SUMMARY The microelectrode technique of intracellular constant current application and intracellular transmembrane voltage recording was used to study the effects of procaine amide (PA) on cardiac excitability. We measured the effect of PA in a concentration equivalent to clinically effective antiarrhythmic plasma levels (5 μg/ml), on nonnormalized and normalized strength-duration and charge-duration curves, membrane characteristics, and cable properties in long sheep Purkinje fibers in normal Tyrode’s solution with [K+]o = 4.0 mM. PA exerted a complex action and influenced passive resistance-capacitance (RC) and active generator properties by decreasing membrane conductance, primarily membrane sodium conductance. Whether PA increased or decreased excitability depended on the relative contribution of the drug-induced alterations in passive and active membrane properties. These findings may explain, in part, the conflicting results of studies on cardiac excitability in the whole animal, as well as the clinical observation that PA may exert both antiarrhythmic and arrhythmogenic effects. The primary mechanism by which PA modifies excitability would seem to differ considerably from that of the structurally similar local anesthetic agent lidocaine.

PROCAIN AMIDE is effective in the treatment of both supraventricular and ventricular arrhythmias, and its clinical and electrophysiological effects have been reviewed recently. In the past, cardiac excitability has been assessed primarily in the whole animal, and the index investigated has been the “threshold” current sufficient to elicit a response in studies on either strength-duration requirements or multiple response thresholds. Conflicting results appear in the literature, with some studies showing procaine amide (PA) to decrease excitability in a variety of species; whereas one failed to show any significant effect. Although in these studies there are many differences in experimental technique, part of the variability in the results may be attributed to the fact that the “current threshold” is determined by a complex set of passive and active membrane properties.

The microelectrode method for intracellular current application and transmembrane voltage recording allows definition of the individual components of excitability which include the resting transmembrane voltage, threshold voltage, membrane conductance, and cable properties. Although the studies have been few, strength-duration and charge-duration curves have been obtained for the isolated Purkinje fiber preparation with this technique and the determinants of excitability analyzed. In our present investigation we studied excitability by applying this microelectrode technique to long cardiac Purkinje fibers to determine the effects of PA at concentrations equivalent to clinically effective antiarrhythmic plasma levels.

METHODS

EXPERIMENTAL ARRANGEMENT

We used Purkinje fiber preparations obtained from female sheep anesthetized with sodium pentobarbital (30 mg/kg). “Long” Purkinje fibers are defined as being over 5 mm in length. The experimental arrangements have been described previously in detail. Briefly, rectangular constant current pulses were passed intracellularly through one microelectrode placed near the cut or ligated end of the long Purkinje fiber and the transmembrane voltage (Vm) was recorded through a second microelectrode. Intracellular current was applied every 2,000 msec during test periods. The tissue bath was kept at virtual ground by use of a Tektronix type 9 operational amplifier which also produced a voltage signal proportional to the current collected by an Ag-AgCl bath ground.

The composition of the Tyrode's solution (mm) was: NaCl, 137; NaHCO3, 13.4; NaH2PO4, 2.4; MgCl2, 1.5; CaCl2, 1.8; dextrose, 5.5; and KCl, 4.0. The Tyrode’s solution was equilibrated with 95% O2 and 5% CO2; the perfusion rate in the tissue bath was 8 ml/min; and the bath temperature was maintained at 35.5–36.5°C.

PA was added to the Tyrode to give a concentration of 5 μg/ml: this is considered to be within the range of clinically effective antiarrhythmic plasma levels. At least an hour of drug perfusion was allowed prior to electrophysiological testing.

CABLE ANALYSIS

We applied small hyperpolarizing current pulses of 100-msec duration and with an amplitude sufficient to produce a change of 4–7 mV in Vm at the recording microelectrode. This electrode was within 100 μ of the stimulating microelec-
trode. This current (I0) was held constant for both the control and PA periods. The recording microelectrode was then repositioned at various distances along the unbranched Purkinje fiber, and the change in Vm in response to I0 was recorded at each site. Interelectrode distances and the dimensions of the Purkinje fiber bundles were measured by a dissecting microscope equipped with an ocular micrometer.16-18 Vh, the transmembrane voltage at the site of application of the stimulus, was determined by plotting Vm on a logarithmic scale vs. interelectrode distance (x) and noting Vm at x = 0. The data were subjected to linear regression analysis (least squares method) and the resultant line was extrapolated to x = 0 to determine Vh. The membrane length constant, λm, was defined as x at which Vm = e−1Vh. Using λm, the estimated fiber radius, and the d.c. input resistance (Vo/I0), the specific membrane resistance (Rm) and the specific myoplasmic resistance (Ri) could be calculated.22 Figure 1 shows a representative plot used to calculate Vh and λm. Because the resting transmembrane voltage (Vr) approximates the potassium equilibrium potential in the normal fiber, the membrane slope conductance (GM) calculated from small hyperpolarizing pulses approximates the membrane chord conductance (gM) and is equivalent to 1/Rm.19 The membrane time constant, τm, was calculated from the change in Vm after current offset of the small hyperpolarizing pulse by noting the time at which the change in Vm had decayed by 84% of its initial value.23

Membrane capacitance (Cm) was calculated as Cm = τm/Rm.22

**STRENGTH-DURATION AND CHARGE-DURATION CURVES**

The threshold voltage (Vth) was defined as the maximal just-subthreshold Vh response recorded by a microelectrode in close proximity (less than 100 μ) to the stimulating microelectrode. Both microelectrodes remained in the same position throughout the experiment. Although a drug-induced change in the length constant would introduce some error in the determination of Vth, the close proximity of the stimulating and recording microelectrodes would limit this error to less than 0.5 mV over a 100-μ distance, as can be deduced from cable analysis (Fig. 1).

A representative recording for a current duration (t) of 100 ms is shown in Figure 2. Strength-duration curves were analyzed in both a nonnormalized form, where the recorded current required to attain threshold (Ith) is plotted as a function of t, and in a normalized form, Ith/I0 vs. τm where I0 is the rheobasic current. Charge-duration curves were also assessed in both the nonnormalized form (Qth vs. t where Qth is the charge threshold) and the normalized form (Qth/I0τm vs. t/τm). Normalization of the curves minimizes the differences in the shape of the curves caused by altered passive membrane properties but does not obscure changes in active generator properties.14,15,17 The implications of such normalization for the long Purkinje fiber are considered further in the Discussion. The Lapicque equation is known to describe the strength-duration curve for long Purkinje fibers,14,15 but its calculation depends on the extrapolation of charge threshold to time zero and, as emphasized by Fozzard and Schoenberg,14 this extrapolation may be in error twofold in either direction. The possibility of large error prevented the use of the Lapicque equation to compare data obtained during the control and drug periods.

**STATISTICAL ANALYSIS**

Levels of statistical significance were assessed by the t-test for paired samples.24
Cable analysis was performed for four long Purkinje fibers before and after exposure to PA. The results are summarized in Table 1. $V_r$ was unaffected by the drug in these, as well as in seven other experiments (Table 2). PA caused a moderate increase in $V_r/I_h$ (7.4% to 21.4%, $P < 0.05$), $R_m$ (9.9% to 40.9%, $P < 0.05$), and $\tau_m$ (22.3% to 40.9%, $P < 0.05$) in all experiments. $R_i$ and calculated $C_m$ were unaffected. $GM$ was decreased by PA (mean change = 21%, $P < 0.05$). Figure 1 shows the result of a typical experiment in which PA increased $V_r$ from 4.4 to 5.4 mV and $\lambda_m$ from 2.44 to 2.63 mm.

**Results**

**CABLE ANALYSIS**

Table 2 summarizes the results of seven experiments. PA produced no significant change in $V_r$. In six of seven experiments (fibers L1–6) PA decreased $V_{an}$, i.e., it made $V_{an}$ less negative. This resulted in an increase of $\Delta V$ (i.e., $V_{an} - V_r$) of 10.5 to 23.0%. Applying the $t$-test for paired samples to data from all seven experiments, $P < 0.001$ for the change in both $V_{an}$ and $\Delta V$. The effect on $I_{th}$ was variable. $I_{th}$ increased for three fibers (5.2% to 12.7%; L1–3); showed little change in three (L4–6); and decreased by 9.4% in one (L7). Figure 2 shows a representative experiment for fiber LI. $V_r$ was unaffected (-89 mV) but $V_{an}$ became less negative (-67 to -63 mV) after exposure to PA. $I_{th}$ increased from 51.7 to 58.3 nA, despite a slight increase of 14% in $R_m$, and $\tau_m$ increased from 20 to 23 msec.

**RESTING TRANSMEMBRANE VOLTAGE, THRESHOLD VOLTAGE, AND THRESHOLD CURRENT**

Table 2 summarizes the results of seven experiments. PA increased by 14%.

The strength-duration curve in Figure 3 was normalized ($I_{th}/I_{an}$ vs. $t/\tau_m$) and is shown in Figure 4. It should be recalled that PA did not change $V_r$ but did make $V_{an}$ less negative. It can be seen that the control and PA normalized strength-duration curves are not superimposable. As compared to the control, the normalized PA curve $I_{th}$ exceeds $I_{an}$ at a longer normalized time, the time constant of the strength-duration curve is longer, and the curve rises more steeply for stimuli of short duration. The result is an upward and rightward shift after action of PA.

The nonnormalized charge-duration curve ($Q_{th}$ vs. $t$) for fiber L1 is shown in Figure 5 and is seen to be shifted upward.

**STRENGTH-DURATION AND CHARGE-DURATION CURVES**

Strength-duration and charge-duration curves were determined before and after exposure to PA for preparations L1–3. After exposure to PA, $V_r$ was unchanged, $V_{an}$ became less negative, $I_{th}$ increased, and the nonnormalized strength-duration curve shifted upward; this shift means that more current was required to attain threshold for each current duration and the tissue was “less excitable” in classical terms. A typical nonnormalized strength-duration curve is shown for fiber LI in Figure 3. In the upper portion, the threshold voltage under the control conditions, $V_{an}(C)$, remained quite constant except for very short duration stimuli when it became somewhat more negative. After exposure to PA, threshold voltage, $V_{an}(P4)$, decreased (i.e., became less negative) for all current durations. In the lower portion, $I_{an}$ is plotted as a function of current duration ($t$). As compared to the control, PA shifted the nonnormalized curve upward, showing that for any current duration more current was required to reach threshold even though $R_m$ had increased by 14%.

The mean values of $I_{th}$ and $V_{an}$ are given in Table 2.

**TABLE 1**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>d (µ)</th>
<th>$V_r$ (mV)</th>
<th>$V_{an}/I_h$ (µA)</th>
<th>$\lambda_m$ (mm)</th>
<th>$R_m$ (Ωcm²)</th>
<th>$R_i$ (Ωcm)</th>
<th>$\tau_m$ (msec)</th>
<th>$C_m$ (µF/cm²)</th>
<th>$gM$ (µS/cm²)</th>
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<td>A. Control</td>
<td>160</td>
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<td>(+9.9)</td>
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<td>66</td>
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<td>(-25.0)</td>
<td>(-4.0)</td>
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<td>(+26.2)</td>
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<td>9.1</td>
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<td>(+36.8)</td>
<td>(-4.2)</td>
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<td>1934</td>
<td>176</td>
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<td>(+26.4)</td>
<td>(+5.7)</td>
<td>(+33.0)</td>
<td>(-2.8)</td>
<td>(-21.0)</td>
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</tbody>
</table>

* $|K_m|$ of solution = 4.0 mm.

%Δ = percent change as compared to the control; d = fiber diameter; $V_r$ = resting transmembrane voltage; $V_{an}/I_h$ = membrane d.c. input resistance; $\lambda_m$ = membrane length constant; $R_m$ = specific membrane d.c. resistance; $R_i$ = specific myoplasmic resistance; $gM$ = membrane conductance; $P$ = level of significance ($t$-test for paired samples); $\tau_m$ = membrane time constant; $C_m$ = calculated membrane capacitance; ns = not significant.
### Table 2: Effect of Procaine Amide (PA) on Resting Transmembrane Voltage, Threshold Voltage, and Threshold Current in Long Purkinje Fibers

<table>
<thead>
<tr>
<th>Fiber no. and experiment</th>
<th>$V_r$ (mV)</th>
<th>$V_{th}$ (mV)</th>
<th>$\Delta V$ (mV)</th>
<th>$I_{th}$ (nA)</th>
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</thead>
<tbody>
<tr>
<td>L1. Control</td>
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<td>-67.0</td>
<td>22.0</td>
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<tr>
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<td>-89.0</td>
<td>-63.0</td>
<td>26.0 (+18.0)</td>
<td>58.3</td>
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<tr>
<td>%Δ</td>
<td>0</td>
<td>-6.0</td>
<td>(+12.7)</td>
<td></td>
</tr>
<tr>
<td>L2. Control</td>
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<td>-64.0</td>
<td>28.3</td>
<td>38.5</td>
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<td>21.9 (-5.9)</td>
<td>40.5</td>
</tr>
<tr>
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<td>(+5.2)</td>
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</tr>
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<td>(+7.7)</td>
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<tr>
<td>%Δ</td>
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</tr>
<tr>
<td>%Δ</td>
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<td>(-0.1)</td>
<td>(+4.8)</td>
<td>(+12.9)</td>
<td>(+2.1)</td>
</tr>
</tbody>
</table>

**P**

- ns
- <0.001
- <0.001
- ns

Current duration = 100 msec; %Δ = percent change as compared to the control; $V_r$ = resting transmembrane voltage; $V_{th}$ = threshold voltage; $\Delta V = V_{th} - V_r$; $I_{th}$ = threshold current; $P$ = level of statistical significance (t-test for paired samples); ns = not significant.

### Discussion

This report represents the first attempt to investigate the effects of PA, in concentrations equivalent to clinically effective antiarrhythmic plasma levels, on the components of excitability by use of intracellular current application and transmembrane voltage recording. In contrast to studies on cardiac excitability in the whole animal or the usual microelectrode techniques which employ extracellular stimulation, this method permits a more quantitative assessment of the changes in passive and active membrane properties that underlie the changes in excitability induced by PA. This

by PA in relation to the control. The relationship for both experimental conditions is quite linear except for stimuli of very short duration. Normalization of the charge-duration curve (Fig. 6) shows the two relationships to be identical when $I_{th}$ equals $I_{rk}$, as would be expected, but the PA curve changes its slope at a value for $t/r_m$ longer than for the control. For stimuli of short duration the PA curve has a higher normalized charge threshold than the control and both relationships are quite linear and parallel, at least to a value for $t/r_m$ of 0.2. At very short durations, the data are difficult to interpret; this is due presumably to loss in charge uniformity. The lines in this Figure were drawn by eye. The implications of these strength-duration and charge-duration curves are considered in the Discussion.

### AUTOMATICITY

The effect of PA on an automatic pacemaker cell in a long Purkinje fiber is depicted in Figure 7. Under control conditions, the rate of spontaneous depolarization was 56/min (cycle length = 1,080 msec) and the maximum diastolic $V_m$ was -80 mV. Twenty minutes after the application of PA the spontaneous rate had decreased to 45/min (cycle length = 1,320 msec) and the maximum diastolic $V_m$ was unaffected. The rate of rise of slow diastolic depolarization was clearly decreased by PA. The difficulty in assessing the apparent threshold voltage from such a photographic recording is clear, but data obtained by using the double microelectrode technique in other fibers would suggest that the actual $V_{th}$ had decreased. Shortly after the lower photograph in Figure 7 was taken, spontaneous depolarization ceased. Similar results were noted in two other preparations that showed spontaneous activity.

**Discussion**

This report represents the first attempt to investigate the effects of PA, in concentrations equivalent to clinically effective antiarrhythmic plasma levels, on the components of excitability by use of intracellular current application and transmembrane voltage recording. In contrast to studies on cardiac excitability in the whole animal or the usual microelectrode techniques which employ extracellular stimulation, this method permits a more quantitative assessment of the changes in passive and active membrane properties that underlie the changes in excitability induced by PA. This
PROCaine amide, \([\text{Vth(PA)}]\) became less negative as compared to the control \([\text{Vth(C)}]\) for all current durations. In the lower portion, the threshold current \((I_{\text{th}})\) is plotted as a function of current duration \((t)\). As compared to the control \((\text{O}---\text{O})\), procaine amide \((\text{---}---\text{---})\) shifted the curve upward, indicating that more current for any current duration was required to attain threshold. See text for discussion.

FIGURE 3 The effect of procaine amide on threshold voltage \((V_{\text{th}})\) and the nonnormalized strength-duration curve in fiber LI. In the upper portion, resting transmembrane voltage \((V_r)\) was unaffected by procaine amide, and the threshold voltage during exposure to procaine amide, \([V_{\text{th(PA)}}]\) became less negative as compared to the control \([V_{\text{th(C)}}]\), for all current durations. In the lower portion, the threshold current \((I_{\text{th}})\) is plotted as a function of current duration \((t)\). As compared to the control \((\text{O}---\text{O})\), procaine amide \((\text{---}---\text{---})\) shifted the curve upward, indicating that more current for any current duration was required to attain threshold. See text for discussion.

The investigation not only adds to our understanding of the mechanism of action of PA, but also demonstrates the usefulness of more quantitative techniques in the evaluation of antarrhythmic drugs.

IMPLICATIONS OF CABLE ANALYSIS AND STRENGTH-DURATION CURVES

Passive Membrane Properties. The influence of altered passive resistance-capacitance (RC) membrane properties can be minimized by normalization of the strength-duration curve for long Purkinje fibers.\textsuperscript{15, 15, 18, 25} For example, an alteration in \(g_M\) alone would tend to produce changes of the same magnitude in \(I_n\), \(I_{\text{rn}}\), and \(\tau_m\). In the normalized strength-duration curves, these changes tend to cancel each other out and result in superimposability of the normalized control and test curves. This has been shown for both the long\textsuperscript{13} and short\textsuperscript{18} Purkinje fiber for lidocaine, which shifts the nonnormalized strength-duration curve upward and to the right ("less excitable" in the classic sense) by increasing \(g_M\) without altering either \(V_r\) or \(V_{\text{th}}\). Normalization of the strength-duration curves obtained in the control and lidocaine situations resulted in the superimposability of both curves. In the present study, PA also shifted the nonnormalized strength-duration curve upward and to the right despite an actual decrease in \(g_M\). According to Ohm’s law, a decrease in \(g_M\) should have resulted in a decrease, rather than in the observed increase, in \(I_{n}\) were \(V_r\) and \(V_{\text{th}}\) unchanged. \(V_{\text{th}}\), however, became less negative after exposure to PA in six of seven experiments (Table 2), and the normalized strength-duration curves for the control and drug periods were not superimposable. This suggests that a drug-induced alteration in active membrane generator properties was influencing excitability.

Active Membrane Properties. Available evidence suggests that the ionic events which cause rapid depolarization (phase 0 of the action potential) are similar for the heart and nerve\textsuperscript{26} and that sodium conductance can be described mathematically in terms of a maximal conductance and voltage-dependent sodium activation and inactivation coefficients.\textsuperscript{26, 27} The initial capacitative current and difficulties in maintaining control of the transmembrane voltage by voltage clamping during the rapid inward sodium current introduce a large error into such direct measurements.\textsuperscript{28, 29} As a result, the assessment of strength-duration curves\textsuperscript{14-18} and the determination of the maximal rate of rise of phase 0 of the action potential\textsuperscript{50-52} have been used as indirect measurements of the state of membrane sodium conductance.

Strength-duration curves provide a great deal of information about the active membrane generator properties. The shape of normalized strength-duration curves can be influenced by altered current-voltage nonlinearities,\textsuperscript{25} by changes in the maximal sodium conductances and the relevant voltage-dependent activation and inactivation variables (which would change membrane accommodation and the finite time for membrane activation),\textsuperscript{28} and by alterations in liminal length and its determinants.\textsuperscript{27} Weld and Bigger\textsuperscript{28} have shown that current-voltage relationships for long Purkinje fibers are little influenced by concentrations of PA similar to those we used; this suggests that the first possibility is relatively unimportant in interpreting our results. The longer time constant for the normalized strength-duration curve in fiber LI during the control \((\text{O}---\text{O})\) and procaine amide \((\text{---}---\text{---})\) situations. Note that procaine amide causes the threshold current \((I_{\text{th}})\) to exceed rheobase current \((I_{\text{rb}})\) at a longer \(1/r_{\text{mb}}\), the curve to be shifted upward and rightward, and the time constant for the strength-duration curve to increase. See text for discussion.
strength-duration curve after exposure to PA suggests that more time is required to produce the required current, charge, and liminal length depolarization necessary to attain threshold. Theoretically, then, the additional current and charge requirement after exposure to PA would not only shift the normalized strength-duration curve upward, but would also necessitate a longer current duration for the attainment of threshold and thereby move the normalized curve to the right. We found such an upward and rightward shift in the normalized strength-duration curve.

Theory, then, suggests that normalization of the strength-duration curve would minimize the influence of altered passive RC membrane properties on the shape of the curve, but would not obscure the effects of changes in the active generator properties of the membrane which are dependent primarily on sodium conductance. It seems reasonable to conclude, therefore, that the upward and rightward shift of the normalized strength-duration curve caused by PA is due to significant alterations in active generator properties of the membrane. A similar interpretation can be given to the effect of PA on the nonnormalized and normalized charge-duration curves which appear in Figures 5 and 6.

In previous studies using microelectrodes the effect of PA on cardiac excitability has been considered in terms of "membrane responsiveness," defined as the relationship between the transmembrane voltage of activation of a premature depolarization elicited during repolarization (phase 3) of the basic driven action potential, and the maximal rate of rise of phase 0 \( V'_{\text{max}} \) of the premature depolarization.\(^{29,32} \) \( V'_{\text{max}} \) is thought to be an indirect measure of the inward sodium current, and therefore to reflect the state of membrane sodium conductance. Of note is our finding that there are alterations in membrane active generator properties at a PA concentration much lower than that required to affect membrane responsiveness.\(^{34} \) Possible explanations include: (1) our studies were performed on a membrane in an essentially steady state, which is not true for membrane responsiveness studies; (2) the use of intracellular constant current application may detect changes more subtle than those which can be detected by extracellular tissue stimulation; or (3) perhaps changes in membrane properties are more readily reflected by current measurements than by assessment of electrically differentiated \( V'_{\text{m}} \) signals.

**IMPLICATIONS REGARDING ARRHYTHMOGENESIS AND ANTIARRHYTHMIC MECHANISMS**

Our study has shown PA to increase the excitatory current requirement of some Purkinje fibers and to decrease it for others (Table 2). This may explain in part some...
of the conflicting reports of studies on excitability in the whole animal.\textsuperscript{10-13} The variability in excitatory current requirement would have remained uninterpretable if the various components of excitability had not been assessed individually. Our investigation has demonstrated that PA alters both passive RC and active membrane properties, with the net threshold current requirement determined by the balance between the two.

The present cable analysis suggests that PA might enhance excitation by normal or abnormal local circuit flow by increasing the d.c. input and membrane resistances, the length constant, and the membrane time constant. This, however, may be counterbalanced by the less negative $V_{th}$ and the decreased "safety factor" due to lessened conductivity. Constant conduction velocity ($\theta$) of a propagated action potential in Purkinje fibers can be described by the relationship $\theta^2 = K a / 2 R C_m$. $R$, $C_m$, and $a$ have been previously defined and represent the relevant passive membrane properties; $K$ is a constant that reflects the active generator properties of the membrane. Our cable analysis shows the relevant passive properties are little changed by PA (Table 1). The strength-duration and charge-duration studies, however, suggest that $K$ is decreased. This is consistent with experimental findings that PA does depress conduction and thereby may impede impulse propagation through the depressed limb of a reentrant circuit to a point at which bidirectional block is produced and reentry prevented.\textsuperscript{34-36} Giardina and Bigger\textsuperscript{21} have presented evidence for man that after the administration of PA conduction in the reentrant circuit is prolonged prior to amelioration or disappearance of reentrant ventricular arrhythmias. The drug-induced slowing in impulse propagation, however, also may be arrhythmogenic. These mechanisms may in part account for the observation that PA can exert both antiarrhythmic and arrhythmogenic effects.

For arrhythmias due to enhanced automaticity, it is interesting to speculate that the decreased slope of slow diastolic depolarization in automatic Purkinje fibers which is caused by exposure to PA (Figure 7) is mediated by a decrease in the inward depolarizing current. The alternative mechanism would be that PA increases the outward repolarizing potassium current, as has been shown for lidocaine.\textsuperscript{16-18} Weld and Bigger,\textsuperscript{33} however, have shown that PA does not have such an action. PA may have the additional antiarrhythmic effect of making the voltage threshold for excitation less negative.

It is of interest to note such a striking difference in effect on membrane conductance between PA and lidocaine despite their structural similarity and common local anesthetic properties. This study provides further justification...
for considering PA and lidocaine as members of different antiarrhythmic drug groups and that these drugs may be classified in terms of their fundamental effects on membrane ionic conductances. Such differing electrophysiological mechanisms as exist between PA and lidocaine may have similar correlates in that their clinical indications and bioelectric complications differ, and a particular arrhythmia may respond to one but not the other, or at times, only to a combination of these antiarrhythmic drugs.

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