Conduction of the Cardiac Impulse

II. SUMMATION AND INHIBITION

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ABSTRACT

A segment of a bundle of canine Purkinje fibers was encased in agar made up in Tyrode solution containing elevated K⁺ (47 mM) to depress the excitability of the segment. At a degree of depression producing total block of conduction in each direction through the depressed segment, exciting both ends of the bundle yielded full excitatory responses in the center of the depressed area. These responses arose with a long latency after excitation of the normal ends outside the depressed segment. Summation occurred over a long interval of relative timing of excitation of the ends. When excitation of one end alone produced a response in the center of the depressed segment, that response sometimes could be inhibited by stimulating the other end. In another preparation a branch emerged from the center of the depressed segment. Summation of excitation in the center of the depressed area resulted in conduction of activity out the branch at an interval appropriate to re-excite the entire heart. When one end of the preparation could excite the branch, stimulation of the other end sometimes inhibited excitation of the branch. The results are important as part of the explanation of phenomena associated with re-entrant arrhythmias.

KEY WORDS: entry block, exit block, parasyysis, Wenckebach phenomenon, ventricular bigeminy, ventricular tachycardia, ventricular fibrillation, transmembrane potentials, concealed conduction, re-entry.

Reduction of excitability and responsiveness in a segment of Purkinje fibers by high K⁺ causes depression of conduction of the impulse in that segment (1). If cells distal to each end of the depressed segment are normal, excitation of either end of the preparation may reveal conduction with delay, 2:1 or higher degrees of block, the Wenckebach type of delay and block, or even more irregular types of depressed conduction including total block.

We now report the effects observed in such preparations when block is complete in both directions. When atrioventricular nodal block is complete in both directions (2), a fiber which shows almost no response to excitation arriving from the atrium or to excitation arriving from the bundle of His may develop a normal response when impulses arrive from both atrium and His bundle simultaneously. We find that the arrival of excitatory impulses from each end of a depressed segment of Purkinje fibers may produce a response of reasonable magnitude in a fiber in the center of the depressed segment, even though that fiber shows almost no response to excitation transmitted towards it from either end alone. That response can appear with a marked latency which is great enough to permit the response to arise after the end of the effective refractory period of the action potentials in the fibers outside the depressed area. Such a delayed response might propagate at a time when it could re-excite the entire heart, thus causing a classic re-entrant arrhythmia.

To test this conclusion we have studied preparations in which a branch emerges from the midpoint of the depressed segment in a
bundle of Purkinje fibers. It is possible to stimulate either normal end of the depressed segment and obtain no conduction either through the segment or out such a branch. Yet, when both ends of the segment are stimulated to give rise to a response in the center of the depressed segment, that response is indeed conducted out the branch at a time appropriate to give rise to a re-entrant excitation of the entire heart.

We have also noted certain inhibitory interactions of a previously unknown kind. When excitation of one end of the preparation gives rise to no conduction either to the remote end or out the branch and excitation of the other end gives rise to excitation transmitted out the branch but not to the remote end, excitation of both ends prevents the transmission of the impulse out the branch, which occurs when the end capable of exciting the branch is stimulated alone.

Methods

The methods used for these experiments have been described (1). Preparations of canine cardiac Purkinje fibers were perfused with oxygenated Tyrode solution (K+ 7.1 mm) in a tissue bath maintained at 37 C. Transmembrane potentials were recorded through intracellular microelectrodes. Stimuli were delivered to either or both of two sites through Teflon-coated silver wires (Fig. 1). Depression of conduction and responsiveness in a segment of the preparation was produced by encasing that segment in agar made up with a modified Tyrode solution containing K+ in a concentration of 47 mmoles/L. Preparations were either unbranched or branched (Fig. 1). The arrangement of stimulating and recording electrodes shown in Figure 1 was used for all experiments. The depressed segment was 8 to 10 mm long. For unbranched preparations one recording electrode was located approximately in the middle of the depressed segment. For branched preparations one recording electrode was located in the branch 2 to 3 mm from its point of origin in the depressed segment. The middle trace in each record shows the activity recorded either from the center of the depressed segment or from the branch; the upper and lower traces show the activity recorded from the ends of the preparation which are outside the depressed segment.

Results

SUMMATION OF EXCITATION

In Figure 2A, when the proximal end of the preparation (upper trace) is excited, the response recorded outside the depressed segment is of relatively low amplitude and shows a slow step preceding the upstroke. Virtually no deflection is seen in the middle of the depressed segment (center trace), and none is seen beyond the depressed segment (lower trace). When the distal site is stimulated, a large amplitude action potential with a rapid upstroke is recorded outside the depressed segment. Within the depressed segment a low amplitude electrotonic deflection is recorded, but there is no conduction through the depressed area to the end remote from the stimulating site. Block is complete in both directions. When both ends of the fiber are
Summation in an unbranched bundle. Upper trace: proximal end; middle trace: center of the depressed segment; lower trace: distal end. A and B show that excitation of either end alone fails to cause a normal response in the center. In C, D, E, and F excitation of both ends evokes a response in the center with a latency that increases as the distal end is excited progressively earlier. Calibrations: time 200 msec, voltage 100 mV.

Figure 2 shows summation with marked latency. The electrical activity within the depressed segment is quite complex. In Figure 3A and B excitation of either end of the fiber alone produces only a small deflection within the depressed segment and no conduction to the other end. In Figure 3C the distal site is excited about 125 msec later than the proximal site. Within the depressed segment (middle trace), the initial deflection is slow and small and closely resembles that seen in Figure 3A; this deflection has nearly ended at the moment that the distal end is excited. Thereupon, a deflection appears which closely resembles that seen in Figure 3B. The slow deflection corresponding to excitation of the distal end does not, however, proceed to repolarization but is interrupted by a fairly rapid upstroke. This response is sufficiently great in amplitude, duration, and upstroke velocity to be considered capable of propagation. It cannot propagate because the fibers on each side of it are refractory, having just conducted impulses toward the center of the segment. The response does produce a marked electrotonic deflection in the repolarization limb of the action potential recorded at the proximal site. As the distal site is excited with greater delay (Fig. 3D), the rapid upstroke seen at the middle site appears later, at a time when it could propagate through a fiber that had been excited almost simultaneously (Fig. 2C), the action potentials recorded outside the depressed area are very like those seen when either end was excited alone, but we see a full excitatory response in the depressed segment. The action potential at the center shows a slow step preceding its upstroke, but the upstroke is reasonably rapid while the amplitude and duration of the response are as nearly normal as one could expect in a fiber in a high K⁺ environment. In Figure 3D, E, and F the distal site was stimulated progressively earlier with respect to the time of stimulation of the proximal site. Summation is obtained over a long set of intervals, and the delay of the response recorded in the depressed area varies according to the relative timing of the excitation of the two ends. In Figure 3F the upstroke recorded within the depressed area is markedly later with respect to the response of either end than it is in Figure 2C. Moreover, the response within the depressed segment arises during the declining phase of the potential change induced by stimulation of the distal end. Figure 2 shows that when depression has progressed within the depressed segment to a point at which no impulse is conducted through the depressed segment in either direction, fibers within the depressed segment are still excitable. Impulses from either end alone cannot excite at the center of the segment, but impulses arriving from both ends can summate and excite at the center of the segment. The records also show that the response induced in the center of the depressed segment can appear with a considerable latency after the time of origin of the impulses which evoke it.

Figure 3 shows summation with marked latency. The electrical activity within the depressed segment is quite complex. In Figure 3A and B excitation of either end of the fiber alone produces only a small deflection within the depressed segment and no conduction to the other end. In Figure 3C the distal site is excited about 125 msec later than the proximal site. Within the depressed segment (middle trace), the initial deflection is slow and small and closely resembles that seen in Figure 3A; this deflection has nearly ended at the moment that the distal end is excited. Thereupon, a deflection appears which closely resembles that seen in Figure 3B. The slow deflection corresponding to excitation of the distal end does not, however, proceed to repolarization but is interrupted by a fairly rapid upstroke. This response is sufficiently great in amplitude, duration, and upstroke velocity to be considered capable of propagation. It cannot propagate because the fibers on each side of it are refractory, having just conducted impulses toward the center of the segment. The response does produce a marked electrotonic deflection in the repolarization limb of the action potential recorded at the proximal site. As the distal site is excited with greater delay (Fig. 3D), the rapid upstroke seen at the middle site appears later, at a time when it could propagate through a fiber that had been excited almost simultaneously (Fig. 2C), the action potentials recorded outside the depressed area are very like those seen when either end was excited alone, but we see a full excitatory response in the depressed segment. The action potential at the center shows a slow step preceding its upstroke, but the upstroke is reasonably rapid while the amplitude and duration of the response are as nearly normal as one could expect in a fiber in a high K⁺ environment. In Figure 3D, E, and F the distal site was stimulated progressively earlier with respect to the time of stimulation of the proximal site. Summation is obtained over a long set of intervals, and the delay of the response recorded in the depressed area varies according to the relative timing of the excitation of the two ends. In Figure 3F the upstroke recorded within the depressed area is markedly later with respect to the response of either end than it is in Figure 2C. Moreover, the response within the depressed segment arises during the declining phase of the potential change induced by stimulation of the distal end. Figure 2 shows that when depression has progressed within the depressed segment to a point at which no impulse is conducted through the depressed segment in either direction, fibers within the depressed segment are still excitable. Impulses from either end alone cannot excite at the center of the segment, but impulses arriving from both ends can summate and excite at the center of the segment. The records also show that the response induced in the center of the depressed segment can appear with a considerable latency after the time of origin of the impulses which evoke it.
RE-ENTRY IN PURKINJE FIBERS

Figure 3
Summation in an unbranched bundle. Upper trace: proximal end; middle trace: center of the depressed segment; lower trace: distal end. A and B show that excitation of either end alone fails to produce a normal response in the center. In C and D excitation of the distal end well after excitation of the proximal end produces a response in the center which is greatly delayed in relation to excitation of the proximal end. Calibrations: time 400 msec, voltage 100 mv.

Figure 4 shows summation over a wide range of relative timing of excitation of the proximal and distal sites. In Figures 4A and 4B excitation of either the proximal (upper trace) or the distal site (lower trace) produces almost normal action potentials outside the depressed area, slow and low-voltage deflections within the depressed area (middle trace), and no transmission to the far end. At the beginning of Figure 4C, excitation at the proximal site precedes excitation at the distal site by about 100 msec; throughout Figures 4C and 4D, excitation at the proximal site is gradually delayed until the proximal and distal sites are excited nearly simultaneously. As that happens, the summation seen within the depressed area occurs with progressively less latency until, in the center of Figure 4D, the upstroke recorded in the depressed segment is quite rapid, its amplitude is high, and it occurs very soon after the action potentials recorded just outside each end of the depressed segment. The right-hand end of Figure 4D and Figures 4E and 4F show the effects of a continuing shift in relative timing of the stimuli so that the distal site is excited progressively earlier than the proximal site. The effect resembles that seen in Figures 4C and 4D. It is instructive to compare the first tracing in Figure 4C with the last tracing in Figure 4F. In each instance summation occurs with a long latency, and the initial deflection seen within the depressed area closely resembles the deflection seen when the corresponding end of the fiber is stimulated alone. The initial slow deflection in Figure 4C resembles the deflection within the depressed area seen in Figure 4B, while that in Figure 4F resembles the deflection seen in Figure 4A. This is to be expected since until the other end is stimulated, one would expect no other deflection than that resulting from stimulation of one end alone, but the similarity shows that subsequent events result from arrival of an impulse from the previously unexcited end rather than from some unpredictable change in the effect of stimulating one end alone. The next event in each tracing is a second slow deflection signaling the arrival of the impulse from the previously unexcited end. Finally, with marked latency a rapid upstroke appears within the depressed area. In Figure 4C one sees at the proximal site (upper trace) an electrotonic deflection corresponding to the upstroke of the response in the depressed segment; no corresponding deflection is seen.
Figure 4 shows the results of an experiment in which a recording electrode is inserted in a branch emerging from the depressed segment. When the proximal site is stimulated (Fig. 5A), a response is evoked in the branch. However, when both ends are stimulated (Fig. 5B), the response in the branch is much larger, indicating that the response evoked by summation within the depressed segment can propagate.

The above results show that it is possible for a segment of Purkinje fibers to be sufficiently depressed to show bidirectional complete block and yet sufficiently excitable to be able to give rise to a reasonably normal response when stimulated by the arrival of impulses from both ends. The excitatory response evoked at the center of such a preparation cannot propagate because the fibers on either side of the recording site have just been excited and are refractory. If there were an unexcited branch at the center, one would expect the response evoked in the center to propagate out that branch. Such an event would provide decisive evidence that the response evoked by summation within the depressed segment can propagate.

Figure 5 shows the results of an experiment in which an electrode is inserted in a branch emerging from the depressed segment. When the proximal site is stimulated (Fig. 5A), a response is evoked in the branch. However, when both ends are stimulated (Fig. 5B), the response in the branch is much larger, indicating that the response evoked by summation within the depressed segment can propagate.
normal action potential is seen at the proximal recording site (upper trace), no response is seen in the branch (middle trace) apart from a slow, low-voltage deflection, and no change is seen at the distal site (lower trace). When the distal end is excited (Fig. 5C), a normal action potential is recorded at the distal recording site, but no response is seen at the proximal site or at the branch. There is complete block between each end and the other end and also between each end and the branch. When both ends are excited, however (Fig. 5B), a normal action potential propagates out the branch. The first action potential in the middle and lower traces is longer than the two succeeding action potentials, reflecting the rate-induced shortening which occurs as regular excitation begins. The rate effect is absent in the upper trace because that site was already excited at a steady rate.

In Figures 6A and 6B excitation of either end of the segment produces a small deflection in the branch and no conduction to the far end. In Figure 6C, when both ends of the fiber are excited almost simultaneously, a virtually normal action potential is recorded from the branch. As in Figure 5, the first action potential in the upper trace and the first action potential in the middle trace of Figure 6C are long, and subsequent action potentials shorten by a rate effect. Figure 6D shows the interesting phenomenon of 2:1 block between excitation in the branch and excitation entering the two ends of the depressed segment. When excitation is transmitted out the branch in this record, it arises with marked latency and occurs during the relative refractory periods of the two impulses entering the ends of the depressed segment.

In the experiment shown in Figure 7, both ends of the preparation were stimulated. In 7A the distal end was stimulated 65 msec before the proximal end. In subsequent records the time of excitation of the distal end was progressively delayed with respect to the time of stimulation of the proximal end. At the earliest interval shown (Fig. 7A), a small deflection but no propagated action potential is seen in the branch. In Figure 7B excitation arises with considerable latency in the branch. As the stimuli applied to the ends become more nearly simultaneous, the latency with which excitation appears in the branch diminishes until it reaches a minimum in Figure 7F. As excitation of the distal site moves later than excitation of the proximal site, the latency of the response in the branch again increases, reaching a maximum in Figure 7K. A further small delay in excitation of the distal site again yields failure of excitation in the branch, and the slow, low-voltage deflection seen in Figure 7L closely resembles that seen in Figure 7A. The shifts in the latency of the response in the branch considerably exceed the changes in relative timing of excitation of the ends. A shift of 8 msec in the time of excitation of the distal site in Figure 7C and Figure 7K gives rise to an increase in delay of the response in the branch of 66 msec.

The records in Figure 8 show an experiment in which excitation of the distal end occurred 5 msec before excitation of the proximal end (Fig. 8A), 10 msec after excitation of the proximal end (Fig. 8B), 25 msec after excitation of the proximal end (Fig. 8C), and
Variation in the time of appearance of excitation in a branch secondary to variation in the timing of excitation of the ends. Upper trace: proximal end; middle trace: branch, lower trace: distal end. In A excitation of the distal end too soon before excitation of the proximal end yields no excitation in the branch. In B to K excitation is seen in the branch with a latency that increases as excitation of the distal end occurs progressively later with respect to the time it was excited in A. In L excitation of the distal end too long after excitation of the proximal end yields no excitation of the branch. Calibration: time 200 msec, voltage 100 mv.

30 msec after excitation of the proximal end (Fig. 8D). The 15-msec change in relative excitation time between Figures 8A and 8B occasioned little increase in the latency of appearance of the response in the branch, while a further delay of 15 msec shown between Figure 8B and Figure 8C occasioned an increase in latency at the branch of 90 msec. In Figure 8C the rapid upstroke seen in the branch arises 150 msec after the rapid upstroke at the proximal site and 125 msec after the rapid upstroke at the distal site. A further increase in the delay between stimulation of the proximal and distal ends of only 5 msec results in failure of propagation in the branch (Fig. 8D).

When stimuli were applied only to the proximal end (first three action potentials) in Figure 9C, a reasonably normal action potential was recorded at that site, but only a small depolarization was seen in the branch and none at the distal end. When only the distal end was stimulated (last two action potentials in Fig. 8B), the results were much the same: an action potential of good amplitude at the distal end, a small depolarization in the branch and none at the proximal end. When both proximal and distal ends were stimulated, the response recorded from the branch varied with the interval between the stimuli applied to the two ends of the preparation. At the beginning of the record shown in Figure 9A, the distal end was stimulated 10 msec after the proximal end; the distal end was stimulated progressively earlier throughout the traces shown in Figure 9A and those shown in Figure 9B, apart from the last two action potentials, where the distal end was stimulated alone. The response recorded from the branch increased in amplitude as the interval between the two stimuli increased. Unlike Figures 5 to 8, however, there was no
Variation in the time of appearance of excitation in a branch secondary to change in the timing of excitation of the ends. Upper trace: proximal end; middle trace: branch; lower trace: distal end. Very small changes in the relative timing of excitation of the ends in A to C cause large changes in the latency with which excitation appears in the branch. A further very small change in timing from C to D causes excitation of the branch to vanish. Calibration: time 400 msec, voltage 100 mV.

FIGURE 9

Variation in the time of appearance of excitation in a branch secondary to change in the timing of excitation of the ends. Upper trace: proximal end; middle trace: branch; lower trace: distal end. Very small changes in the relative timing of excitation of the ends in A to C cause large changes in the latency with which excitation appears in the branch. A further very small change in timing from C to D causes excitation of the branch to vanish. Calibration: time 400 msec, voltage 100 mV.

Inhibition

Figure 10 shows effects obtained from a simple depressed segment without a branch. In Figure 10A excitation of the proximal end results in an action potential at the proximal
Improvement in the response of a branch as the result of "warming-up." Upper trace: proximal end; middle trace: branch; lower trace: distal end. Most of the increase in the size of the response in the branch is the result of a progressive increase in the responsiveness of the branch, not the result of shifts in the time of excitation of the ends. See text for discussion.

Calibration: time 400 msec; voltage 100 mv.

Excitation of one end inhibiting the response in the center of a segment evoked by excitation of the other end. Upper trace: proximal end; middle trace: center of depressed segment; lower trace: distal end. In A excitation of the proximal end evokes no response in the center. In B excitation at the distal end evokes an action potential in the center. In C to E excitation of both ends evokes a response in the center at a later time than when the distal end is excited alone, and the increased latency varies with the relative timing of the excitation of the ends. In F the timing is such that the response in the center is much reduced in size, probably to a level incapable of propagation out a branch were a branch present. In G excitation of both ends produces effects resembling those seen either in C to E or in F.

Calibrations: time 200 msec; voltage 100 mv.
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A depressed area in Figure 10B has a notched upstroke. When proximal and distal ends are excited simultaneously, summation occurs (Fig. 10C) since the upstroke of the action potential in the center is faster and is uninterrupted by notches. As excitation of the distal site is delayed with respect to the time of excitation of the proximal site, however, the action potential in the depressed segment arises with progressively greater delay (Figs. 10D, E, and F) until finally, in the second set of action potentials in Figure 10F, activity in the center appears to have been inhibited, the action potential being replaced by a low-voltage deflection with a slow time course. Figure 10C shows a series of seven consecutive action potentials obtained by exciting the distal site later than the proximal site. Occasionally, the fiber in the center responds with a long latency, and occasionally, it does not respond except with a slow, low-voltage deflection. These records suggest that the ability of excitation of the distal site to give rise to excitation at the center of the depressed segment is interfered with by prior excitation of the proximal site, even though excitation of the proximal site alone does not give rise to an action potential at the center. At one set of relative times of excitation, summation can arise (Fig. 10C), and at another set of intervals, prior excitation of the proximal site increases the delay with which excitation at the center arises, as compared with the delay with which it arises in response to excitation of the distal site alone. At yet another set of intervals, prior excitation of the proximal site prevents or inhibits excitation which could have arisen had the distal site been excited in the absence of excitation of the proximal site.

The records in Figure 11 were obtained from the branch of a preparation which clearly demonstrated inhibition. At the beginning of the trace shown in Figure 11A, only the proximal end of the preparation was stimulated; normal action potentials were recorded from the proximal end (upper trace), and responses of good amplitude were generated by the branch (middle trace), and there was no spread of activity to the distal end (lower trace). When only the distal end of the preparation was stimulated (last three action potentials of Fig. 11C), the records from the branch showed only small depolarizations, and there was no spread of excitation to the proximal end.

In Figure 11A when, during regular stimulation of the proximal end, stimuli were

**FIGURE 11**

Excitation of a branch by stimulation of one end of a depressed segment inhibited by stimulation of the other end. Upper trace: proximal end; middle trace: branch; lower trace: distal end. In A excitation of the proximal end alone gives rise to regular excitation of the branch until the distal end is also stimulated whereupon excitation of the branch is inhibited. In B excitation of both ends gives rise to no excitation in the branch; then stimulation of the distal end is stopped, whereupon excitation appears in the branch. In C the first three action potentials of the proximal end excite the branch, and then excitation of the distal end is begun while excitation of the branch is inhibited. Calibration: time 400 msec, voltage 100 mV.

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applied with constant delay to the distal end, the response that had appeared in the branch after each proximal action potential disappeared and was replaced by small depolarizations synchronous with the proximal and distal action potentials. This inhibition of the response of the branch persisted until, in Figure 11B, stimulation of the distal end was terminated. After three more proximal action potentials the response generated by the branch was comparable with that seen at the beginning of Figure 11A. In Figure 11C stimulation of the distal end of the preparation was resumed after the first three proximal action potentials, and again this inhibited the response generated in the branch.

This figure also shows "warm-up" of the response recorded from the branch (Fig. 11B); a change in the duration and shape of repolarization of the proximal action potential when spread of activity into the branch is inhibited (Figs. 11A and C); prolongation of the response recorded from the branch induced by the first action potential generated by the distal end of the preparation (Figs. 11A and C); and rate-dependent changes in the responses recorded from the branch after the end of each period of inhibition (Fig. 11B).

Figure 12 shows that inhibition may be either complete or incomplete. At the beginning of Figure 12A, only the distal end of the preparation was stimulated. After the third distal action potential, stimulation of the proximal end was begun: the responses generated by the branch (middle trace) are irregular until, after the seventh distal action potential, stimulation of the distal end was terminated. Thereupon, each proximal action potential evoked a response in the branch. Stimulation of the proximal end only was continued until the middle of the trace shown in Figure 12B when stimulation of the distal end was begun. Two of the subsequent proximal action potentials generated responses of good amplitude in the branch, but the response to the remaining six proximal action potentials was inhibited.

The records obtained from the branch in this figure show complex variations. The response that follows the first proximal action potential in Figure 12A appears to result from greatly delayed summation of the distal and proximal responses; the response to the next proximal action potential appears only as a prolongation of repolarization of the prior response in the branch; the response to the next proximal action potential is of full amplitude; and the response to the next is only partially inhibited. In Figure 12B the two

![Figure 12](http://circres.ahajournals.org/)

Excitation of a branch by one end of a depressed segment inhibited by excitation of the other end. Upper trace: proximal end; middle trace: branch; lower trace: distal end. In A the inhibitory (distal) end is stimulated before stimulation of the excitatory (proximal) end is begun. Four action potentials of the excitatory end produce only two action potentials and one abortive action potential in the branch, but when the stimulation of the distal end is stopped, the branch responds regularly to excitation of the proximal end. In B the branch responds regularly to excitation from the proximal end; during stimulation of the distal end, eight action potentials from the proximal end give rise to only two action potentials in the branch. Calibration: time 400 msec, voltage 100 mv.
large responses generated by the branch are of long duration, and the second of them shows a clear second phase of depolarization which causes a small change in membrane potential at the proximal recording site. A similar proximal reflection of the response in the branch is shown by the first proximal action potential in Figure 12A.

Discussion

TERMINOLOGY

We have used the terms summation and inhibition descriptively. The term summation refers to the effect seen when two stimuli are sent into a segment and result in excitation where a single stimulus fails to result in excitation. That phenomenon has the characteristics of spatial summation, in the sense in which that term is used by neurophysiologists, since the summation of excitatory events depends on stimulating two spatially different sites rather than on stimulating the same site sequentially. The term inhibition is used descriptively to imply that there are fibers which, when excited, are able to stop or prevent activity which results from the excitation of other fibers.

SUMMATION

We have previously described and discussed in detail the electrical responses which arise in depressed fibers (1). We have also considered the means by which such responses give rise to excitation with great delay, and we have outlined the ways in which small, low-voltage deflections might summate beyond a point of block. To that discussion we need add little to explain the summation and excitation shown above. One important addition stems from the fact that when an action potential propagates towards a region of block, it propagates toward a fiber which, both at and beyond the point of block, has a different space constant than that of a fiber in which an action potential is traveling from both ends at once. During the upstroke of an action potential, the membrane resistance is low, and the space constant is reduced; during the plateau the membrane resistance is high, and the space constant is increased (3). Both of these changes in the space constant affect electrotonic spread. The forward electrotonic spread of depolarization of each of the impulses invading a fiber from its opposite ends will thus differ from that seen when either impulse invades the fiber in the absence of the other.

We must make the same proviso we made in our previous article (1): the events recorded by the electrode within the depressed segment need not be the immediate cause of the action potential which arises by summation. The family of events described must, however, be the sorts of events which, alone or cooperatively, bring the fiber within the depressed segment to its threshold. Our results show clearly whether the fiber from which we record does or does not develop an action potential, and they show clearly that that fiber can develop an action potential when excited from both ends and not when excited from either end alone. We cannot assert that a particular time relationship between the application of the stimuli to the ends of the fiber is the same as the time relationship between the electrical events thereby evoked within the depressed segment. A delay in the excitation of one end of the fiber with respect to the time of excitation of the other end might result in a much greater delay in the summation of the responses in the center of the fiber since the transmission of the impulse into the center varies according to the degree to which excitation has advanced into that fiber from the other end. Delays in summation which are greater than the shifts in timing of excitation of one end of the fiber may, in fact, result from mechanisms quite similar to those which lead to inhibition.

INHIBITION

We have shown that the arrival with suitable timing of a wave of excitation from one end of a segment may inhibit excitation in the center of that segment and may prevent transmission out a branch, transmission which occurs freely when the other end of the segment alone is excited. If the end of the segment that induces inhibition is stimulated during activity of the end that is able to excite the branch, the action potentials in the center
of the segment and the branch are actively suppressed; if it is excited prior to stimulation of the end capable of exciting the branch, then stimulation of that end fails to give the excitatory responses in the center and the branch which it would otherwise have done. We assume that when the inhibitory end is stimulated, the action potentials to which it gives rise invade and die out in some fibers of the bundle, thereby diminishing their responsiveness. Those fibers are then unable to take part in the excitatory response to which they would normally have contributed when the other end of the bundle was stimulated. This mechanism resembles that of concealed conduction, with the important difference that the impulse dies out in a depressed fiber rather than in a fiber made refractory by previous activity.

RE-ENTRY

The notion that re-entry may occur as the result of slow conduction in a continuous pathway that is part of a circuit in which one-way block is present has long been advanced as a possible mechanism for re-entry, and we have shown (1) that conduction slow enough to meet the requirements of such postulated mechanisms can be induced in segments of Purkinje fibers. The records shown above demonstrate that if the ends of a depressed segment are excited, an impulse can arise in the center of that segment and propagate out a branch with considerable latency. We believe that such an impulse could propagate out the branch and give rise to a re-entrant extrasystole.

The idea that two greatly impaired impulses entering a segment from its opposite ends can summate and give rise to excitation is new. The suggestion that such summation can result in re-entry by exciting a branch that emerges at the point where summation occurs is also new. For that reason discussion of how this mechanism could cause re-entry in the whole heart is in order. Were a segment of Purkinje fibers to be appropriately depressed, summation could occur at its center when its ends were excited by the arrival of the normal wave of excitation of the heart. In our experimental situation summation with great delay usually required that there be some difference in the time of excitation of the ends of the bundle, this could occur in an in situ preparation as the result of normal differences in the time of arrival of the impulse at the opposite ends of the fiber or as the result of some small delay in another short segment of slightly depressed fibers.

The ability of the excitation arising by summation at the center of the depressed segment to travel out the branch requires the branch to be excitable. Since the branch enters the depressed segment at its center, the branch might well be protected from the normal wave of excitation by entry block, at least at the point of its junction with the depressed segment. One also could postulate that much of the branch is shielded from excitation by entry block at the end of the branch remote from the depressed segment.

It is possible to invent many networks of Purkinje fibers or myocardial fibers containing depressed segments from which a branch emerges. Each of these networks would require different conditions of timing or entry block to ensure that excitation of the ends of the depressed segment might give rise to a re-entrant extrasystole. It is equally easy to construct circuits in which the re-entrant impulse would in turn re-excite the depressed segment, causing a ventricular tachycardia. The important feature common to all of these models is the existence of excitation arising with a long delay as the result of summation at the center of a depressed segment, and we believe that the further investigation of that phenomenon will shed light on the nature of many re-entrant arrhythmias.

We cannot explain on the basis of our own investigations how the appropriate degree of depression might arise in the whole heart. It is true that the profuse network of intracavitary false tendons and subendocardial Purkinje fibers is protected from anoxia by its exposure to the intracavitary blood. The larger bundles of Purkinje fibers do carry their own blood supply, and certain infarcts in regions involving the bundle branches are notoriously prone
to cause arrhythmias. We believe that if a bundle of in situ Purkinje fibers or a suitable myocardial syncytium were to lose its blood supply or become anoxic, the fibers in that bundle or syncytium would acquire characteristics very similar to those that we have induced by high $K^+$ and would thereby acquire the characteristics needed to cause re-entry via summation in the center of a depressed segment.

**Implications for other networks of excitable tissue**

The properties of the depressed segment and of the depressed segment from which a branch emerges have been catalogued in detail in this and a previous article (1). Those properties include slow conduction (excitation with marked delay), one-way conduction, Wedensky inhibition (better conduction at slow rates than at high rates), summation of individually subthreshold excitatory responses, and inhibition. These are properties classically regarded as peculiar to the nervous system. In 1917 Keith Lucas and Edgar D. Adrian attempted to explain the properties of the central nervous system as depending on depressed and decremental conduction in nerve fibers (4). This explanation was not discarded until, in the course of the following decade, anatomical studies more and more definitely showed that the central nervous system of higher forms is not a reticulum and physiological studies showed that the properties in question are those of synapses. We have shown that interposition of a region of depression in a reticulum of fibers can confer integrative properties on that network. The presence of two or more depressed segments, with or without emergent branches, could obviously produce exceedingly complex interactions of excitation and inhibition.

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**References**

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