THE CONDITIONS FOR INITIATING "ALL-OR-NOTHING" REPOLARIZATION IN CARDIAC MUSCLE

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ABSTRACT Solutions have been computed for the point polarization of an infinite cable-like membrane obeying the equations used to reproduce the Purkinje fiber action potential (Noble, 1960, 1962*a*) in order to determine the conditions for initiating all-or-nothing repolarization during the action potential plateau. It was found that all-or-nothing repolarization would not be obtainable during the first half of the action potential in spite of the fact that the membrane current-voltage relations contain regions of negative conductance. At the point at which the all-or-nothing response is first obtained, the computed threshold is large and repolarization almost back to the resting potential would be required in order to initiate the response. The results are discussed in relation to the experimental evidence at present available on repolarization in heart muscle.

INTRODUCTION

The mechanism of the cardiac action potential has received considerable attention recently and, while it is generally agreed (Draper and Weidmann, 1951; Weidmann, 1955, 1956; Brady and Woodbury, 1960; Hoffman and Cranefield, 1960) that the initial rapid depolarization is probably produced by a regenerative increase in sodium permeability as in nerve, the mechanism of the much slower repolarization is still disputed. The equations formulated by Hodgkin and Huxley (1952) to describe the electrical activity in squid nerve, when modified to describe long-lasting action potentials (FitzHugh, 1960; Noble, 1960, 1962*a*, 1962*b;* Brady and Woodbury, 1960; George and Johnson, 1961), imply a repolarization mechanism which is regenerative. By applying repolarizing currents during the plateau it should therefore be possible to initiate an all-or-nothing, propagated repolarization response before the natural repolarization occurs. The experimental information at present available shows that this phenomenon can be obtained (Weidmann, 1951; 1956; Cranefield and Hoffman, 1958; Chang and Schmidt, 1960) but its occurrence depends rather critically on the experimental conditions and in some circumstances it cannot be obtained at all (Johnson and Tille, 1960, 1961).

There is no doubt that if the polarizing currents were applied uniformly to the membrane then failure to obtain all-or-nothing repolarization would be conclusive evidence against the applicability of any simple modification of the Hodgkin-Huxley equations to cardiac muscle. However, in all these experiments, non-uniform polarization, usually with microelectrodes, has been employed and it is therefore necessary to determine more precisely the conditions under which non-uniform polarization may initiate an all-or-nothing response.

The experiments referred to may be divided into two categories. Those of Johnson and Tille involved passing current through one barrel of a double-barreled microelectrode inserted into a *sheet-like* preparation, the wall of the rabbit ventricle. They recorded the voltage displacement with the second barrel and they found that the relations between voltage displacement and polarizing current during the plateau are virtually linear. This result was interpreted as indicating voltage independent ionic conductances and Woodbury (1961, 1962*a,* 1962*b*) and George and Johnson (1962) have formulated models making this assumption. It has been shown in a previous paper (Noble, 1962*c*) that this conclusion does not necessarily follow from Johnson and Tille's results and that solutions of the differential equations for non-uniform polarization of a sheet-like membrane (Woodbury and Crill, 1961) obeying modified Hodgkin-Huxley equations described remarkably linear polarizing current-voltage relations.

The experiments of Weidmann (1951, 1956) and of Chang and Schmidt (1960) involved passing current through a microelectrode inserted into *cable-like* preparations (mammalian Purkinje fibers). In these conditions, the polarizing current-voltage relations during the plateau are non-linear and strong enough currents applied after a certain time during the plateau will initiate an all-or-nothing response. The threshold for this response is often rather large. For example, Weidmann's (1951) Fig. 5 shows an experiment which required polarization to or even beyond the resting potential. It has been suggested (Woodbury, 1961, 1962*b*) that this indicates that the negative conductance responsible for the response does not occur in the potential range of the action potential.

The experiments of Cranefield and Hoffman (1958) are difficult to classify, but as they used papillary muscles instead of the ventricle wall and large external electrodes for polarizing the muscle, their situation probably approximated more closely to the cable case than to the sheet case.

The computations described in this paper were done to define the conditions for initiating all-or-nothing repolarization in a cable-like preparation with a membrane obeying the equations formulated to describe the Purkinje fiber action potential (Noble, 1960, 1962*a*). We have also confirmed Weidmann's experimental finding that it is not possible to initiate all-or-nothing repolarization during the early part of the Purkinje fiber action potential using point polarization.

THEORY AND COMPUTATION

Convention for Referring to Membrane Potential. Two symbols for the membrane potential will be used in this paper:

E_m is the membrane potential in millivolts expressed as the inside potential minus the outside potential.

V is the *displacement* of E_m from a "stable" zero current value, usually the plateau potential. Thus, if the plateau potential $= E_0$ then $V = E_m - E_0$.

Current-voltage relations will be plotted in terms of E_m. Variations of voltage with distance will be plotted in terms of V.

The Purkinje fibers of ungulates frequently extend for some distance in a connective tissue sheath before branching and, in favourable circumstances, the equations of cable theory (*e.g.* Hodgkin and Rushton, 1946) may be applied (Weidmann, 1952). The simplest form of solution to these equations arises if the fibre is assumed to be infinitely long and to have a membrane conductance which is independent of the membrane potential. Steady polarization of the fiber with an intracellular point electrode then produces a membrane voltage deflection, V, whose magnitude declines exponentially as the distance, x, from the polarizing electrode increases. The input resistance of the fiber is $\frac{1}{2}\sqrt{r_i/g_m}$, where r_i = resistance of unit length of intracellular fluid to axial flow of current (i_a) and g_m = conductance of membrane in unit length of fiber to radial flow of current (i_m), so that when g_m is constant the relation between the electrode current and the voltage deflection at any point along the fiber is linear.

When g_m varies with the membrane potential, the polarizing current-voltage relation will be non-linear. It is important to note that the shape of the polarizing current-voltage relation will be different from that of the membrane current-voltage relation unless the polarizing current is applied uniformly to the membrane (Cole and Curtis, 1941), so that the effects of non-uniform polarization cannot be obtained directly from the shape of the membrane current-voltage relation without reference to the cable properties of the fiber.

In order for an all-or-nothing regenerative response to be obtained, the appropriate current-voltage relation must not only be non-linear but must also contain a range of potentials over which the conductance is negative. The membrane current-voltage relations given by the Hodgkin-Huxley equations do contain negative conductances and in the equations used to describe the Purkinje fiber action potential it is possible to simulate all-or-nothing reprolarization with uniform currents almost throughout the duration of the plateau (Noble, 1962*a*). To determine whether all-or-nothing repolarization may be obtained with currents applied at one point in the fiber it is necessary to solve equation (1):

$$\frac{d^2V}{dx^2} = r_i i_m \tag{1}$$

where i_m is a function of V given by the membrane current-voltage relation. To obtain this function, the same assumptions were made as in a previous paper (Noble, 1962*c*, equations (4)–(13)), *i.e.* the sodium current was equated to the steady state current while the potassium current was equated to the instantaneous current obtained by setting the time-dependent component of the potassium conductance to the value which it attains at each time during a normal computed action potential. Four times after the beginning of the action potential were chosen: 100 msec ($n = 0.582$); 150 msec. ($n = 0.645$); 170 msec. ($n = 0.665$); 200 msec. ($n = 0.687$). The membrane current-voltage relations obtained in this way are shown in Fig. 1.

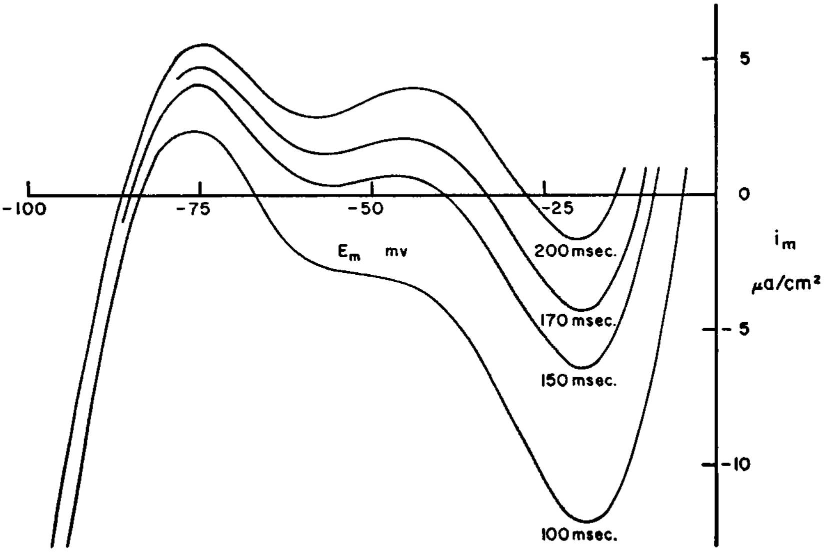

FIGURE 1 Membrane current-voltage relations given by equations used to reproduce the Purkinje fiber action potential (Noble, 1962*a*). Abscissa: membrane potential in mv. Ordinate: total membrane current ($I_{Na} + I_K$) given by steady state sodium current and the potassium current obtained by assuming the slow time-dependent component of g_K to have the values which it attains at each time during a normal computed action potential. Description in text.

At each time, the curve crosses the current axis at three points, two of which (the "plateau" point on the right and the "resting potential" point on the left) are stable since di_m/dV is positive. The middle points, at which di_m/dV is negative, are unstable and for the case of uniform polarization of the membrane they define the *voltage* thresholds for the initiation of an all-or-nothing repolarization. At voltages positive to this threshold, the sodium current is greater than the potassium current and, in the absence of applied current, the membrane potential would return to the plateau. At voltages negative to the threshold voltage, the potassium current exceeds the sodium current so that, once the membrane has been repolarized beyond this voltage, the repolarization process would continue even when the applied repolarizing current is switched off. As the action potential proceeds, the voltage threshold approaches the plateau potential and, at the end of the plateau, the steady state current-voltage relation (not shown in Fig. 1) no longer crosses the voltage axis in the region of the plateau and the more rapid phase of repolarization then begins (FitzHugh, 1960; Noble, 1962*a*).

The *current* threshold for uniform polarization is at the minimum of the i_m/E_m curve. Currents larger than the current at this point would repolarize the membrane beyond the threshold voltage if applied long enough to charge the membrane capacity. This current threshold is over 10 μa/cm^2 at 100 msec. and about 2 μa/cm^2 at 200 msec.

If the membrane potential in the absence of applied current is at the plateau (right-hand stable point) then the membrane conductance (i_m/V) for repolarizing currents is positive until the middle, unstable point is reached. Between this point and the left-hand stable point, the membrane conductance is negative. This negative conductance grows larger in both magnitude and voltage range as the action potential proceeds.

In order to solve equation (1) it is necessary to obtain initial values for V and $\mathrm{d}V/\mathrm{d}x$ for at least one point, x. This was done by making the voltage deflection at $x = 0$ very small (-0.1 mv from the right-hand stable point) so that i_m could be assumed to be a linear function of V. We then have:

$$\frac{\mathrm{d}V}{\mathrm{d}x} = \pm\frac{\mathrm{V}}{\lambda} \tag{2}$$

where $\lambda = \sqrt{r_m/r_i}$ and $r_m = V/i_m$. The sign determines whether V is increasing or decreasing with distance which depends on whether the polarizing electrode is on the positive or negative side of x.

The values of r_i and λ affect the current and distance scales in the computations but do not influence the shape of the V/x or V/i_a relations; *i.e.* by suitable adjustment of the x and i_a scales, relations for one pair of values of r_i and λ will fit the relations for any other pair of values. A value of 1 mm was chosen for λ at 100 msec. As the membrane resistance to small currents increases during the plateau, λ also increases. The values of λ at other times are: 1.16 mm (150 msec.); 1.33 mm (170 msec.); 1.8 mm (200 msec.). The computed membrane resistance at 200 msec. is about equal to the resting resistance (Noble, 1962*a*) and, since the resting space constant in Purkinje fibres is about 1.9 mm (Weidmann, 1952) these values for λ roughly correspond to experimental values. The value of λ determines the ratio r_m/r_i but not the absolute magnitudes since these also depend on the fibre diameter. Purkinje strands vary greatly in diameter and the input resistance will be high in thin strands (Weidmann, 1952) and low in thick strands (Hutter and Noble, 1960; Hall, Hutter, and Noble, 1963). It was therefore decided to compute solutions for a "standard" fibre with 1 cm^2 of membrane per cm of fibre. This corresponds to an impossibly large fibre (1 cm circumference) but the results require only a very simple scaling to be applied to experimental situations. For a fibre of radius r cm the computed axial currents should be multiplied by $2\,\pi r$.

Equation (1) was solved at each time as two simultaneous 1st order equations:

$$\frac{dV}{dx} = Y$$

$$\frac{dY}{dx} = r_i i_m$$

The integration method used was that of Runge-Kutta. dV/dx at $x = 0$ was set so that the voltage deflection increases in magnitude with x. The axial current was calculated from equation (3):

$$i_a = -\frac{1}{r_i}\frac{dV}{dx} \qquad (3)$$

The relation between the polarizing current and the voltage deflection for point polarization is then obtained by plotting i_a at x against V at $x - d$ where d is the distance between the polarizing and recording electrodes.

The computations were terminated either when $|V|$ exceeded 150 mv or when it was evident that V was oscillating (see Results).

RESULTS

The computed voltage deflections and axial currents are plotted against distance at each time in Figs. 2 and 3. The voltage deflection is shown as a continuous curve in

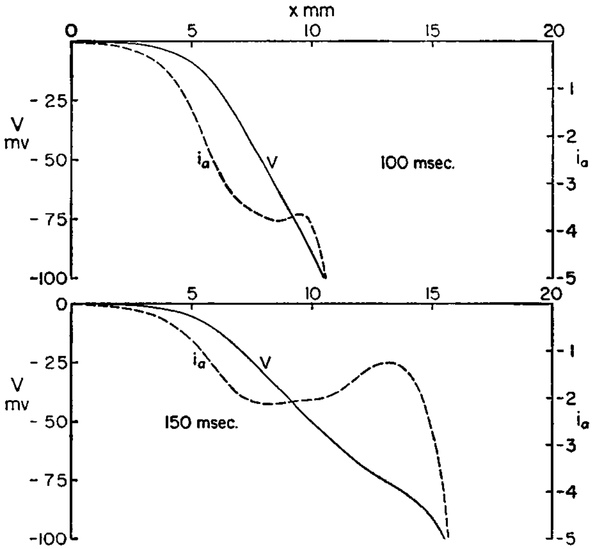

FIGURE 2 Computed variations in voltage deflection (continuous curves) and axial currents (interrupted curves) at 100 msec. and 150 msec. for initial voltage deflections of —0.1 mv from the plateau potential. Note that in both cases i_a/V (the input conductance) is always positive.

each case while the axial current curves are interrupted. At 100 msec. the magnitude of the voltage deflection increases exponentially at first but, after reaching about −20 mv, deviation from an exponential curve becomes apparent. The axial current increases in magnitude until a voltage deflection of −62 mv is reached. This is the point at which the membrane current reverses (Fig. 1) and the axial current now declines slightly in magnitude until $V = -79$ mv when i_m reverses again and $|i_a|$ continues to rise. It should be noted that at all points the input conductance (i_a/V) is positive.

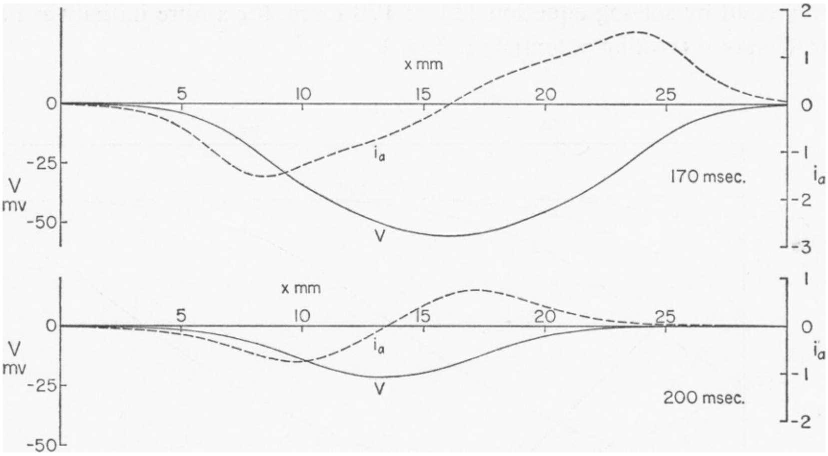

FIGURE 3 Computed variations in voltage deflections and axial currents at 170 msec. and 200 msec. Note that in each case the magnitude of the voltage deflection reaches a maximum at which point i_a reverses and the effective conductance becomes negative. The voltage deflection and axial current then return towards zero. A small error in the initial conditions or in the computation means that this will not happen at the same point for both V and i_a so that the computed solution eventually oscillates (not shown on this distance scale).

At 150 msec. the result is very similar. It takes a greater distance for a given voltage deflection to be reached and the kink in the axial current curve becomes more marked. This is to be expected since the region of reversed membrane current is larger (Fig. 1).

At 170 msec. and 200 msec. (Fig. 3). the results are quite different from those at the two earlier times. The decline in $|i_a|$ when the region of reversed membrane current is reached is now so large that the axial current itself reverses and the effective conductance becomes negative. The magnitude of the voltage deflection then declines and eventually oscillates (not shown in diagram). With the initial conditions chosen, no steady state solution exists for which $|V|$ is greater than the maximum value reached in each case. However with initial conditions appropriate to the case of point polarization of a fiber at the resting potential (left-hand stable point—Fig. 1) steady state solutions exist for all values of V. This is illustrated for the 170 msec. case in Fig. 4 which shows the steady state solutions for a fibre "clamped" at various voltages between the resting potential and plateau at one point, $x = 0$. The solutions leading to the plateau were obtained from Fig. 3 (170 msec.) by shifting the zero on the distance axis until the required voltage deflection at $x = 0$ was obtained. The remainder of the V/x curve was then plotted. The solutions leading to the resting potential were obtained in the same way from a V/x curve obtained by solving equation (1) at 170 msec. for a fibre initially at the left-hand stable point (resting potential) in Fig. 1.

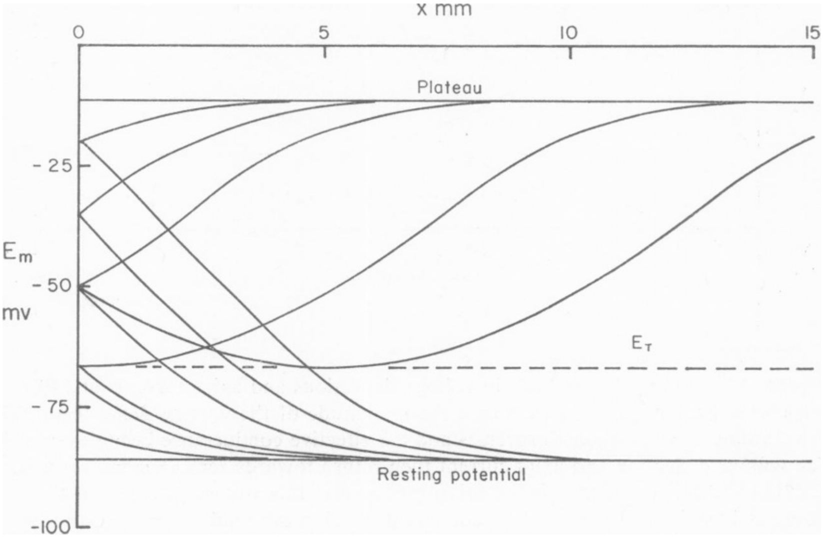

FIGURE 4 Steady state solutions for spatial spread of voltage deflection in a fibre "clamped" at one point at various voltages between the plateau and resting potential at 170 msec. Between E_T and the plateau, solutions leading to the resting potential and to the plateau exist. Between E_T and the resting potential, only solutions leading to the resting potential exist. At —20 mv and —35 mv only one plateau solution is shown although two solutions exist. Both plateau solutions are shown at —50 mv.

Between the plateau potential and the point labelled E_T three steady state solutions exist for each voltage, two of which lead to the plateau while the other leads to the resting potential. For the sake of clarity the second plateau solution is only shown for the —50 mv case. Between E_T and the resting potential only one steady state solution exists at each voltage and this leads to the resting potential. This is taken to indicate that point polarization of a fiber from the plateau to beyond E_T would initiate an all-or-nothing repolarization of all areas of the membrane to the resting potential. This phenomenon is not itself reproducible in the present computations since these are limited to steady state solutions whereas the repolarization response is a transient. However, the computations are sufficient to establish the conditions for the initiation of the all-or-nothing response and it is evident that it would not be obtained at 100 msec. and 150 msec. At 170 msec. and 200 msec. the response would be obtained if the fiber were polarized beyond the maximum voltage deflections in Fig. 3.

Another way of expressing these results is to plot the polarizing current-voltage relations, *i.e.* to plot i_a against E_m since, at the polarizing electrode, the polarizing current = i_a. This has been done in Fig. 5 for the case in which the recording and polarizing electrodes are at the same point ($d = 0$).

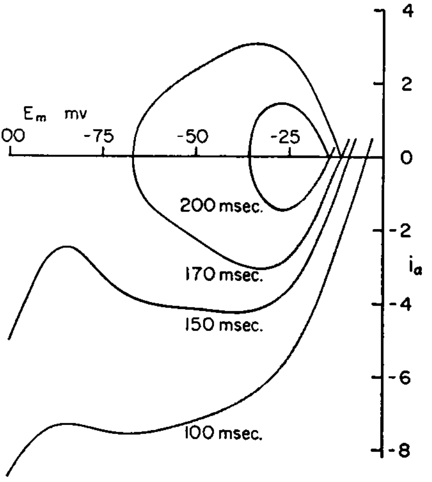

FIGURE 5 Polarizing current-voltage relations (i_a plotted against the membrane potential). Note that the relations at 100 msec. and 150 msec. are non-linear but do not contain a region of negative conductance. The relations at 170 msec. and 200 msec. recross the voltage axis at the steady state threshold for initiating the all-or-nothing response.

At 100 msec. and 150 msec., the curves are very non-linear and at some points the slope is negative. The chord conductance, however, is always positive. This is in contrast to the corresponding membrane current-voltage relations at these times (Fig. 1).

At 170 msec. and 200 msec. the polarizing current-voltage curves bend right back and recross the voltage axis at the steady state threshold for repolarization. Each curve then describes a mirror image of itself on the negative conductance side of the voltage axis. At 170 msec., the threshold voltage displacement is large and repolarization almost back to the resting potential would be required in order to initiate the all-or-nothing response. At 200 msec. the steady state threshold voltage displacement is smaller.

These polarizing current-voltage relations contrast markedly with those obtained from point polarization of a sheet membrane obeying the same ionic current equations (Noble, 1962*c*). The virtually linear relations in the sheet case were brought about by very large redistributions of the polarizing current (Noble, 1962*c*, Fig. 4). Some redistribution also occurs in the cable case but the effect is not as large as in the sheet case. Non-linearity is therefore still very evident in the polarizing current-voltage relations.

DISCUSSION

The computations described in this paper show that in order to initiate all-or-nothing repolarization with point polarization of a cable-like membrane it is necessary but not sufficient that the membrane current-voltage relation should contain a negative conductance region. Inspection of Fig. 1 in relation to the results obtained suggests that the relative magnitude and voltage range of the negative conductance are the important factors. In the membrane current-voltage relations at 100 msec. and 150 msec., when all-or-nothing repolarization cannot be obtained with point polarization, we have:

$$\int_{E_1}^{E_2} i_m \, \mathrm{d} V < \int_{E_1}^{E_0} i_m \, \mathrm{d} V \tag{4}$$

where E_0 is the right-hand (plateau) stable point, E_1 is the middle (unstable) point and E_2 is the left-hand (resting potential) stable point. At 170 msec. and 200 msec., when all-or-nothing repolarization can be obtained, this inequality is reversed.

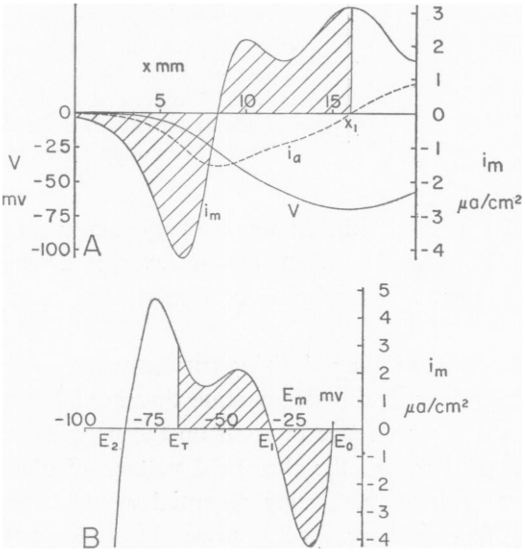

FIGURE 6 Analysis of computed results for 170 msec. case.

A. Computed V, i_a and i_m plotted against x. The areas formed by the i_m curve and the distance axis are shaded up to the point at which i_a reverses.

B. Membrane current-voltage relation with areas shaded up to the steady state threshold voltage. It is shown in the text that in each diagram the shaded areas are equal.

The critical condition occurs when these two integrals are equal. This is illustrated in Fig. 6 which shows a more detailed analysis of the results obtained at 170 msec. Fig. 6A shows the computed voltage deflection, axial current and membrane current plotted against distance. The areas formed by the membrane current curve are shaded up to the point at which the axial current reverses. Fig. 6B shows the membrane current-voltage relation with the areas shaded up to the computed steady state threshold voltage.

Integration of equation (1) gives:

$$\frac{1}{r_i}\left(\frac{\mathrm{d}V}{\mathrm{d}x}\right)_x = (-i_a)_x = \int_{-\infty}^{x} i_m \,\mathrm{d}x \tag{5}$$

When $x = x_1$, $i_a = 0$ and V is at the threshold voltage. Hence

$$\int_{-\infty}^{x_1} i_m \,\mathrm{d}x = 0 \tag{6}$$

and the shaded areas in Fig. 6A must be equal. Now i_m is a function of V which is itself a function of x so that it should be possible to obtain a relation comparable to equation (6) for the i_m/V relation. If the inequality in equation (4) is reversed, as it is at 170 msec. and 200 msec., then there will be a voltage, E_T, such that

$$\int_{E_0}^{E_T} i_m \,\mathrm{d}V = 0 \tag{7}$$

From (1) and (7):

$$\frac{1}{r_i}\int_{E_0}^{E_T} \frac{\mathrm{d}^2 V}{\mathrm{d}x^2}\,\mathrm{d}V = 0 \tag{8}$$

Hence

$$\frac{1}{2r_i}\int_{E_0}^{E_T} \frac{\mathrm{d}}{\mathrm{d}V}\left(\frac{\mathrm{d}V}{\mathrm{d}x}\right)^2 \mathrm{d}V = \frac{1}{2r_i}\left[\left(\frac{\mathrm{d}V}{\mathrm{d}x}\right)^2\right]_{E_0}^{E_T} = \frac{1}{2r_i}\left\{(r_i i_a)^2_{E_T} - (r_i i_a)^2_{E_0}\right\} = 0 \tag{9}$$

Since $i_a = 0$ at E_0, i_a at E_T must also be zero. Hence E_T is the steady state threshold voltage. If there is no value of E_T for which equation (7) is true then all-or-nothing repolarization cannot be obtained with point polarization.

In general, $(E_0 - E_T) > (E_0 - E_1)$. This means that the region of negative membrane conductance is entered before E_T is reached. There has been some confusion in the literature concerning this point. Weidmann (1951, 1956) has shown that at the point (about 1/3rd of the way along the plateau) at which he could first obtain all-or-nothing repolarization in the Purkinje fibre action potential, the threshold at the current electrode is near the resting potential, and Woodbury (1961) has suggested that this indicates that "there are highly voltage dependent components of the membrane conductance, but in a range outside that covered by normal repolarization." According to this view, natural repolarization is not regenerative, *i.e.* it does not pass through a region of negative conductance (*cf.* Woodbury, 1961, Fig. 9; Johnson, Tille, Wilson, and George, 1961). In fact, exactly the opposite conclusion should be drawn from Weidmann's result. If E_T is near the resting potential then, over a large range of voltages between the resting potential and the plateau, the membrane conductance must be negative. In our computed results at 170 msec., E_T is nearly -70 mv while E_1 is about -30 mv. The region of negative membrane conductance is therefore entered 40 mv before the threshold voltage is reached.

Fig. 7 shows a summary of our results in terms of the normal computed action potential, by plotting the variations in E_1 (steady state threshold for uniform polarization), E_T (steady state threshold for point polarization of an infinite cable) and E_2 (resting potential to which the membrane would go after an all-or-nothing repolarization). The region between E_1 and E_2 is the region of negative membrane conductance which grows larger towards the end of the plateau. If the modified Hodgkin-Huxley theory is correct, virtually all the rapid phase of repolarization is regenerative. With uniform polarization, an all-or-nothing response should be obtainable throughout the duration of the plateau, whereas point polarization of an infinite cable should not initiate a response during the earlier stages of the plateau. So far as the experimental evidence on point polarization of Purkinje fibres is concerned, the agreement with these results is good. Weidmann (1951) has shown that the all-or-nothing response cannot be initiated before a certain time during the plateau. We have confirmed this finding in some experiments on sheep Purkinje fibres. The time at which all-or-nothing repolarization could first be obtained was usually about half way through the plateau which is later than in Weidmann's published records. This difference is probably due to differences in the length of the preparations and the degree of branching. An all-or-nothing response should be obtainable earlier in a short preparation and later in a preparation which branches extensively. If the branching is very extensive, the situation will approximate more closely to the sheet case and all-or-nothing repolarization may not be obtainable at all (Noble, 1962*c*)

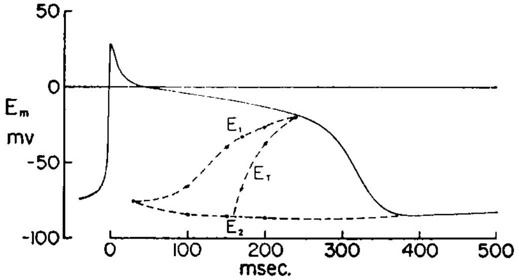

FIGURE 7 Variations in E_1 (steady state threshold for uniform polarization), E_T (steady state threshold for point polarization of infinite cable) and E_2 (membrane potential after initiation of all-or-nothing repolarization) during a normal computed Purkinje fiber action potential. Note that no threshold for point polarization exists during the first half of the action potential.

The main deficiency in the computations described in this paper is that they are limited to steady state solutions by neglecting the capacity current and the time dependency of the sodium permeability changes. This means that, in addition to the fact that the all-or-nothing response cannot itself be reproduced, the computed values for the threshold are almost certainly too close to the plateau. During square wave point polarization, the potential of a region of membrane at a distance from the polarizing electrode takes longer to change than does the potential of a region close to the electrode since the capacity of a region of membrane at a distance from the electrode has to be charged or discharged through the series resistance of the intracellular fluid (Hodgkin and Rushton, 1946). This means that as the current pulse duration is decreased, the area of membrane polarized sufficiently to reach the region of negative membrane conductance will decrease even if the current strength is increased to keep the maximum voltage deflection at the current electrode constant. A larger voltage deflection at the current electrode will therefore be required in order to initiate an all-or-nothing response. Thus, it is possible for the threshold voltage to be negative to the resting potential and thresholds as close to the plateau as the computed value of E_T at 200 msec. in Fig. 7 are unlikely to be observed experimentally.

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A preliminary communication of these results has appeared elsewhere (Hall and Noble, 1963).
Mr. Hall is a Bayliss-Starling scholar.

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