of potentials in other myocardial fibers may be correlated directly with disorders of rhythm (5, 36, 69b, 109, 145, 191, 245, 246, 273, 274, 285, 286, 289, 311, 312). In general, ectopic focal activity is dependent on a latent or potential pacemaker becoming regenerative with the capacity to fire independently. This may result from 1) an increase in the steepness of the slope of the diastolic depolarization, 2) a shift of the threshold potential to more negative values, and 3) a decrease in the maximum diastolic potential (V_{mdp}), the latter approaching threshold and the fiber becoming more excitable. If the diastolic depolarization is rapid, phase 0 of the action potential will be sodium-dependent; if it is slow, the sodium system is likely to be inactivated by the process of accommodation to a variable degree (211) and the phase 0 may become dependent on the slow inward current (47). Focal activity, initiated from the range of normal resting potential (*i.e.*, between −70 to −90 mV) as described by a number of investigators (69b, 218, 311), may be preceded by a subthreshold oscillation (103, 218, 311); since the resulting action potential will be closely related to the availability of the fast sodium inward current, the pacemaker activity in this range of potentials will be depressed by reducing the availabil-

ity of the sodium current as by local anesthetics (27, 28, 309; see below) or by increasing the steady state degree of activation of the current underlying pacemaker activity (i_{K_2}). In contrast, the oscillatory activity at lower membrane potentials (*i.e.*, in the range of −40 to +10 mV), over which range the fast sodium current is completely inactivated (308), is thought to be controlled by two other current systems (*i.e.*, i_{x_1} *and* i_{si}).

B. Oscillatory Activity at the Plateau

The current voltage relationship in heart muscle is N-shaped and shows three intersections with the voltage axis. This N-shape becomes obvious in "all-or-nothing repolarization" (299, 306) or by means of voltage clamping through a larger range of potentials (109, 213). Thus, heart muscle fibers have two stable states, the resting potential and, if the inward background current is increased, a "resting voltage" somewhere near the plateau. Moreover, it has been shown in Purkinje fibers that oscillatory activity at the plateau range of potentials can be maintained if the current-voltage relation is very flat and if it has a slight negative slope. Under these circumstances minute current changes produce comparatively large changes in potentials (109). Oscillations at the plateau have been recorded in Purkinje fibers which have failed to recover fully from the initial "shock" of excision of the tissue. Such low voltage oscillations have also been observed in low external K-concentrations (35, 201), in anoxia (285, 311), in chloride-free solutions (145), in solutions of very low ionic strength (289), following treatment with ouabain (200), dinitrophenol (285), aconitine (247), and in Na-free and Ca-rich solutions (14, 15, see below). From the standpoint of the genesis of clinically relevant arrhythmias, low voltage oscillations may be particularly significant in hypokalemia, digitalis glycoside toxicity, and in anoxia or ischemia, in which sodium-mediated inward current ("fast response") may be inactivated to varying degrees (172).

C. Mechanism of Low Voltage Oscillations

A possible mechanism underlying low voltage oscillation has been presented in detail by Hauswirth *et al.* (109). A single cycle of oscillation may be represented by a closed trajectory (72, 157). A point on this trajectory represents the potential and net ionic current at a particular time during the cycle. It also determines the position of the instantaneous current voltage relation at that time. An upward movement of the current voltage relation is generated by the activation of x_1 which approaches its steady state value ($x_{1\infty}$) according to a first order differential equation (213). The variation in x_1 may also be described by a trajectory in the x_1, V plane (fig. 14).

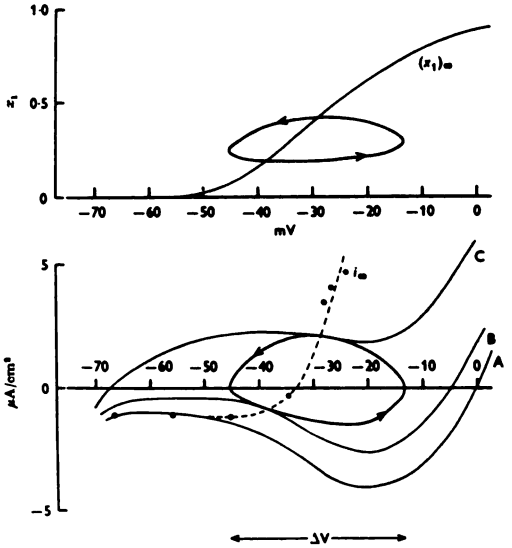


FIG. 14. Phase plane representation of mechanism of oscillation. Top, sigmoid curve shows experimental relation between $(x_1)_\infty$ and the membrane potential. [From Hauswirth, Noble and Tsien (109).] The closed trajectory shows possible variation in x_1 during oscillation. Bottom, points show steady state membrane current measured experimentally. Curves labelled A, B, and C show probable instantaneous current voltage relations when x_1 is zero (A) and when x_1 has minimum (B), and maximum (C) values reached during oscillation. The closed trajectory illustrates a way in which current and voltage may vary during oscillation. Further description is in the text. [From Hauswirth, Noble and Tsien (109) by permission of the Cambridge University Press.]

In the range of potentials over which the oscillations occur the current voltage relations are fairly flat (*i.e.*, the slope conductance is always small) so that relatively small current changes will give rise to large variations in the points at which the current-voltage relation intersects the voltage axis. The variation in the stable point voltage (V_{SP}) during the oscillation may therefore be much larger than the variation in membrane potential itself, which is limited by the rate at which the membrane capacitance can be charged by the small net ionic currents. Conversely, since very small current changes are required, only minor changes in the activation variable, x_1, will occur. Hence, the oscillations may occur at a frequency which is high compared to that which might be expected if time were needed for large changes in x_1 to occur. Thus, the time constant of x_1 is of the order of 1 sec whereas each half cycle of the oscillation is often smaller than this.

D. Conditions for Quiescence and Instability

It can be seen from figure 14 that, during each cycle, x_1 must equal $(x_{1\infty})$ at two points corresponding to the maximal and the minimal values of x_1. Since one of the conditions for quiescence is that $x_1 = (x_{1\infty})$, it may be asked as to what ensures that the oscillation is maintained. A quiescent potential requires not only that $x_1 = (x_{1\infty})$ but also that the net ionic current should be zero. This condition is obviously not satisfied at the maximal and the minimal values of x_1 in figure 14 since ionic current flowing at these times ensures that the potential should continue to change beyond a point at which $x_1 = (x_{1\infty})$. However, the condition for zero current will be satisfied at a point *within* the closed trajectory of x_1, V or of i, V, and this point is given by the intersection of the steady state current voltage relation with the voltage axis. This is shown in figure 14 as the interrupted line and the point at which it intersects the voltage axis is called the center (157).

In order for the center to form a possible quiescent potential it must be stable. An adequate condition for stability is that the slope of the instantaneous current voltage relation at this point should be positive. In this case, the amplitude of the oscillation will depend on the initial conditions and the oscillation will be damped. However, some preparations which are initially quiescent and which do not show a marked negative slope conductance in the oscillation range may, nevertheless, oscillate for a prolonged period or even indefinitely following the application of a short pulse. In general, it can be shown that the condition for instability is

$$-(\partial i/\partial V)_t \gg \tau_1^{-1} \cdot C_m \qquad (54)$$

where $(\partial i/\partial V)_t$ is the instantaneous slope conductance. From this equation it can be seen that the condition for instability is that the slope conductance should be negative and that its magnitude should be greater than $\tau_1^{-1} \cdot C_m$. Since C_m is about 10 μF/cm^2 and τ_1^{-1} is about 1 sec^{-1} the minimum negative slope conductance required for instability is about 0.01 mmho/cm^2 or about 0.1 μA/cm^2/10 mV. In a typical preparation with a membrane area equal to about 0.05 cm^2, the current in response to a 10 mV step would be about $5 \cdot 10^{-9}$ A. It is difficult to obtain reliable measurements of currents as small as this under voltage clamp conditions in most experiments so that the negative slope conductance in an oscillating preparation may not be very apparent experimentally.

It is, however, significant that preliminary voltage clamp experiments (114) have shown recently that, unlike the mechanism proposed above by Hauswirth *et al.* (109), the net inward current during low voltage oscillation may be provided by the second slow inward current (i_{si}) whereas the net outward current necessary for repolarization is generated by i_x.

Of particular significance in this context are the observations of Aronson and Cranefield (14, 15), who showed that low voltage

oscillations in Purkinje fibers may also be obtained in Na-free and Ca-rich solutions. Although the voltage clamp data in such preparations are not definitive, it is nearly certain that the net inward current during depolarization may be mediated essentially by the passage of Ca ions through the slow channel (i_{si}). The action potential generated by such an ionic mechanism has been termed the "slow response" (47); i_{si}-dependent sustained rhythmic activity may occur normally in the sinoatrial node and the AV node (47, 77, 317, 327) as well as in the simian mitral valve (318). Slow channel activity of this type, however, appears to be of potentially greater significance in the genesis of experimental and clinical cardiac arrhythmias (47). Available data indicate at least two discrete forms of electrophysiological phenomena mediated by the slow response. The first (to be discussed under "Reentry"), appears to be associated with the development of reentrant arrhythmias due to unidirectional block and very slow conduction (47, 321). The other mechanism described as low voltage oscillations in short preparations (109) and in longer Purkinje fibers (15), also mediated largely by changes in slow channel activity, may be involved in some forms of focal ectopic arrhythmias. It appears possible that slow depolarization, designated "slow calcium response" (or calcium spikes) by Surawicz (270), can induce spontaneous propagation of action potentials without the primary assistance of impulses initiated by automatic activity in other parts of the heart. Such focal activity, which may be accentuated by catecholamines (47, 272), has been found, for the most part, to be stimulus-dependent (50) but a spontaneous generation of slow response automaticity has also been observed. For example, a rapid succession of calcium-dependent depolarizations has been demonstrated in Purkinje fibers after depolarization had been induced by square wave cathodal pulses (146). Furthermore, spontaneous depolarizations occurred after release of voltage clamp in short segments of canine Purkinje fibers; the amplitude of such depolarizations correlated with the strength of the inward current flowing at the time of clamp release (6). These overall data thus suggest that under appropriate experimental conditions, single or repetitive depolarizations of a spontaneous nature may develop in partially depolarized cardiac muscle due to the local action of calcium, catecholamines, or other depolarizing influences. Of particular clinical relevance are hypoxia and ischemia which can enhance automaticity and are known to depolarize the resting membrane resulting in a decrease in $\dot{V}_{max}$ of the action potential (47, 83, 84, 172). Hypoxia may depolarize the resting membrane more than it affects V_{th}—an effect that might accentuate automaticity.

Oscillatory activity induced by some other potentially arrhythmogenic influences also need to be considered. For instance, low voltage oscillations induced by markedly depressed external potassium concentrations have been demonstrated in the plateau range of potentials (35, 36, 201); in this setting normal resting membrane potential could be restored when the external K-concentration was elevated to normal levels. Hypokalemia is known to enhance automaticity, decreasing the current needed to attain threshold by causing maximum diastolic potential to approach V_{th} while increasing membrane resistance (58). Moreover, evidence has recently accumulated to indicate that digitalis-induced automaticity may be mediated by oscillations in diastolic membrane potential of a different nature than those of "normal" pacemaker activity (9, 71). A number of discrete mechanisms for digitalis-induced automaticity have been described at least in the Purkinje fibers. Digitalis has been shown to decrease the magnitude of i_{K_2} without effect on its voltage-dependence for activation (16). The suggestion has also been made that digitalis may block the electrogenic sodium pump with the resulting decrease in the time-dependent outward current (149).

Although it has been postulated that digitalis may alter the slow response (i_{si}), a clear dependence of digitalis-induced automaticity on the i_{si} is unlikely in light of the experimental work of Lederer and Tsien (173). Perhaps the most likely basis for enhanced automaticity after digitalis may be related to transient inward depolarization, T_i (243), or oscillatory afterpotentials (71); the ionic mechanism of such oscillatory activity is however unclear as yet, but it appears to be distinct from i_{K_2} or i_{si} (173). TI, normally absent or negligible in magnitude, is augmented by high concentrations of Ca, by low concentrations of K, and by moderate degrees of stretch of the fiber; it is considered to provide a mechanism of automaticity responsible for complex atrial and ventricular arrhythmias following digitalis intoxication (9). It must nevertheless be emphasized that this is not the only mechanism of digitalis-induced arrhythmias. Toxic concentrations of cardiac glycosides are known to produce excessive slowing of conduction permitting reentry (see below). Reduction in conduction in this setting may be due to the decoupling effect of digitalis on cardiac cells (313), to the decrease in the resting membrane potential due to loss of intracellular K (200), and to the shift of the h_∞-curve in the hyperpolarizing direction (163).

E. The Interval-Duration Relation

It has been known for some time and recently has been substantiated in greater detail (86, 110) that the duration of the action potential in Purkinje and ventricular fibers is dependent on the frequency of stimulation. When a premature action potential is elicited in Purkinje or ventricular fibers the duration of the second impulse becomes shorter depending on the degree of prematurity of the stimulus. Similarly, it is known that the duration of the action potential is shortened when the preparation is stimulated regularly at a high stimulus frequency. Moreover, in accordance with the low value of h, a premature action potential has been shown to have a very low rate of rise (308) with a very low conduction velocity of the conducted impulse. It has been demonstrated by Gettes *et al.* (86) and by Hauswirth *et al.* (110) that the interval-duration relation in Purkinje fibers describes a similar time course as the time constant of the outward plateau current, i_{x_1} (see above). Action potentials obtained by numerical computation on the basis of a mathematical model also show abbreviation and a low rate of rise of the action potential when elicited before the "fiber" is fully repolarized (106, 180, 207). This behavior of the cardiac action potential is particularly relevant in the generation and maintenance of arrhythmias, accounting for the observations that short action potentials and slow conduction tend to increase the probability of disturbances of rhythm. Thus, a premature action potential may, under unfavorable circumstances, reexcite subjacent cells leading to chaotic electrical activity and nonuniformity (192).

F. Reentry

Although reentry as a form of deranged impulse propagation constituting the underlying mechanism of certain types of cardiac arrhythmias has been considered for many decades, it is only during the last 10 years that experimental and clinical verification of this possibility became conclusive (94, 95, 196, 219, 242). Moe (194) has clearly summarized the fundamental requirements of a reentrant loop: 1) block of an impulse at some site within the conducting network; 2) slow conduction over an alternative pathway; 3) delayed activation of tissue beyond the block; and 4) reexcitation of tissue proximal to the block. Hence, under normal conditions, assuming a conduction velocity of about 2 m/sec (59, 307) and a duration of a Purkinje fiber action potential of 400 msec, the wave of excitation is 80 cm long and a potential reentrant circuit would have to be at least of the same length to permit reentry. This is, of course, extremely unlikely in the intact human heart. On the other hand, with the conduction velocity reduced to 0.03 m/sec (320, 321) and an

impulse duration of, *e.g.*, 200 msec, the spatial extension of the excitation wave is only 6 mm and reentry can readily occur if the loop is slightly longer. What has been called "circus movement" (175) or reentry (192, 194, 320, 321) is essentially a wave of excitation travelling either around an anatomical obstacle (320, 321), an anatomical loop (320), or along functional pathways (192, 194) which are varying in position, number, and size (197). To provide evidence for the functional existence of these processes and to delineate the directions in which impulses travel to permit reexcitation of other cells, recordings of transmembrane potentials from different sites are therefore necessary. Using microelectrode techniques, Wit *et al.* (320, 321) and Allessie *et al.* (2) have indeed demonstrated that if conduction velocity is slowed excessively, an impulse can be made to travel around an anatomical loop under experimental conductions *in vitro* (see below). In the intact heart, tissues which normally have i_{si}-dependent phase 0 depolarization may have conduction velocities low enough for the establishment of unidirectional block and reentry or other forms of reexcitation. For example, clinical reentrant supraventricular tachycardia commonly occurs in patients *without* heart disease. In this arrhythmia, clinical and experimental studies have revealed the existence of the reentrant pathway that includes a portion of the atrioventricular node (94, 317, 319) which has i_{si}-dependent action potentials (47, 327). There is evidence that the sinoatrial node also has slow response action potentials and can constitute a part of the circuit permitting the development of echoes and sustaining reentrant arrhythmias (37, 41, 47, 99, 187, 317). Another well-substantiated instance of reentrant arrhythmia utilizing anatomical pathways is found in the preexcitation syndrome, in which a short-circuiting atrioventricular tract for impulse conduction has been demonstrated. Here, programmed electrical stimulation of the heart has shown that during rapid tachycardias, the atrioventricular node together with the accessory tract constitute a reentrant loop for antegrade and retrograde conduction of the abnormal impulse (315).

G. Reentry due to Multiple Wavelets

A mechanism of reentry based on the concept of nonhomogeneity and related to atrial fibrillation has been suggested by Moe (192). As summarized by Moe (194), this mechanism "has been recognized as a disorganized excitation process in which, because of the nonhomogeneity, many independent wavelets circulate almost randomly, changing in velocity, number, direction, and breadth as they encounter tissue in various stages of excitability (30, 192). Unlike flutter, no fixed circuit is necessary and no obstacle is required. Fibrillation can be induced in a mathematical two-dimensional area (197) or in a closed surface without holes. It is certainly reentrant; it is almost certainly not a simple circus movement" (194). However, no direct evidence for this mechanism has been obtained although its existence seems very probable from several mosaics of experimental recordings (188, 189, 195) and computer simulations (193, 197).

H. Reentry due to Depressed Conduction

Wit *et al.* (320, 321) have described a model of reentry (already alluded to) which is based on the concept of 1) unidirectional block, and 2) very slow conduction, a model which was originally suggested by Schmidt and Erlanger (247). Wit *et al.* (321) provided evidence that a circus movement may occur in networks of Purkinje fibers in which delay is induced locally by depression of short segments or in which slow conduction is induced by high K and epinephrine. One of the possibilities arising from the concept presented is shown in figure 15.

In the records shown in figure 15 [from Wit *et al.* (320)], the driven impulse initiated a circus movement in the network shown diagrammatically in A. The preparation obtained from a calf heart was depressed by the exposure to high K and epinephrine. In B and C, each impulse is

numbered in the order of its appearance in time, and the site at which that impulse was recorded is similarly numbered in the diagrams at the right of the tracings. In B, the initial driven impulse blocked in the clockwise direction and failed to travel much beyond A, as suggested by the low amplitude of the response at A (impulse 2). That the driven impulse travelled counterclockwise is shown by activity at c being followed by the activity at b and thereafter by activity at a, which in turn reexcited c (response 5). It thus appears that there is a site of one way block that prevents excitation from reaching a when the approach is from b. The sequence shown in C includes a further complete circuit of the loop by the impulse. The conditions are the same as in B except that response 5 is followed by another circuit in the counterclockwise direction, exciting b, a, and c in that order to give rise to responses 6, 7, and 8.

The *in vitro* model of reentry as outlined above from the work of Wit *et al.* (320) may

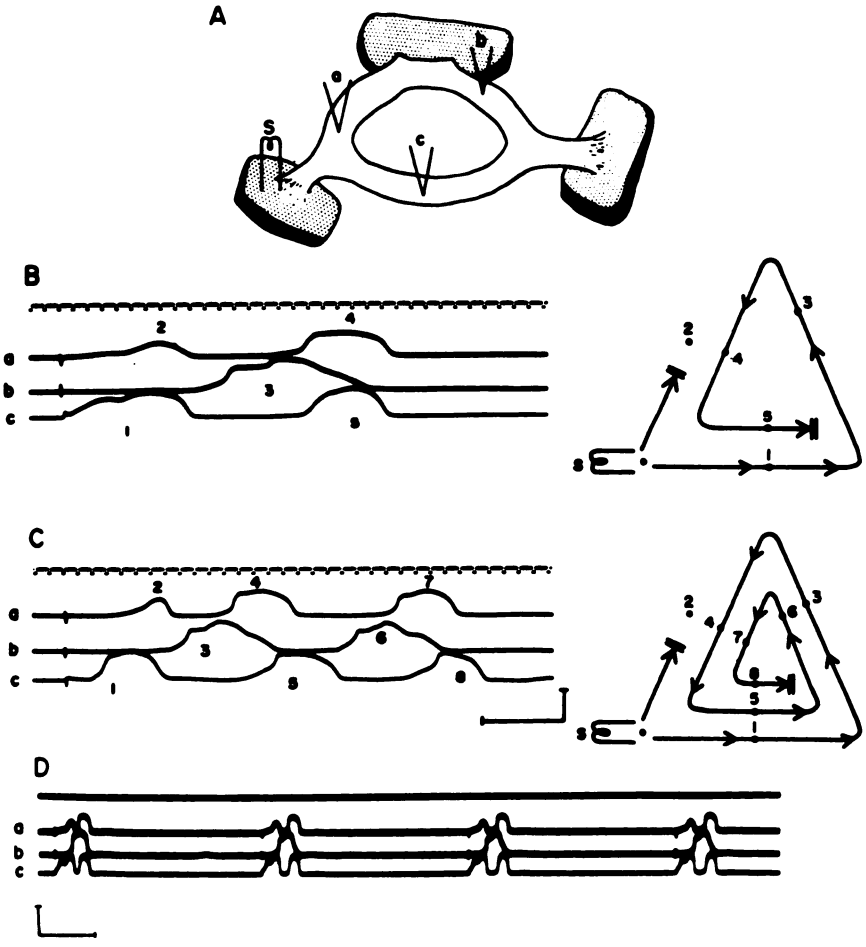


FIG. 15. The preparation used (A) was taken from a calf heart. The stimulus site is *S*, the recording sites are *a*, *b*, and *c*. In this preparation the drive blocked in the clockwise direction near *a* while travelling in the counterclockwise direction. A partial circuit of reentry is shown in B, a full circuit in C. In B and C, each action potential is numbered; the same numbers appear in the diagram to show the order in which each response appeared at each site. In the diagram the base of the triangle corresponds to *c*, the left side to *a*, and the right side to *b*. Calibration for B and C: vertical 100 mV; time marks at 100 msec intervals. The records in D show regular repetition of the sequence of reentry shown in B. Calibrations: vertical, 100 mV; horizontal, 3 sec. [From Wit, Cranefield and Hoffman (320) by permission of the American Heart Association.]

be applicable to a number of experimental and clinical conditions. The central requirement here is severe depression of conduction velocity as might result from a decrease in the maximal Na-conductance (fast response) or the development of the i_{si}-dependent potentials (slow response) or possibly from a combination of both electrophysiological phenomena. The velocity of conduction in tissues with i_{Na}-mediated phase 0 depolarization is related to the integrity of the sodium system both during the steady state as well as nonsteady state of reactivation following previous depolarization. Maximal Na conductance will therefore be depressed by such factors as the loss of the integrity of ionic channels themselves as in the case of tissue death or by their specific inhibition as may be produced by tetrodotoxin (288); an alteration of the h inactivation variable as in hyperkalemia (309) or by the inhibition of Na^+-K^+ pump as in digitalis toxicity (249) also may reduce markedly Na conductance with consequent reduction in conduction velocity. The depression of the fast response and the emergence of the slow response may be particularly significant in myocardial ischemia (172). However, in light of the recent work from Moe's laboratory (154, 155) the possibility has arisen that grossly depressed conduction is not always necessary for the generation of a reentrant cardiac arrhythmia.

I. Macro- and Micro-Reentry

As already considered above, under conditions of a slow conduction velocity and a short refractory period, an impulse may travel around an anatomical obstacle (175) or along a predetermined pathway as in a Purkinje fiber network, provided that the latter provides a sufficiently long circuit. This type of what may be called "macro-reentry" is distinct from what has been designated "miniature" or "micro-reentry". Experimental verification of such small reentrant loops is, of course, difficult since the size of these microcircuits is usually beyond the capability of available recording techniques. However, in the presence of very slow conduction and short refractory period of the order of 40 msec (242), reentry may be demonstrated within loops no more than a few millimeters in circumference (242, 320, 321). The possibility must also be considered that micro-reentry may result from a local delay in repolarization. For instance, myocardial fibers in close juxtaposition may undergo repolarization at markedly varying rates; those which repolarize more slowly may draw repolarizing currents from those with relatively rapid repolarization, thereby depolarizing again with a low rate of rise producing premature action potentials (30, 138). This mechanism may be particularly significant in myocardial infarction; at least in the dog with experimental infarction, surviving Purkinje fibers have been found to be depolarized with long action potential durations (83, 84, 172). A close juxtaposition of such fibers to normal myocardial fibers are thus conducive to the development of reentrant ventricular arrhythmias.

The above discussion of reentry mechanisms would clearly suggest that reentrant arrhythmias are likely to be aborted by 1) prolonging the refractory period, 2) by accelerating conduction as might be achieved by hyperpolarizing the membrane or by augmenting the excitatory sodium current (i_{Na}), 3) by eliminating the disparity in the excitatory states of adjacent myocardial cells, or 4) by reducing the magnitude of the membrane current components responsible for the different rhythm disturbances. These various mechanisms will be discussed further in the sections in which the effects of individual antiarrhythmic agents are considered at a greater length.

J. Altered Excitability and Arrhythmogenesis

As mentioned above and discussed in detail by Arnsdorf (9), an alteration in excitability may constitute a discrete arrhythmogenic mechanism independently of primary changes in impulse generation and impulse conduction. In classical electrophysiology, cardiac excitability has been

evaluated by strength-duration curves in the intact heart stimulated by bipolar surface electrodes; the lowest applied current that elicited a regenerative response was termed excitability "threshold" (30, 100). The membrane events determining such a current threshold are, however, complex and not readily amenable to study by the standard microelectrode techniques. Recent investigations have therefore employed multiple microelectrode techniques of intracellular constant current application and voltage clamping which have allowed quantitative delineation of individual components of cardiac excitability (77). Under these conditions, the components of strength-duration and charge-duration curves such as resting membrane voltage, threshold voltage, membrane conductance, and cable properties of the fiber can be assessed and the effects of different pharmacological agents on these electrophysiological parameters determined. Such studies are just beginning (11, 12) and are likely to contribute much to the understanding of the precise mode of action of different antiarrhythmic compounds. It must, however, be emphasized that the significance and the relevance of the data acquired from such experimental investigations will need to be evaluated in terms of known electrophysiological actions of antiarrhythmic drugs established in preparations *in vivo* and *in vitro*. The ultimate goal, of course, is an accurate delineation of the membrane effects of these drugs, which will lend precision to the current understanding of their fundamental actions which are therapeutically relevant in the control of cardiac arrhythmias.

On the subject of excitability it is pertinent to indicate that conduction in cardiac muscle is determined by a factor proportional to the surge of the excitatory inward current (i_{Na}) as well as by the passive electrical properties of heart muscle (see equation 12). Thus, even in the absence of a change in the fast i_{Na}, an alteration in the passive electrical properties of the cardiac tissue may have a significant effect on conduction and the configuration of the action potential although as yet this possibility has not been exhaustively investigated in relation to the action of drugs and procedures known to influence rhythm and conduction in the heart. It has been known for some years that isolated cardiac tissue preparations develop a tendency toward spontaneous activity during stretch (164). Deck (55) studied the cable properties of Purkinje fibers under conditions of stretch and demonstrated a decrease in the time constant and in the internal resistivity (R_i) whereas R_m and the length constant were increased. Of interest was the finding that under these conditions, conduction was improved and the negative chronotropic effect of diminishing the diameter of the fiber was offset by a decrease in capacitance and internal resistivity. In the setting of excessively depressed conduction, an acceleration of conduction by this mechanism might be expected to be antiarrhythmic but no clinical or experimental correlates of this phenomenon have been established. On the contrary, it is known that stretch lowers the maximum diastolic potential and increases the steepness of the pacemaker potential (33, 164, 290) thus increasing excitability and the propensity to cardiac arrhythmias (273, 274). In solutions containing high concentrations of calcium the electrical constants of Purkinje fibers following stretch did not, however, show a significant change (221) but in calcium-free media, the steady state current voltage relationship lost its negative slope with the rapid deterioration of the fiber (221). It therefore appeared that calcium was essential for the "healing over" after excision, *i.e.*, for the building of high resistances at the ends of the fiber (57).

Voltage clamp data are still limited with respect to the action of the known arrhythmogenic compounds; the only agent that has been examined in some detail is halothane (105). Cardiac arrhythmias frequently occur during halothane anesthesia and electrophysiological studies employing standard microelectrode techniques have

shown that the compound markedly shortens the action potential duration and the effective refractory period, producing a pronounced disparity of the refractory period between Purkinje and ventricular fibers. Subsequently, the cable properties of Purkinje fibers were studied by Hauswirth (105a), who found that halothane produced an increase in R_i and a decrease in the λ, results which have been interpreted in terms of electrical uncoupling. The slowing of the conduction velocity by a factor of two by halothane (see equation 12) was probably due to an increase in R_i. However, since the arrhythmogenic propensity of halothane is particularly marked in the presence of sympathomimetic amines, it would be of interest to examine the effects of halothane on the cable properties of Purkinje fibers against the background of varying levels of catecholamines.

IV. Comparative Mechanisms of Action of Antiarrhythmic Drugs

In the last two decades, numerous antiarrhythmic agents, of varying potency, pharmacological diversity, as well as structural complexity have been introduced (18, 19, 60, 250, 258–260, 263, 264, 303). As yet, the effects of the cardiac membrane currents of relatively few of these as well as the conventional agents have been examined and much of the information of this kind in the membrane of excitable tissues has been obtained in nerve (121–125, 171, 198, 202–204, 281). However, despite the methodological difficulties of clamping cardiac fibers in relation to their somewhat complex cellular geometry, voltage clamp data on drug actions on the cardiac membrane are increasing and are likely to grow rapidly in the future (88, 97, 108, 165, 169, 170, 224, 279, 296, 297, 308). Whether all the newer information will be directly relevant in the characterization of antiarrhythmic drugs and whether such data will be of potential value in establishing a more rational basis for therapy of cardiac arrhythmias in the clinic is still uncertain. For the present, it will clearly be of significance to relate the voltage clamp data on antiarrhythmic compounds to the existing framework of comparative drug mechanisms which have been elucidated by standard microelectrode techniques in isolated cardiac muscle and correlated with gross electrophysiological effects in experimental animal models (54) and in man with heart disease (245). A discussion of such a framework of drug action thus constitutes a logical preamble to the description of voltage clamp data and their application to the understanding of antiarrhythmic mechanisms.

A. Classification of Antiarrhythmic Mechanisms on the Basis of Standard Microelectrode Data

Different investigators have classified antiarrhythmic actions somewhat differently (26, 118, 231, 255, 262, 263, 303) although many of the earlier conflicts in data (27, 28, 262) are now being resolved by the use of more appropriate and clinically relevant experimental models (228–230, 233). Although not universally accepted, it is the belief of the authors that the currently available antiarrhythmic compounds may reasonably, if a little simply, be classified into four discrete categories (255, 262, 263, 303). This categorization is based on the observation that virtually all known antiarrhythmic agents have one dominant electrophysiological action on the myocardial cell, which may be modulated by the drug's subsidiary myocardial effects as well as by its extracardiac actions so that its net pharmacological effect on the heart may not be entirely predictable from the *in vitro* data. A simplified categorization of antiarrhythmic actions is presented in Table 1.

Class I agents in general are potent local anesthetics on nerve as well as on the myocardial membrane although their sensitivities in this respect may differ markedly, so that very much lower concentrations produce comparable electrophysiological effects in myocardial than in nerve fibers (258). The dominant electrophysiological property of this class of drugs has been

TABLE 1
*Classification of antiarrhythmic agents**

	Depression of fast response	Inhibition of sympathetic activity	Homogeneous prolongation of the action potential duration	Depression of the slow response
Class I	Quinidine Procainamide Lidocaine Disopyramide Diphenylhydantoin Mexiletine Tocainide Aprinidine			
Class II		Propranolol Other β-antagonists		
Class III			Amiodarone Bretylium	
Class IV				Verapamil

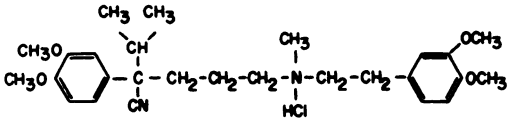
* Classification is based on the identification of the single dominant electrophysiological or pharmacological property demonstrated *in vitro*. Additional associated properties may modify the net effect of the drug *in vivo*. All four classes of drugs exert a depressant effect on the pacemaker potentials *in vitro* except for bretylium which may increase automaticity unless the tissue has been treated with reserpine (see text).

related to their ability to reduce the maximal rate of depolarization (MRD) in cardiac muscle. In concentrations which are clinically relevant, the change in the MRD is associated with an increase in the threshold of excitability, a depression in conduction velocity, and a marked prolongation in the effective refractory period. These alterations, which occur without a significant change either in the resting membrane potential or the action potential duration, are invariably associated with the inhibition of the spontaneous diastolic depolarization in automatic cells. However, this effect on pacemaker cells is usually seen in very much lower concentrations of the drugs than those which influence conduction velocity or electrical threshold of excitability. By depressing spontaneous diastolic depolarization, local anesthetic compounds can thus control arrhythmias due to enhanced automaticity or decreased excitability and by altering the refractory period, they are likely to be effective in aborting reentrant tachyarrhythmias. Class I agents include quinidine, procainamide, disopyramide, mexiletine, ajmaline, tocainide and, although still somewhat controversial, lidocaine and diphenylhydantoin (DPH) also appear to have a major component of their action, at least from gross electrophysiological observations, related to the inhibition of the MRD of the cardiac action potential. However, it is noteworthy that the controversy is now being resolved in favor of the contention (262) that lidocaine and DPH exert their fundamental actions on heart muscle essentially by selectively depressing cardiac depolarization in ischemic or hypoxic cells (68, 69a), a setting in which the salutary effects of Class I agents are of particular therapeutic significance. For example, El-Sherif *et al.* (68, 69a) showed that lidocaine and DPH depressed ischemic cardiac cells which constituted parts of the reentrant pathway in drug concentrations found previously in some studies to facilitate the electrophysiological properties of *normal* cardiac cells (68). It will be evident that these most recent data (68, 69a) not only negate the possibility that lidocaine and DPH can abolish reentrant rhythms by improving conduction in the reentrant circuits, but they also provide a strong justification for the proposed categorization of these compounds as Class I agents. Aprindine is a newer agent which also appears to act essentially by depressing the MRD but like DPH it may have additional electrophysiological properties. The structural for-

mulae of some of the newer agents are shown in figures 16 and 17. It is noteworthy that the β-adrenoceptor blocking compound, propranolol, has not been included in this class of drugs although it has often been classified in this category. The justification for this is discussed below.

The basis for classifying agents which block sympathetic stimulation into a separate category (Class II) stems from the observation that hyperactivity of the sympathetic nervous system has been shown to be a significant factor in the genesis of certain cardiac arrhythmias (256). Indeed, an ablation of the sources of the sympathetic transmitter has been found to be antiarrhythmic (256), and sympathetic blockade either acting presynaptically as by the use of adrenergic neuron blocking drugs (18, 19) or by competition at the receptor sites as by specific β-adrenoceptor blocking compounds (256) has been shown to lower the incidence of clinical and experimental arrhythmias. The largest experience has been with β-adrenoceptor blocking drugs, which, soon after their introduction, were found to be potent local anesthetics on nerve (91) with comparable effects on cardiac muscle (258, 260, 303). The subsequent controversy (53) that followed centered on the issue of the relative contributions of adrenergic blockade and Class I effects in the antiarrhythmic correlates of β-adrenoceptor blockade (258). It is not the intent here to review the relevant experimental findings in detail but merely to point out that the controversy appears to be resolved in favor of the belief that β-adrenoceptor antagonists, in therapeutically relevant concentrations, act largely and perhaps exclusively by adrenergic blockade

VERAPAMIL



AMIODARONE

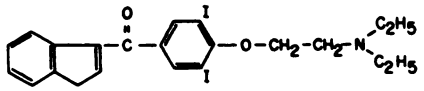
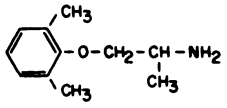
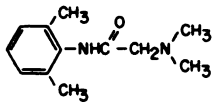


FIG. 17. Chemical structures of two novel antiarrhythmic agents: verapamil (a calcium antagonist) and amiodarone (a benzfuran derivative), both potent coronary vasodilators with antiarrhythmic activities.

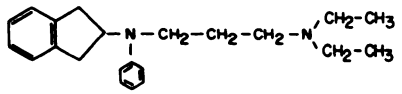
MEXILETINE



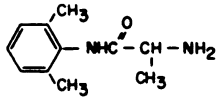
LIDOCAINE



APRINDINE



TOCAINIDE



DISOPYRAMIDE

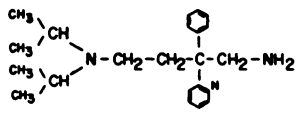


FIG. 16. Chemical structures of some recently introduced antiarrhythmic agents which depress the fast response in cardiac muscle and in nerve. The structure of the local anesthetic, lidocaine, is shown for comparison. Note the structural similarities between lidocaine, mexiletine and tocainide.

and that their associated local anesthetic properties, apparent in high concentrations, may be largely irrelevant in the control of cardiac arrhythmias (256, 303). Their principal electrophysiological effect on heart muscle in clinically relevant concentrations is the depression of phase 4 depolarization. A justification, therefore, exists for classifying these drugs and others which inhibit sympathetic activity, by whatever mechanism, into a discrete class of antiarrhythmic compounds and a detailed evaluation of their effects in therapeutically meaningful concentrations on individual membrane currents in heart muscle under voltage clamp conditions is of particular significance (see below).

The justification for attributing an independent antiarrhythmic mechanism (Class III) to drugs which produce a "pure" prolongation of the action potential duration stems from the observation that in thyrotoxicosis atrial arrhythmias are common but they are rare in hypothyroidism. Furthermore, it has been shown recently (81) that in experimentally-induced thyrotoxicosis in rabbits, atrial intracellular potentials were abbreviated markedly in duration and in hypothyroidism they were prolonged significantly and homogeneously. No other electrophysiological parameters in atrial muscle were affected by variations in the thyroid state. A situation analogous to the effects of hypothyroidism and cardiac intracellular potentials was found later with the chronic administration of the antianginal drug amiodarone (20 mg/kg/daily for 6 weeks), a benzfuran derivative (fig. 17), which produced "pure" prolongation of repolarization in atrial as well as ventricular muscle (259). Amiodarone has since been found to be a potent antiarrhythmic drug in the clinic (60, 237, 238). Amiodarone is not a local anesthetic on nerve or cardiac membrane and in experimental studies it has been shown to have an extremely weak Class I action. Similarly, the drug does not exhibit competitive β-receptor blocking properties although it does have a mild, noncompetitive inhibitory effect on sympathetic stimulation (39). The antiarrhythmic actions of amiodarone were, therefore, attributed to its property of prolonging the action potential duration with the consequent lengthening of the effective refractory period (255, 259). Experience has indicated that amiodarone may be the most potent antiarrhythmic agent for the control of refractory ventricular tachyarrhythmias and for the prophylaxis of recurrent supraventricular tachyarrhythmias including atrial fibrillation or flutter, complicating the Wolff-Parkinson-White syndrome (237). A detailed understanding of its antiarrhythmic mechanism, therefore, may be of significance not only from the immediate therapeutic standpoint but also in relation to structure-activity relationships of antiarrhythmic drugs and for the search for newer compounds. The effects of benzfuran derivatives on cardiac muscle under voltage clamp conditions are thus likely to be of crucial pharmacological importance.

As discussed above, recent experimental studies have indicated the significance of the slow response in the genesis of certain types of cardiac arrhythmias. It is known that with the depression of the fast response, marked reduction in conduction velocity may result from the emergence of the slow response and action potentials with pacemaker activity may arise entirely on the basis of i_{si}. Thus, the presence of slow response may lead to the initiation of arrhythmias both on the basis of reentry as well as enhanced automaticity. Experimental studies (48) have clearly indicated that the slow response can be suppressed effectively by the selective calcium antagonist, verapamil (a papaverine derivative), which has been demonstrated to have potent antiarrhythmic actions both in the experimental animal (263) as well as in man (120). In clinically relevant concentrations, verapamil does not have Class I, Class II, or Class III antiarrhythmic actions and in terms of the present knowledge, it is therefore justifiable to classify its action independently (Class IV) of other conventional compounds (253, 254). It is of interest that

the drug does not have much effect on the refractory period of the anomalous conduction pathways in the preexcitation syndrome and its major antiarrhythmic effect appears to be mediated through the profound inhibition of the atrioventricular transmission system which is essential for the reentrant supraventricular tachyarrhythmias which respond promptly and almost predictably to the intravenous administration of calcium antagonists (120, 254). One of the major contributions of voltage clamp in cardiac muscle has been in elucidating the mode of action of verapamil and other calcium antagonists such as D600 with respect to their beneficial effects in arrhythmias. The details of the experimental studies which deal specifically with voltage clamp data on a number of antiarrhythmic agents are presented in the sections of the review that follow. The discussion will be confined essentially to the actions of the commonly known agents and of the newer compounds which constitute potentially significant landmarks in the development of antiarrhythmic drugs. References to other compounds, ions, and toxins will only be made if a discussion of their effects bears importantly on the mechanisms of action of the main antidysrhythmic compounds under consideration.

B. Voltage Clamp versus Standard Electrophysiological Techniques

1. Compounds Influencing the Fast Sodium Current. Tetrodotoxin (TTX) may be considered a prototype of agents which alter the fully activated current-voltage relationship. Although this compound cannot be used clinically, it is of much interest to membrane biophysicists since it specifically blocks the fast sodium channels (198). This is brought about by the reduction in the absolute magnitude of the fast sodium current without appreciably affecting the kinetics (276). Thus, it may be concluded that TTX does not influence the electrical field near the sodium channels (which would result in a shift of the kinetics along the voltage axis); it acts rather by "plugging" the sodium channels in an all-or-nothing fashion (159). In Hodgkin-Huxley terminology, this would mean that $\overline{g_{Na}}$ is reduced since this parameter is proportional to the number of the fast sodium channels. In this context it is of interest to note that low levels of Na in the external media produce results similar to those after the administration ot TTX (309) (fig. 18).

Other agents chemically related to TTX such as saxitoxin exert essentially the same effect (159, 203). It is of interest that the effect of TTX on $\overline{g_{Na}}$ in cardiac muscle has been related to an antifibrillatory action (241). However, TTX acts more specifically on nerve, blocking conduction at a concentration 0.01 mg/liter, whereas concentrations of 10 to 30 mg/liter are needed to produce a comparable effect in mammalian Purkinje fibers (63). Such a preferential neurosensitivity will preclude its potential clinical application but it is of biological significance insofar as the toxin has effect neither on the mammalian pacemaker po-

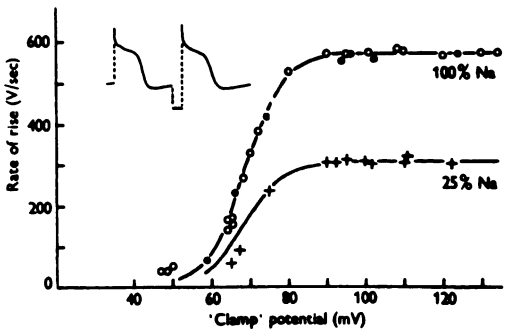


FIG. 18. Relationship between "clamp" potential and maximal rate of rise of action potential. Open circles refer to a preparation in Tyrode solution, crosses to the same preparation in a test solution containing 25% of the normal sodium; closed circles are values obtained after changing back to Tyrode solution. Smooth curves are calculated from the equation

$$h_\infty = 1/(1 + \exp^{(V_h - V)/5})$$

where V is the "clamp" potential and V_h is the potential at which h_∞ is half maximal. The values obtained in low sodium could be fitted if the curve for normal Tyrode was scaled down to 54%. [From Weidmann (308) with permission of the author and the *Journal of Physiology*.]

tential (241) nor on atrioventricular conduction (305).

Particularly noteworthy are the cardiac electrophysiological properties of the neuroleptic drug, droperidol, which is also known to exhibit antiarrhythmic actions. It has a TTX-like component of action despite the fact that its antiarrhythmic activity may largely be due to a delay of reactivation of the fast sodium current (104, 165). A limited number of so-called local anesthetic or Class I antiarrhythmic drugs have been studied under voltage clamp conditions in cardiac muscle. It has been found that in frog atrial muscle high concentrations of propranolol (279) and "therapeutic" concentrations of quinidine (61, 178) 1) reduce the number of the fast Na channels ($\overline{g_{Na}}$), 2) do not influence the inactivation kinetics, and 3) prolong the time necessary for the "recovery from inactivation." Very similar results were reported by Kohlhardt (166) in voltage-clamped ventricular fibers under the influence of procaine, quinidine, and propranolol. These data would therefore indicate that under the influence of these drugs the refractory period may considerably outlast the duration of the action potential (104, 165, 166, 178, 279).

Inactivation kinetics of the fast sodium current in cardiac muscle and nerve have been studied by a number of investigators and may be of significance when considering the overall electrophysiological properties of different antiarrhythmic agents. h_∞ is shifted in the depolarizing direction by calcium ions, both in nerve (222) as well as heart muscle (309). In internally perfused squid giant axons, Chandler *et al.* (38) showed that the localization of h_∞ is dependent on ionic strength. Perfusing an axon internally with only 50 mM potassium and despite maintaining isotonicity with sucrose, h_∞ was shifted by about 20 mV in the depolarizing direction. In cardiac fibers, h_∞ is shifted in the hyperpolarizing direction by some of the so-called Class I antiarrhythmic drugs such as procaine, quinidine, and diphenylhydramine hydrochloride (309), lidocaine (27, 28), and ajmaline (117, 119) (fig. 19).

There has been some confusion as far as the methods of determining the "steady state" degree of availability are concerned: Weidmann (308, 309) voltage-clamped a Purkinje fiber within a limited space but, nevertheless, obtained conditions close to steady state. Trautwein and Schmidt (292) and Heistracher (117) injected constant current into a Purkinje fiber and their con-

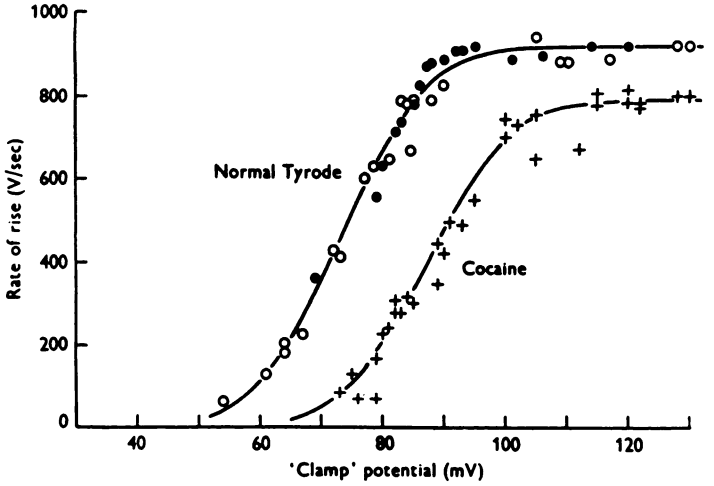


FIG. 19. Effect of the local anesthetic agent cocaine on relationship between membrane "clamp" potential and maximal rate of rise of action potential. The values obtained under the influence of cocaine could be fitted if V_h (see legend for figure 18) was shifted by 16 mV in the hyperpolarizing direction. [From Weidmann (309) with permission of the author and the *Journal of Physiology*.]

ditions may have been not very far off the steady state. Bigger and coworkers (26–28) stimulated a fiber at various times during the repolarization phase of the action potential. Their experimental results (relating varying levels of membrane potential to the maximum rate of depolarization of the action potential) was called "membrane responsiveness" which may be expressed in mathematical terms: by $h_\infty \cdot (1 - e^{-t/\tau})$. Since most of the Class I antiarrhythmic drugs not only alter the kinetics of *in*activation but also those of *re*activation, "responsiveness" may not closely approach the steady state inactivation $(1 - h_\infty)$ because h may not have enough time to reach h_∞. As Weidmann (308) demonstrated, the location of "h_∞" on the voltage axis is frequency dependent. "h_∞" appears to be shifted in the hyperpolarizing direction during higher frequencies of stimulation since it cannot be determined whether the translocation of the curve represents a real shift, or a delay of reactivation as a combination of both phenomena. Some of the discrepancies in the literature at least with respect to the action of certain Class I agents such as lidocaine may be due to these differing methodological approaches. However, it is appreciated that the evaluation of drug effects by the use of "membrane responsiveness" as a parameter does offer the advantage of experimental simplicity in comparison to the technical complexity of voltage clamping. A great deal of preliminary information of the mode of action of an antiarrhythmic drug may thus be obtained initially by this technique, but voltage clamp is desirable for the elucidation of the fundamental mechanisms of drug action at the cardiac membrane.

The available data on the electrophysiological effects of quinidine as elucidated by voltage clamp as well as by standard microelectrode techniques are reasonably concordant and are in line with observations in intact animals and man (253). However, the precise ionic mechanisms through which the drug affects the pacemaker current (i_{K_2}) or through which it prolongs the terminal phases of repolarization (301) are still not clearly defined. It is reasonable to assume, however, that in common with all the Class I antiarrhythmic drugs, the negative chronotropic effect of quinidine, at least in isolated atrial preparations, is related to a diminution of the background inward current (i_{Na}) which depolarizes the membrane as i_{K_2} deactivates. The electrophysiological actions of disopyramide, mexiletine, tocainide, and aprindine—all potent local anesthetics on nerve (253)—have not as yet been studied under voltage clamp conditions but general similarities of their overall electrophysiological properties as delineated by conventional techniques with those of quinidine suggest a common fundamental mode of action. This is further emphasized by the fact that these drugs as a class impede conduction and prolong the refractory period of the accessory pathways in the preexcitation syndrome in man (266, 315). However, it is conceivable that such differences in their electrophysiological properties as might be demonstrated by voltage clamp techniques may be helpful in accounting for their variable effects in the control of experimental and clinical arrhythmias. Indeed, in the case of procainamide, another Class I agent, data acquired from the microelectrode technique of intracellular constant current application and intracellular voltage recording may explain, in part, the divergent results of studies on cardiac excitability in the whole animal as well as the observations that the drug, like quinidine, may exert both antiarrhythmic and proarrhythmic actions (12).

In therapeutically relevant concentrations (4–8 μg/ml), procainamide is known to depress phase 4 depolarization and the MRD of the action potential of canine Purkinje fibers superfused with homologous blood from donor animals (230). Although the direct effects of procainamide on the rapid inward sodium current under voltage clamp conditions have not been measured, Arnsdorf and Bigger (12) recently investigated the changes after clinically effective concentrations (5 μg/ml) of the drug on

nonnormalized and normalized strength-duration curves, membrane characteristics, and cable properties in long sheep Purkinje fibers. After procainamide, V_r remained unchanged, V_{th} became less negative, I_{th} was augmented, and the nonnormalized strength-duration curve shifted upward so that more current was needed to attain threshold for each current duration, *i.e.*, the tissue was "less excitable" after procainamide. Normalized strength-duration curve was also shifted upward as well as to the right by procainamide. Thus, procainamide decreased excitability primarily by making V_{th} less negative in spite of little change or an actual decrease in subthreshold membrane potassium conductance and no change in V_r (12). Notable was the observation that at times procainamide enhanced rather than decreased excitability as indicated by changes in i_{th}; the drug had an effect on both passive and active membrane properties with the net i_{th} requirement determined by the balance between the two. This variability may account for the observed antiarrhythmic and arrhythmogenic properties of the drug in intact animal and man.

The overall experimental findings are consistent with the knowledge that procainamide depresses conduction and may thereby retard impulse propagation through the depressed segment of a reentrant loop to the extent that unidirectional block is converted to a bidirectional one and reentry is eliminated (230). This is also consistent with the evidence in man that after procainamide the reentrant circuit is lengthened prior to the termination of reentrant ventricular arrhythmias (89). The precise mechanism whereby procainamide decreases automaticity is, however, not clearly established; it may be mediated by a decrease in the inward depolarizing current but it may also act by making the V_{th} for excitation less negative. Weld and Bigger (314) have shown that, unlike lidocaine, the drug does not increase the outward repolarizing current but no information exists regarding the effects of the drug on i_{si}-dependent automaticity.

In contrast to the electrophysiological studies with procainamide, those with lidocaine and DPH have produced seriously divergent results which have been subject to variable interpretation of their fundamental mode of action on the cardiac membrane. Bigger and Mandel (27, 28) investigated the effects of a range of concentrations of lidocaine on the electrophysiological properties of isolated cardiac muscle. Concentrations of the local anesthetic which were clinically applicable (1.5–6.0 μg/ml) had no depressant effect on the MRD or membrane responsiveness but phase 4 depolarization accentuated or produced by hypoxia, stretch, or catecholamines, was depressed (27, 28). Of interest was the observation that lidocaine *increased* membrane responsiveness slightly but significantly with smaller increases in the overshoot potential and conduction velocity (27, 28). In Purkinje fibers as well as ventricular muscle, lidocaine shortened the action potential duration and refractoriness but prolonged the recovery of excitability relative to repolarization (24, 27, 28). However, it so happened that these studies, which did not show the expected depression of membrane responsiveness by lidocaine, utilized media low in external K concentration (3 mM); in subsequent studies (252, 262), in which K levels were in the physiological range (K = 5.6 mM), lidocaine exhibited electrophysiological effects on cardiac depolarization not unlike those of quinidine. Thus, in clinically relevant concentrations lidocaine reduced the MRD with a dimunition in the overshoot potential and conduction velocity with an elevation of threshold of excitability (262). These findings *in vitro* utilizing physiological media with no normal levels of external potassium have also been confirmed in experiments in which Purkinje fibers were superfused with homologous blood from donor blood having appropriate levels of serum K (233).

In view of these reports, the studies involving effects of lidocaine on components of excitability in long mammalian Purkinje fibers in media containing K of 4.0 mM, published recently by Arnsdorf and Bigger

(11), are particularly relevant. As determined by small hyperpolarizing pulses, lidocaine increased membrane conductance and decreased both the λ and τ. The drug shifted nonnormalized strength-duration curve toward higher current levels necessary to elicit an action potential without altering V_r or V_{th}. These effects of lidocaine may be compared to those of procainamide, which also decreased excitability (*i.e.*, increased I_{th}) but by making V_{th} less negative; in contrast, lidocaine increased I_{th} primarily by increasing the subthreshold membrane conductance with little change in V_{th} or V_r. The clinical significance of these differences between procainamide and lidocaine with respect to their antiarrhythmic activity are unknown, since the two drugs have a very similar spectrum of action in the control of ventricular arrhythmias especially in the context of acute myocardial infarction. The studies of Arnsdorf and Bigger (11) utilized a very narrow range of concentrations; the possibility exists that in somewhat higher concentrations, the effects of lidocaine may approximate those of procainamide much more closely and, as in the case of quinidine, the drug may alter the kinetics of the sodium system (40). Furthermore, the effects of lidocaine on partially ischemic or hypoxic Purkinje fibers under voltage clamp conditions will be more definitive in delineating the fundamental antiarrhythmic actions of the drug. From standard microelectrode studies (316) it is known that very much lower concentrations of lidocaine may depress the MRD of the action potential in ischemic Purkinje fibers than those which depress this parameter in normal cardiac fibers. It is thus possible that in ischemic muscle, lidocaine may well alter the passive and active membrane properties relevant to conduction velocity, a possibility that requires experimental verification.

Lidocaine, both *in vivo* and *in vitro*, appears to have little effect on the firing frequency of the sinoatrial node (262). It might therefore be inferred that the drug does not significantly influence the ionic mechanism underlying the pacemaker current in the normal sinus pacemaker; no studies have, however, been reported to test the effect of the drug in "clamped" sinoatrial fibers. High concentrations of lidocaine also failed to suppress slow channel-dependent automatic depolarizations in depolarized guinea pig ventricular myocardium (147). Weld and Bigger (314) recently reported the effects of lidocaine (1 to 5 μg/ml) on the diastolic currents in mammalian Purkinje fibers using two-microelectrode voltage clamp technique. At 1 μg/ml concentration, lidocaine did not affect the amplitude of i_{K_2}, which was, however, decreased by 5 μg/ml concentration throughout the voltage range of pacemaker depolarization. Furthermore, lidocaine (1–5 μg/ml) increased the steady state outward transmembrane current which could be attributed to a variable contribution from both an increase in time-independent outward potassium current (i_{K_1}) and a decrease in background inward current. Thus, lidocaine may decrease the slope of phase 4 depolarization by enhancing the net outward K^+ current and may widen the difference between V_{mdp} and V_{th} by repolarizing the membrane of tissue depolarized by injury (10, 11, 158, 314). The effect of lidocaine, which is often effective in the control of digitalis-induced arrhythmias, on transient inward current described by Lederer and Tsien (173) is unknown but clearly merits study.

As in the case of lidocaine, controversy also exists regarding the fundamental mechanism of action of DPH, a drug which, in recent years, has proved to be the most effective agent in the control of digitalis-induced arrhythmias. In atrial and Purkinje fibers, DPH in therapeutic concentrations (5–25 μg/ml) was reported to shift membrane responsiveness in the depolarizing direction (26, 267) and at only higher concentrations did the drug produce a membrane depressant effect. However, as in the case of lidocaine, the effect of DPH was found to be K-dependent, insofar as the membrane depressant effect of the drug was reversed or nullified by K concentrations of 3.0 mM or lower (252, 255, 262); phase 4 depolarization was depressed by DPH even in media low in external K (267).

Relatively little information is available on the effects of DPH on cardiac membrane currents. Lipicky *et al.* (177) studied the action of the drug in squid giant axons by means of voltage clamp technique: in the absence of any significant shift in either m or h variables, they attributed the action of DPH solely to a decrease in $\overline{g_{Na}}$. At least in the lower concentration range, the effects of DPH are likely to be similar on the cardiac membranes and in many but not all respects resemble those of lidocaine. At higher concentrations DPH may alter the kinetics of the sodium system and probably decrease the slope of phase 4 depolarization by the mechanism (see above) suggested for lidocaine (228, 314), but further studies under voltage clamp conditions are necessary to define the membrane actions of this anticonvulsant antiarrhythmic compound. It will be of interest to correlate the results of such studies with those acquired by standard intracellular microelectrode techniques using depressed and normal canine Purkinje fibers (228) superfused with homologous blood or Tyrode solution. In this preparation, therapeutically meaningful concentrations of DPH produced slight to moderate decreases in action potential amplitude, the MRD, and membrane responsiveness with somewhat greater decreases in action potential duration in normal fibers. Fibers which were moderately depressed by ouabain (125 μg/liter) or stretch, which tended to reduce action potential duration, V_{mdp} and MRD, DPH increased these variables. Of particular significance was the observation that in Purkinje fibers which were markedly depressed by Na-free media or stretch and in which "slow responses" developed, therapeutic concentrations of DPH decreased the action potential amplitude, V_{mdp}, and the MRD; enhanced automaticity and ouabain-induced delayed after depolarizations, presumably similar to those described by Ferrier and Moe (71) and Lederer and Tsien (173), were also suppressed by DPH. Thus, the overall electrophysiological properties of DPH as an antiarrhythmic agent are complex with features in common with those of lidocaine on the one hand and with those of verapamil (see below) on the other. Since the effectiveness of DPH lies dominantly in digitalis-induced arrhythmias, further elucidation of its effects on various components of cardiac excitability will need to be explored in the setting of its interactions with cardiac glycosides. From the standpoint of the "net" antiarrhythmic effects of the compound, the fact that it also depresses cardiac sympathetic nerve activity that is mediated by an action on the central nervous system (92) merits consideration.

2. Cardiac Membrane Currents and Adrenergic Inhibition and Excitation. The electrophysiological properties of β-adrenoceptor blocking drugs relate to two discrete factors, namely, the ability of this class of drugs to specifically and competitively antagonize β-receptors in the heart and the fact that they may possess potent local anesthetic properties which may exert membrane effects on nerve or myocardium independently of sympathetic antagonism (256, 261). Although it is unlikely that the local anesthetic property of β-antagonists is of much therapeutic relevance, it is of pharmacological interest to review the studies which have been done with propranolol, still the "reference" for β-adrenoceptor blocking drugs.

The concentrations of propranolol which have been thought to be therapeutically relevant and which produce substantial blockade of cardiac β-adrenoreceptors range between 50 to 100 ng/ml (44). Standard microelectrode techniques (46, 52, 302) have shown that the threshold concentration for the depression of the MRD or membrane responsiveness is at least 10-fold higher (1 μg/ml) and there are β-adrenoceptor antagonists whose therapeutic effects are indistinguishable from those of propranolol but they do not exhibit membrane depressant properties even at concentrations over a 100-fold greater than those which produce near complete blockade of β-receptors (268). Thus, from the standpoint of antiarrhythmic actions it is

unlikely that the local anesthetic property of propranolol is of therapeutic significance unless, as in the case of lidocaine (316), very much lower concentrations of the drug alter the rapid sodium system in ischemic or damaged tissues. There is, however, little doubt that high concentrations of propranolol can affect the fast inward sodium current in nerve as well as in myocardial fibers (46, 52, 302, 326). In squid axons under voltage clamp conditions propranolol (approximately 100 μg/ml concentration) reduced $\overline{g_{Na}}$ without altering the inactivation kinetics but it did suppress the steady-state outward potassium current. Using the double sucrose gap voltage clamp technique on frog atrial muscle fibers, Tarr *et al.* (279) found propranolol (10 μg/ml) to suppress the maximum magnitude of the inward sodium current (i_{max}) by about 50%, associated with a proportional reduction in the maximum transient conductance. The steady state inactivation curve was shifted +4 mV toward more negative potentials by propranolol but the 5% decrease in Δh, although significant, was not sufficient to account for the reduction in I_{max}. The rate of activation or inactivation of i_{Na} was sometimes prolonged by the drug, accounting for the lengthening of the effective refractory period. Thus the overall data demonstrate that propranolol suppresses i_{Na} by blocking Na channels, thereby producing a reduction in g_{Na}. These data cannot as yet be compared with those for the antiarrhythmic agents, such as quinidine and procainamide, which have not been studied in the model of frog atrial fibers in double sucrose gap. In view of the extremely high concentrations of propranolol necessary to demonstrate the observed changes in the electrophysiological properties of cardiac muscle, it is however dubious whether such effects of propranolol and related β-antagonists contribute significantly to the overall antiarrhythmic actions of this class of compounds. By inference, their antiarrhythmic effects therefore result essentially from the inhibition of β-receptors. For this reason, the relation between cardiac membrane currents and adrenergic receptor excitation is of particular significance.

In general, evidence for the existence of a direct relationship between a membrane current system and a cell receptor is thought to be secure when the current in question is changed in one direction by the application of a drug exciting the receptor (agonist) and altered in exactly the opposite direction by the administration of an agent blocking the receptor in a competitive fashion (antagonist). To be able to use an individual current system as a test parameter in its relation to a receptor system, the application of voltage clamp technique is needed since in "free running" action potentials it is only possible to differentiate various current components activated at different voltage ranges. One of the earliest reports about the application of an adrenergic agonist (adrenaline) and a specifically acting antagonist (pronethalol) in heart muscle under voltage clamp conditions was that of Hauswirth *et al.* (108). Adrenaline produced a shift in the kinetics of the pacemaker current of about 25 mV in the depolarizing direction (101, 108, 296, 297) leaving the kinetics of the fast sodium channel unchanged (292). As a consequence of this shift, s did not cross s_∞ after about 1.6 sec (see fig. 12) but had to deactivate further (fig. 20). Moreover, with adrenaline this deactivation occurred about four times more quickly (fig. 21). Computer calculations based on a mathematical model (179, 180) show that these changes quantitatively account for the positive chronotropic effect of adrenaline (107, 180). In addition, isoproterenol and the phosphodiesterase inhibitor, theophylline (248, 296, 297), also shift the s-kinetics in the depolarizing direction thereby causing a positive chronotropic effect. As far as the action of adrenaline on s-kinetics is concerned, since this catecholamine stimulates α- as well as β-receptors and since both receptor systems are found in Purkinje fibers (49), it could not be concluded that the positive chronotropic effect on the pacemaker current was mediated solely through the excitation of β-receptors.

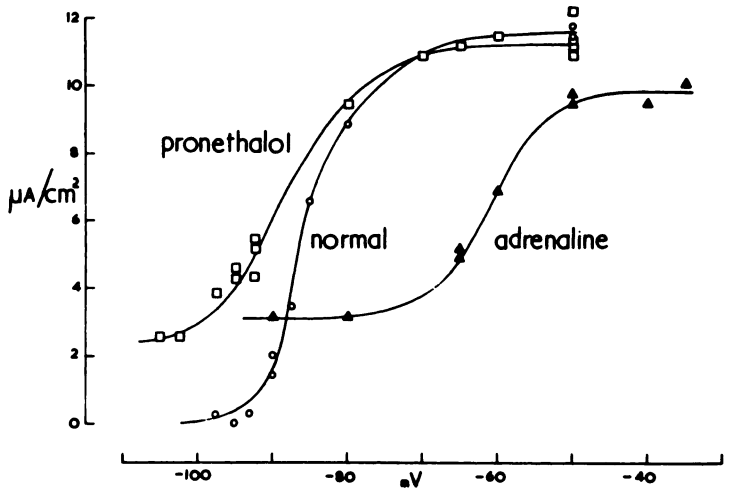


FIG. 20. Relations between steady state degree of activation (s_∞) of slow K-current and membrane potential, measured in terms of current immediately following return to holding potential (−80 mV). Open circles, normal Tyrode; closed triangle, adrenaline, ($5 \cdot 10^{-7}$ g/ml); and open squares, pronethalol (10^{-6} g/ml). [From Hauswirth, Noble and Tsien (108) with permission of the American Association for the Advancement of Science.]

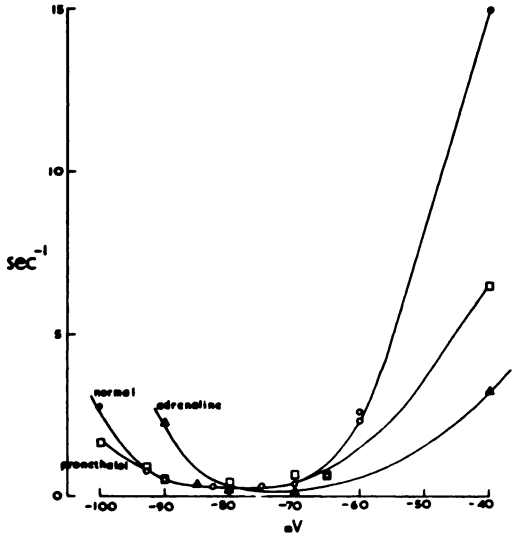


FIG. 21. Voltage dependence of rate of change of slow potassium current measured in terms of reciprocal of time constant (τ_s^{-1}) of current change. Symbols are the same as in figure 20. [From Hauswirth, Noble and Tsien (108) with permission of the American Association for the Advancement of Science.]

Furthermore, the shift back in the s-kinetics toward control (see fig. 20) by pronethalol does not provide decisive evidence that this occurs as a result of β-receptor blockade since pronethalol is a strong local anesthetic (91) and the possibility of a functional nonspecific antagonism of pronethalol in addition to the adrenergic effect of the drug on the pacemaker current could not be ignored (see below).

A. α-ADRENOCEPTORS AND CARDIAC MEMBRANE CURRENTS. The evidence for the existence of β-receptors in cardiac Purkinje fibers was provided by Cranefield *et al.* (49). Under the influence of methoxamine, the rate of rise as the differentiated upstroke of the action potential was reduced only, when the external K^+ concentration was increased to 16 mM with the resting potential being altered to about −60 mV. The remaining spike was probably due to the slow inward current, i_{si}, since the fast sodium current is largely inactivated at this voltage range. The application of phentolamine reverses the diminution of the upstroke, thus indicating that, whatever the current system may be, this effect is related to α-receptors. This finding is also compatible with the report of Trautwein and Schmidt (292), who showed that in normal K^+ concentration adrenaline did not alter the availability of the fast sodium current ("h_∞"). In addition, it was recently demonstrated that methoxamine reduces the

membrane resting potential by about 5 mV (112) and this may be an additional, although not the only, reason for reducing dV/dt_{max}. Tsien (296) applied phenylephrine (an α-agonist) in the presence of propranolol to cardiac Purkinje fibers and studied the current underlying pacemaker activity, i_{K_2}. He did not find any shift of the activation curve of the pacemaker current, s_∞. His findings were later confirmed in a somewhat extended study by other authors (112), using methoxamine. These overall findings thus exclude a relationship between i_{K_2} and α-adrenoceptors. However, at variance with these conclusions are the finding of Rosen *et al.* (235), who recently reported that phenylephrine reduced the spontaneous rate of discharge in Purkinje fibers. A change in the spontaneous firing rate under these conditions may result from alterations in such parameters as maximal diastolic potential, threshold potential, and the slope of the diastolic depolarization. Each of these parameters are again determined by several other components like equilibrium potential, location of the kinetics on the voltage axis, and instantaneous current-voltage relationship. The finding that i_{K_2} is not dependent on α-adrenergic receptors (112, 296) may therefore well be compatible with the result reported by Rosen *et al.* (235). On the other hand, Hauswirth *et al.* (112) showed that the instantaneous current which may be attributed largely to i_{K_1} is shifted in the inward direction with methoxamine. This effect is difficult to reconcile with the finding that α-adrenergic stimulating drugs reduce the spontaneous frequency (235). Clearly, further investigation of the relationship between pacemaker potential and α-adrenoceptors is needed.

B. β-ADRENOCEPTORS AND CARDIAC MEMBRANE CURRENT SYSTEMS. Tsien (296) first suggested that i_{K_2} may be controlled by β-receptors on the grounds of the following experimental observations: 1) α-receptors did not control i_{K_2} for reasons discussed above; 2) propranolol by itself did not alter the pacemaker current; and 3) following the application of adrenaline, propranolol competitively reversed the effect of adrenaline on i_{K_2}. Tsien's (296, 297) analysis was confirmed and considerably extended by Hashimoto *et al.* (102) and Hauswirth *et al.* (113). Procaine was found not to influence i_{K_2} thus excluding the possibility that the associated local anesthetic property of propranolol may offset the effect of adrenaline on i_{K_2}. Similar observations were reported by Weld and Bigger (314) with respect to the effect of lidocaine on i_{K_2}. Furthermore, atenolol (tenormin, ICI66082, ICI Ltd, England), a β-adrenoceptor antagonist without local anesthetic activity (257), also competitively blocked the effects of adrenaline (102) and penbutolol (HOE893), a β-blocking drug *with* local anesthetic action, without adrenaline pretreatment did not exert effect on i_{K_2} and whereas, following the administration of adrenaline, the *l*-isomer of penbutolol was about 10 times more effective in blocking the adrenergic action than the *d*-isomer (113). These findings together with those of Tsien (296, 297) already cited provide strong evidence that i_{K_2} is controlled *via* β-adrenoceptors. Moreover, Reuter (224) applied identical concentrations of isoprenaline through a microelectrode to the outside of the membrane as well as by injection into the interior of the cell. Since no positive chronotropic effect was apparent following intracellular application of isoprenaline, he concluded that the β-adrenoceptors were located at the outer surface of the membrane.

It has been demonstrated that the effect of catecholamines is mimicked closely by cyclic AMP and enhanced by the administration of phosphodiesterase inhibitors like theophylline or Ro 72956 (296–298). However, the molecular basis for the common mechanism has not yet been clarified. Hauswirth *et al.* (108) proposed that adrenaline simply adds positive charge to the outside of the membrane, thereby producing the same effect as hyperpolarization. This possibility now appears untenable from the experimental results reported by Tsien (296, 297). He suggested that the

effects of catecholamines and phosphodiesterase inhibitors are brought about by changing the fixed negative charges at the interior of the membrane. This may result if these agents bring about a specific and direct phosphorylation of proteins near the i_{K_2}-channel (294); alternatively, it may be that catecholamines and phosphodiesterase inhibitors lead to an increased rate of calcium uptake by the sarcoplasmic reticulum, a fall in the levels of intracellular Ca^{++}, and removal of calcium from specific binding sites near i_{K_2} channel. The latter possibility would be expected to cause the voltage dependence of all the current systems to be shifted but this is not the case. For example, the kinetics of the fast sodium current are not changed significantly by adrenaline (142, 163, 292). On the other hand the first possibility is attractive but the evidence for it so far available is not entirely convincing. Tsien (297) has deduced his hypothesis on the grounds that phosphodiesterase inhibitors like theophylline mimic or enhance the effect of adrenaline; in maximal effective concentrations these agents partially abolish the chronotropic action, thus indicating a common final mechanism. On the other hand, La^{3+} ions do not show abolition of the chronotropic effect. However, nothing is known about how such a discrete phosphorylation may come about and to which kind of molecule the phosphate ion may bind.

The dependence of the slow inward current (i_{si}) on an adrenergic receptor system is less certain. In Purkinje fibers Reuter (221) showed that adrenaline increased i_{si} and subsequently he analyzed this effect in much more detail. He (224) found that, in contrast to i_{K_2}, the variables d_∞ and f_∞ controlling the degree of activation of i_{si} are not shifted and for this reason, the augmentation of i_{si} under the influence of adrenaline was attributed to the increase of the fully activated conductance, g_{si}. However, Reuter (224) did not repeat the experiments following inhibition by a specific β-adrenergic blocking drug. Thus, it remains uncertain whether i_{si} is controlled by β-receptors or whether the effect of adrenaline on this current component is due to a direct membrane effect.

From the standpoint of antiarrhythmic actions of β-adrenoceptor blocking drugs, the effects of these agents on membrane currents in relation to β-receptor blockade need to be correlated with the known antiarrhythmic spectrum of these drugs. The data do not provide strong evidence to suggest that these drugs will influence reentrant arrhythmias since they do not alter those parameters of membrane property relevant to conduction velocity and refractoriness. Nevertheless, it is known that they do abort supraventricular tachycardias, due to atrioventricular reentry (256); here, their action is, in all probability, dependent on the inhibition of sympathetic impulse traffic in the atrioventricular mode with a secondary influence on the refractory period unrelated to alterations in the primary membrane effects in the nodal fibers. A clear rationale on the basis of pharmacological and electrophysiological considerations, however, exists for their efficacy in situations in which disorders of rhythm can be related to sympathoadrenal hyperactivity (256). Arrhythmias in this context undoubtedly arise on the basis of enhanced automaticity due to an augmentation of Δi_{K_2} and are therefore expected to be inhibited by specific β-adrenoceptor blocking drugs. As already discussed, the nature of the pacemaker phenomena in different ectopic tachyarrhythmias are essentially unknown and the mechanism of suppression of such ectopic activity by β-adrenergic blocking drugs remains inferential. For example, it is known that enhanced automaticity due to cardiac glycosides may be suppressed by β-antagonists (36) but there are no data on the effects of these drugs on the membrane currents underlying digitalis induced afterdepolarizations or TI's (9, 71). Similarly, there is paucity of data on the effects of β-antagonists on slow channel-dependent oscillations known to give rise to ectopic arrhythmias following coronary occlusion (316). A precise knowledge of the

ionic basis of such interactions in pathological situations is likely to provide a more rational basis for the control of arrhythmias by β-adrenoceptor blocking drugs.

3. Compounds Influencing Potassium Currents. In heart muscle, a number of discrete potassium current components (see above) have been identified and it is conceivable that each may be influenced individually by different pharmacological agents, ions, and hormones. Since such currents are the major determinants of repolarization, interventions which shorten or lengthen the action potential duration are likely to act *via* their effects on outward K currents and thereby influence the genesis as well as the control of cardiac arrhythmias. For example, as discussed, isolated and homogeneous prolongation of the action potential duration is likely to constitute an antiarrhythmic mechanism whereas shortening of the action potential duration will be proarrhythmic by corresponding alterations in the absolute refractory period. As in the case of the fast depolarizing sodium current, interventions may either alter the number of potassium channels ($\bar{g}_K$) or they may affect the kinetics of the potassium currents (171) (see equation 47).

Perhaps the potassium current so far studied in the greatest detail under the influence of drugs and ions is the pacemaker current (i_{K_2}) in Purkinje fibers. The available data on this current as it is affected by the local anesthetic antiarrhythmic agents and β-antagonists have been presented in the previous sections. Here it may be of general interest to consider the modifications of i_{K_2} due to changes in external ion concentration and pH. Unlike calcium or adrenaline, lowering of pH produces hardly any shift of the *s*-kinetics (second factor in equation 54) but decreases the absolute magnitude of the rectifier function $\overline{i_{K_2}}$ (first factor in equation 54). Hence, the time-dependent pacemaker current is diminished and consequently pacemaker activity is retarded (34, 116). Noble and Tsien (212) have shown that the fully activated current-voltage relation ($\overline{i_{K_2}}$) shows strong inward-going rectification with a negative slope at potentials positive to −75 mV (see also ref. 1). An increase of the extracellular K-concentration from 2.7 mM to 6 mM does not only shift the potassium equilibrium (−reversal) potential in the positive direction but also abandons the negative slope and, to a large extent, also the inward-going rectification (fig. 22). Since the latter is necessary for pacemaking (207, 212) it is not surprising that the pacemaker activity ceases in high potassium concentration despite the fact that the resting potential decreases, which in other situations normally would enhance automaticity (33, 290). In this context it should be noted that the *s*-kinetics are not shifted by changes in the external K-concentration (212). The effects of changes in external K-concentration are particularly significant in relation to the actions of major local anesthetic antiarrhythmic agents which may be K-dependent (289); the interaction may be an indirect one through effects on i_{K_2} or on resting membrane voltage, a major determinant of the MRD and conduction velocity (308, 309).

A variety of interventions like high external calcium (162, 282), prolonged administration of cardiac glycosides (66, 163, 200, 201), metabolic inhibition (181), halothane (105), adrenaline, and cyclic AMP (294–298) shorten the action potential duration. All such interventions are arrhythmogenic and the mechanisms underlying their actions at the membrane levels are likely to provide a rational basis for therapy. The shortening of the action potential may be brought about either by influencing the slow inward current or by increasing g_K. The latter may depend on the level of the intracellular potassium (184). Isenberg (148) injected Ca^{++} into Purkinje fibers; the observed shortening of the action potential was attributed to an increase of the potassium conductance although no direct evidence for the hypothesis was provided (148). On the other hand, Kass and Tsien (162) showed in voltage clamp experiments that high Ca_o^{++} and adrenaline behave quite

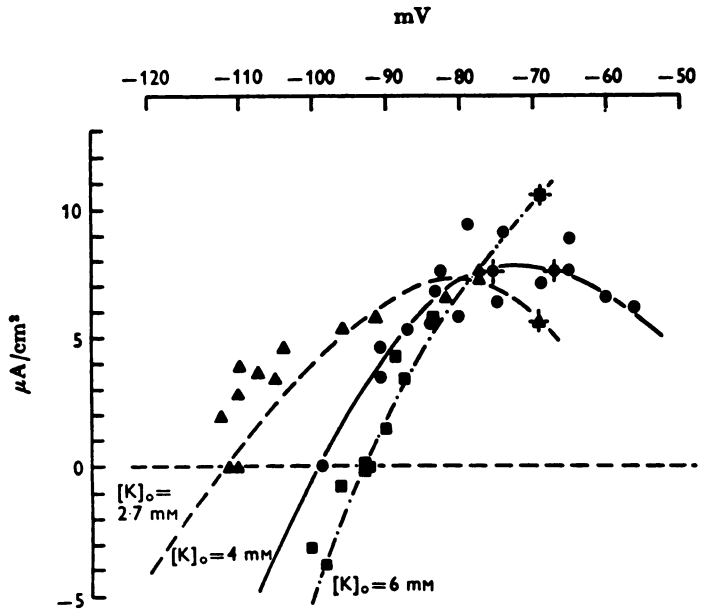


FIG. 22. Rectifier functions of i_{K_2} at 2.7 mM $[K]_o$ (dashed line), 4 mM $[K]_o$ (solid line) and 6 mM $[K]_o$ (dashed-dotted line). The points were obtained by dividing the time dependent current during step depolarization by the current change on return to the holding potential and multiplying this "rectifier ratio" by total amplitude of steady state curves of activation related to different K-concentrations used. The relations cross each other on the positive side of the reversal potentials and (with the exception of the curve obtained in 6 mM $[K]_o$) they show negative slopes at about 25 mV positive to reversal potentials. The curves have been drawn by eye through points to indicate typical shape of relations. [From Noble and Tsien (212) with permission of the authors and the *Journal of Physiology*.]

differently with regard to their influence on i_{x_1} despite the fact that both agents have significantly similar effects on the action potential configuration. Earlier repolarization is governed by two factors. First, calcium-rich solutions generally raise the plateau voltage; in turn, the higher plateau level accelerates the time and voltage dependent current changes which trigger repolarization. Increases in plateau height imposed by depolarizing current consistently produced shortening of the action potential (162).

A second factor in the action of calcium ions involves i_{K_1}, the non-time-dependent instantaneous background current. Raising $Ca_o^{++}O$ enhances i_{K_1} and thus favors faster repolarization. Adrenaline, on the other hand, shifts the activation curve of the plateau current ($x_{1\infty}$) in the hyperpolarizing direction besides enhancing i_{S_i}; thus, the plateau is elevated with an additional increase in activation of i_{x_1}. Both mechanisms are expected to lead to a shortening of the plateau (162). In ventricular muscle, small doses (1 mM) of theophylline did not change the outward current. However, larger doses (5 mM) of this substance shifted $x_{1\infty}$ in the hyperpolarizing direction, thereby providing more hyperpolarizing current and thus shortening the plateau (248). Whether the observed abbreviation of the plateau by adrenaline and theophylline can be prevented by β-adrenergic blocking drugs awaits experimental study.

Certain major antiarrhythmic drugs have also been found to produce an abbreviation of the action potential duration, in particular DPH and lidocaine (26, 27, 262). Although such shortening of the action potential has been proposed as an antiarrhythmic mechanism (27), a critical appraisal of the overall data on the relationship between accelerated repolarization and arrhythmogenesis makes this possibility extremely unlikely. The ionic mechanism for the accel-

erated repolarization following DPH is not known but may be similar to that described for lidocaine (10, 11). In the context of antiarrhythmic actions, perhaps lengthening of the action potential duration is of greater practical and theoretical interest. Experimental and clinical observations have clearly indicated that prolongation of the action potential duration may, under certain circumstances, be proarrhythmic and under others it may clearly be antiarrhythmic (81, 255, 260). Such differences may be accounted for by postulating variable rates of repolarization in the myocardium: homogeneously occurring repolarization with consequent lengthening of the absolute refractory period is thus likely to diminish the likelihood of arrhythmias whereas inhomogeneity in repolarization with marked temporal dispersion in the recovery of excitability will predispose to derangement of rhythm (255, 270). The mechanism of antiarrhythmic actions of bretylium tosylate, as an agent which is extremely effective in recalcitrant ventricular fibrillation (18, 19), is of interest in this regard. In normal Purkinje (29, 325) but not in atrial (219) fibers, bretylium has been shown to prolong the action potential duration with a consequent lengthening of the effective refractory period but the effects of the drug on various repolarizing K current systems are not known. Under voltage clamp conditions, the drug has been shown to enhance the magnitude of the inward Na current by augmenting the maximum Na conductance with effect neither on inactivation nor reactivation kinetics (178). It is, however, conceivable that this effect on the inward Na current is a feature seen only in depressed tissue and is mediated by release of catecholamines, a possibility that may be tested by the use of specific β-adrenergic blockade or prior reserpinization of the preparation. The possibility thus remains that the fundamental mode of antifibrillatory action of bretylium is the homogeneous prolongation of the action potential duration; the ionic mechanisms which form the basis for this electrophysiological change need further elucidation.

It is noteworthy that a number of local anesthetic antiarrhythmic drugs such as quinidine, procainamide, and disopyramide also prolong the action potential duration to a variable extent (253, 255, 301). The ionic mechanism underlying this alteration has not been studied under voltage clamp conditions but it is undoubtedly of significance insofar as clinical observations are concerned. Agents which combine the proclivity to depress the fast response as well as that for delaying terminal repolarization phases of the cardiac action potential appear to have a greater efficacy in the elective and prophylactic control of atrial fibrillation in man (253). Isolated prolongation of the action potential duration in atrial muscle in hypothyroidism (81) also appears to be a potent antifibrillatory mechanism, the converse in hyperthyroidism in which atrial repolarization is markedly accelerated (81). Again, the study of the ionic mechanisms underlying the repolarization processes in atrial muscle removed from animals with chronic experimental hyperthyroidism and hypothyroidism is likely to yield data which may provide further insight into the relationship between fibrillatory activity and the time course of repolarization in cardiac muscle. Particularly significant in this respect are the electrophysiological effects of the benzfuran derivative, amiodarone hydrochloride (39). After chronic administration in animals, amiodarone was found to produce a uniform prolongation in the action potential duration in atrial, ventricular, and Purkinje fibers (60, 259) without effect on the resting membrane voltage but with minor effects on the MRD of membrane responsiveness (60). The drug has the most potent antifibrillatory and antiarrhythmic actions in both experimental and clinical cardiac arrhythmias (60, 236, 237). Very little, however, is known about its effects on various cardiac membrane currents but because of its extreme potency as an antiarrhythmic agent and the fact that its major action is on repolarization rather than depolariza-

tion phases of the action potential, a detailed evaluation of its electrophysiological effects on heart muscle under voltage clamp conditions is likely to be of much theoretical and practical significance. Again, it needs to be emphasized that the electrophysiological changes produced by amiodarone on cardiac muscle are clearly different from the well-known clinical situations in which prolonged repolarization tends to be associated with an arrhythmogenic propensity. For example, in acute drug testing in man, quinidine and procainamide are known not uncommonly to exacerbate ventricular arrhythmias (85); similarly, certain psychotropic drugs such as thioridazine (quinidine) may produce recurrent ventricular tachycardia in some patients (75). It should be appreciated that all these compounds alter repolarization as well as depolarization phases of the cardiac action potential associated with changes on the electrocardiogram not dissimilar to those produced by severe degrees of hypokalemia. The possibility must therefore be considered that the major factor responsible for arrhythmogenicity of procainamide and allied compounds is the variable effect of these agents on repolarization and depolarization, which are likely to be most pronounced during acute drug administration (85) or during the occurrence of excessive drug concentrations.

4. Agents Which Modify the Second Slow Inward Current. Some inorganic ions like Ni, Co, and Mn (168, 217, 304) and several pharmacological agents such as acetylcholine (32), verapamil, and its methoxy derivative, D600 (168), have been shown, under voltage clamp conditions, to inhibit the channel conducting the second slow (calcium) inward current (223, 238). However, it is still not known whether these compounds are totally selective or whether they may also block other current systems. Since the slow current component is thought to play a role in the generation and conduction of very slow travelling impulses of low amplitude (320, 321) it is possible that these ions and substances may have an antiarrhythmic effect in certain types of reentrant and ectopic arrhythmias (see above). Reuter (221) has shown that adrenaline enhanced the second slow inward current. He (224) demonstrated that neither the activation nor the inactivation kinetics of the current were, however, shifted along the voltage axis by adrenaline. The experimentally observed increase in i_{si} was attributed to an increase of $\overline{g_{si}}$ (224, 226). This may result from: 1) a widening of the exist ing calcium channels, thereby causing less specificity. This would lead to a shift of the calcium reversal potential, E_{Ca}; 2) another possibility would be that adrenaline causes opening of additional specific calcium channels which had been closed previously. Since E_{Ca} is not shifted with adrenaline it is rather likely that the second possibility holds true (225, 227). Unlike adrenaline, higher doses of theophylline shift the activation variable of the slow inward current (d_∞) and thereby the threshold of i_{si} in the negative direction (225). Vassort *et al.* (300) showed in voltage clamped atrial fibers that adrenaline increased the magnitude of the second slow inward current although it is not entirely clear from their records whether it influenced the instantaneous current voltage relationship or the kinetics of the slow inward current.

Of significance are the recent observations of Kass and Tsien (161) that various calcium antagonists like Mn^{++}, La^{++}, or D600 abolished the slow inward current in Purkinje fibers but they failed to act selectively. Moreover, these agents decreased the steady state degree of activation of i_{x_1} and increased the time independent outward plateau current. It was also demonstrated that raising the external Ca concentration had a rather similar action on i_{x_1}, possibly mediated by changes in the amount of membrane surface charge. It must be emphasized, however, that of all the calcium antagonists which have been evaluated, verapamil hydrochloride is the only compound which has been studied systematically in experimental and clinical cardiac arrhythmias (120, 263, 317, 323). Its

electrophysiological actions on cardiac muscle, delineated either by standard microelectrode techniques (234, 263, 317) or under voltage clamp conditions (161, 168), differ strikingly from those of all other antiarrhythmic drugs (255). In concentrations in which the drug exerts its therapeutic actions, verapamil has no effect on the upstroke velocity of the action potential, or the membrane responsiveness in atrial, ventricular, or Purkinje fibers (103, 232, 263). These findings are consonant with the data from voltage clamp studies indicating no effect of the drug on g_{Na} or the kinetics of the fast inward sodium current in Purkinje fibers (168). Consistent with the selectivity of its action on i_{si} (168) the drug was found to accelerate early repolarization in atrial (263) and Purkinje (232) fibers without an alteration in the time for complete repolarization. Of note was the fact that verapamil depressed spontaneous diastolic depolarization originating at normal levels of membrane potentials in canine Purkinje fibers (48), representing another potential mode of action of the drug; the precise ionic mechanism underlying this effect needs elucidation. Tsien (296) clearly showed that D600, another inhibitor of the slow inward current, has no influence on i_{K_2}. This suggests that any influence of calcium antagonists on the pacemaker activity must be due to effects of these compounds on current components other than i_{K_2}. Thus the effects of verapamil on the pacemaker potential need further study. On the other hand, it should be emphasized that enhanced automaticity arising on the basis of i_{si}-dependent spontaneous depolarizations as might occur in ischemia might be responsive to low concentrations of verapamil. Verapamil is known to be effective in controlling digitalis-induced arrhythmias (120, 147) but as yet there are no reports on the effects of verapamil on digitalis-induced TI's or after depolarizations (9, 71). However, the available experimental data clearly suggest that the antiarrhythmic actions of the drug may be accounted for by its ability to depress the i_{si}-dependent potentials; the i_{si}-dependent fibers in the atrioventricular node undoubtedly constitute the principal locus of verapamil's action in terminating reentrant supraventricular arrhythmia for which the drug is the most potent pharmacological agent available (120).

C. How Well is the HH-Theory Applicable to Heart Muscle in Relation to Drug Action?

It is not the aim here to review all the arguments in favor and against the applicability of the HH-theory to heart muscle. The subject still continues to be the source of much discussion and controversy (21, 97, 156, 180, 184, 205, 265, 278).

Ignoring all the objections regarding the difficulties of "clamping" the fast sodium current in heart muscle, for slower current components, and assuming the existence of a more or less uniform polarization, one may obtain some indication in favor or against the hypothesis that the HH-theory may well serve as a meaningful description of drug action in cardiac membranes in a rather simple way. Running the HH-equations (or their modifications adjusted for heart muscle) describing the various current components on the computer (23, 180, 207) one could change the mathematical parameters in such a way as to mimic the voltage clamp results, *i.e.*, feeding experimental information into the model. The result should be computed action potentials which would resemble the ones recorded experimentally under the influence of a particular drug. This has been done fairly recently in an attempt to reconstruct the actions of some widely used pharmacological agents. The actions of increased concentrations of calcium and of adrenaline on the pacemaker potential of Purkinje fibers and the effect of a diminution of the second slow inward current have been mimicked by mathematical reconstructions (107, 180). Similarly, the actions of high and low pH (34) and the actions of TTX and local anesthetics (106) have been simulated by numerical computations. The fact that the

actions of drugs can be mimicked rather closely cannot, of course, be regarded as "evidence" against the objections concerning the accuracy of voltage clamp data in heart muscle (156). In fact, the aims of these computations are 2-fold: First, they could be used as a feedback to give some indication as to how good the approximation between the voltage clamp records and the currents flowing at the membrane really is. Second, when the assumption is made that the model is "correct," such computations may provide some information about the relative importance of various current components and how their modification may influence the shape and the duration of the action potential.

However, it should be emphasized that there is an "important heuristic difference" between the model of McAllister *et al.* (180) and the original HH-model (133). McAllister *et al.* (180) stated: "Unlike the squid model, it is impossible to obtain all the required information from voltage clamp analysis of a single fiber. Moreover, there is a substantial degree of natural variation between Purkinje fibers in the relative magnitudes and speeds of different current components. Since the slow changes in potential occurring in cardiac fibers are generated by very small currents it is entirely possible that the magnitudes and rates we have used in our equations will require further modification in future applications." McAllister *et al.* (180) continued: "Although it is tempting to determine what modifications are required to reproduce, *e.g.,* abnormal rhythms [*cf.* Hauswirth *et al.* (109)], we doubt the wisdom of exploring such modifications without also studying such phenomena experimentally. The equation described here should be helpful in determining how experimentally known changes in particular ionic currents produce their overall effects, but less appropriate as a basis for purely theoretical explorations."

V. Summary

Although the voltage clamp technique has been used for over two decades to study excitation and contraction phenomena in cardiac muscle, serious attempts to investigate drug effects, in particular those of antiarrhythmic compounds, on individual ionic membrane current systems and their kinetics during the inscription of the action potential in different types of cardiac fibers, have begun only relatively recently. In heart muscle the technique, utilizing either the double microelectrode method or sucrose gap, has inherent limitations because of unfavorable fiber geometry which may preclude fair uniformity of voltage change during clamp. In the case of the double microelectrode technique, the current is limited by the electrode impedance and the clamp may have difficulty in accurately following large transient currents.

Despite these and other limitations of the method, there is surprising agreement on the available voltage clamp data with respect to the ionic basis of the normal cardiac and pacemaker potentials. However, the use of the technique for the elucidation of drug effects on the cardiac membrane is so much in its beginnings that the conclusions that may be drawn from measured parameters under voltage clamp conditions must still be tentative, requiring more detailed study and correlation with data acquired by other experimental methods. As a first approximation, it is nevertheless becoming increasingly apparent that the fundamental mechanisms of action of antiarrhythmic drugs may be interpreted from their effects on various membrane currents during different phases of the cardiac action potential in pacemaking and nonpacemaking tissues.

Voltage clamp has permitted the separation of depolarizing inward currents into a kinetically fast transient (fast response) carried by Na and a kinetically much slower transient (slow response) carried by calcium and sodium; repolarizing currents, three or four in number, with complex time and voltage dependent characteristics, are carried largely but probably not exclusively by potassium. The kinetic properties of the other currents do not strictly resemble those described for giant squid axons by

Hodgkin and Huxley. The fast response, the main determinant of conduction velocity, is reduced in low Na media and in heart muscle it is less sensitive to TTX than that in nerve. The slow response, present normally in sinoatrial and atrioventricular nodal fibers, may develop under pathological conditions such as myocardial ischemia but appears to be distinct from "transient inward current" developing in high concentrations of cardiac glycosides. The best studied of the outward currents is the pacemaker potential in Purkinje fibers, i_{K_2}, the deactivation of which unmasks a substantial inward current. There is growing evidence to indicate that ionic mechanisms other than or additional to i_{K_2} may be involved in the normal sinoatrial automaticity or in other pacemaking phenomena such as those in arrhythmias. The time-dependent outward current i_{x_1}, developing in the region of the plateau of the action potential, is important in repolarization in Purkinje fibers but its significance in the working myocardium is uncertain. Its reversal potential is more positive than that for K, so ions other than K may be involved in its generation. A current (i_{K_1}) that is instantaneously activated, carried by K and showing inward-going rectification, appears to serve as the primary background outward current in Purkinje fibers as well as in the working myocardium. The significance of the transient chloride conductance that appears to occur in Purkinje fibers is unknown.

There is paucity of data regarding changes in ionic currents and relevant membrane conductances involved in the recognized categories of arrhythmogenesis: altered impulse propagation, automaticity and excitability. The relationship of these final pathways of arrhythmogenesis to alterations in the action potential duration is uncertain but it is recognized that interventions such as halothane, anoxia, or ischemia, which markedly accelerate repolarization, are proarrhythmic. Depression of conduction velocity or unidirectional block may occur as a consequence of attenuated fast response or following its replacement by the slow response; these are conducive to reentry which may also result from inhomogeneity in repolarization in subjacent myocardial fibers. The ionic mechanisms underlying enhanced automaticity under pathological conditions are uncertain but may be mediated partly by slow response dependent potentials. Of particular interest are low voltage oscillations found in Na-free Ca-rich solutions, hypokalemia, or ischemia; the precise mechanisms for the oscillations of the membrane potential are possibly different but they may all give rise to potentially lethal regenerative depolarizations. The concept of altered excitability as an arrhythmogenic mechanism *in vitro* independently of changes in impulse generation or impulse propagation is relatively new but the various membrane components of excitability in long mammalian Purkinje fibers can now be studied by the double microelectrode and constant intracellular current application technique.

It is suggested in this review that for the present a reasonable approach—which may need revision in the near future in light of further data—is to categorize antiarrhythmic mechanisms by considering the effects of known agents on: 1) the fast inward sodium current; 2) the relationship between membrane currents and adrenergic receptor excitation and inhibition; 3) repolarization currents; and 4) slow inward calcium currents. TTX selectively blocks the fast sodium channel in an all-or-nothing fashion without altering its kinetics but because of its extreme neurotoxicity it is of little therapeutic significance; droperidol, a neuroleptic antiarrhythmic drug, has a TTX-like component of action on the cardiac membrane but it also delays the reactivation of the fast sodium current. Therapeutic concentrations of the so-called local anesthetic drugs—quinidine, lidocaine, procainamide, and presumably the newer agents mexiletine, tocainide, and disopyramide—also reduce the number of Na channels without influencing the inactivation kinetics but they all prolong the time necessary for the recovery from inactivation; under their influence, the refractory

period may greatly outlast the duration of the action potential and phase 4 depolarization is markedly retarded. Although only elucidated for lidocaine, these agents may decrease the slope of phase 4 depolarization by enhancing the net outward K current and may widen the difference between the V_{mdp} and V_{th} by repolarizing the membrane of tissue depolarized by injury. In long mammalian Purkinje fibers, lidocaine and procainamide shift the nonnormalized strength-duration curve upward without affecting V_r but procainamide makes V_{th} less negative while lidocaine has little effect on V_{th}. There are no comparable data on ischemic tissues or on the effects of these drugs on digitalis-induced transient afterdepolarizations. The effects of DPH are very similar to those of lidocaine and the local anesthetics but it has an additional effect on the slow inward current.

The major effect of propranolol, in therapeutically meaningful concentrations, is merely on the activation of i_{K_2}, and only in very high concentrations do the effects on the fast Na current become apparent. It is now certain that the effect on i_{K_2} is mediated by β-adrenergic receptors independently of α-receptors as well as that of associated local anesthetic properties present in some β-adrenoreceptor antagonists. The ionic mechanisms underlying the homogeneous prolongation of the action potential, which is considered an antiarrhythmic mechanism, and what is produced by interventions such as the ablation of the thyroid gland or administration of compounds such as amiodarone or bretylium is uncertain. Since amiodarone is the most potent antiarrhythmic compound as yet synthesized, a detailed knowledge of its effects on various cardiac membrane currents is likely to be of much theoretical and practical significance. Detailed voltage clamp data are, however, available on the effects of verapamil, a papaverine derivative, which has been shown to selectively block the slow inward current in normal Purkinje fibers and to inhibit the slow response in experimentally-induced pathological states. The findings are of therapeutic relevance since the drug predictably terminates virtually all cases of supraventricular tachycardias due to atrioventricular nodal reentry.

Voltage clamp studies in the last decade or so have therefore provided much insight into the ionic basis of the cardiac action potential and the pacemaker potential. It is becoming increasingly likely that many physiological and pharmacological processes in the intact heart may be understood in terms of alterations in cardiac membrane currents. Only the integration of results obtained by the currently available techniques in preparations *in vitro*, in the isolated heart and intact animals as well as man, with those of voltage clamp if it can be improved further to be utilized in various types of cardiac fibers is likely to provide the rational framework for the understanding of the genesis and the pharmacological control of cardiac arrhythmias.

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APPENDIX I

The abbreviations used throughout the review are:

V_m Transmembrane potential expressed as potential of the intracellular fluid with respect to the extracellular fluid (mV).

V_r Resting value of V_m (mV).

V Transmembrane potential expressed as the deviation of intracellular potential from the resting value ($V = V_m - V_r$).

x Distance along the fiber (cm).

i_a Intracellular axial current (μA).

i_m Membrane current per unit length of fiber ($2\pi a \cdot I_m$); ($\mu A \cdot cm^{-1}$).

i_c Membrane capacity current per unit length of fiber ($2\pi a \cdot I_c$); ($\mu A \cdot cm^{-1}$).

i_i Membrane ionic current per unit length of fiber ($2\pi 1 \cdot I_i$); ($\mu A \cdot cm^{-1}$).

I_i Ionic (resistance) current ($\mu A \cdot cm^{-2}$).

I_o Constant current applied to the interior of a fiber at $x = 0$; (μA).

r_m Membrane resistance per unit length of fiber ($= R_m/2\pi a$); ($\Omega \cdot cm$).

r_a Intracellular resistance to flow of current along the fiber ($= R_i/\pi a^2$); ($\Omega \cdot cm^{-1}$).

R_m Membrane resistance ($\Omega \cdot cm^2$).

R_i Intracellular resistivity ($\Omega \cdot cm$).

t Time (msec).

c_m Membrane capacitance per unit length of fiber ($= 2\pi a \cdot C_m$); ($\mu F \cdot cm^{-1}$).

C_m Membrane capacitance ($\mu F \cdot cm^{-2}$).

Θ Conduction velocity (m/sec).

a	Fiber radius (cm).
K	$\Theta^2 \cdot 2R_i \cdot C_m/a$.
λ	Space constant $[\sqrt{(R_m \cdot a/2R_i)} = \sqrt{(r_m/r_a)}]$; (cm).
τ	Time constant (msec).
V_0/I_0	Input resistance (Ω).
V_{th}	Threshold voltage (mV).
Q_{th}	Charge necessary to bring V_r to V_{th} (nC).
V_{mdp}	Maximal diastolic potential.