Genesis of Cardiac Arrhythmias

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An arrhythmia is caused by an abnormality in the rate, regularity, or site of origin of the cardiac impulse or by certain disturbances in the conduction of the impulse such that the normal sequence of activation of the atria and ventricles is disturbed. Arrhythmias thus may be said to result from abnormalities of impulse initiation, impulse conduction, or both.

Activity of Automatic Cells

The normal rhythm of the mammalian heart results from spontaneous excitation of cells in the sinoatrial node. These cells possess the property of automaticity. The transmembrane potential of working muscle fibers in the atria or ventricles demonstrates a rapid depolarization on excitation (phase 0), a period of variable duration during which the cell repolarizes (phases 1, 2, and 3), and then a stable resting potential (phase 4), which persists until the next propagated impulse arrives and causes excitation. In contrast, in cells of the sinoatrial node, repolarization is not followed by a period during which the transmembrane potential is stable. Instead, immediately after the end of repolarization the membrane potential begins to decrease slowly. This slow depolarization during phase 4 lowers the transmembrane potential toward the threshold potential, the value of transmembrane potential at which excitation occurs. If the slow depolarization attains the threshold potential, excitation occurs and the cell develops an action potential which then propagates to excite adjacent cells and, normally, the rest of the heart. All cells which demonstrate this slow diastolic depolarization are said to be automatic. This mechanism for spontaneous firing has been called the normal automatic mechanism to differentiate it from other changes in the transmembrane potential which can, under abnormal conditions, initiate automatic firing. Also, there are other causes for slow depolarization during phase 4 which are not necessarily associated with automaticity.

In addition to the cells of the sinoatrial node a number of other groups of specialized cardiac cells also possess automaticity and can serve as automatic pacemakers. These include: cells in the specialized atrial fiber tracts which connect the sinoatrial and atrioventricular nodes and lead from the sinoatrial node to the left atrium, cells in and around the coronary sinus ostium, cells in the more distal parts of the atrioventricular node (NH region), and cells in the His-Purkinje system. Most evidence indicates that cells in the more proximal parts of the atrioventricular node (AN and N regions) do not show automatic firing except perhaps under extreme experimental conditions.

The rate at which normally automatic cells fire is controlled primarily by the activity of the autonomous nervous system and secondarily by other changes in the local environment of the cells. Important in relation to the latter consideration is the extracellular K+ concentration, pH, pO2, and the extracellular concentration of Ca++. In addition to the local chemical environment of the cells, another significant regulator of the rate at which an automatic cell would fire is the frequency at which it has been stimulated. If an electronic pacemaker or an ectopic focus gains control of the atrial rhythm and causes activation at a rate significantly higher than the intrinsic sinus rate, and if these impulses succeed in depolarizing the sinoatrial node, the automaticity of the node will be depressed. As a consequence, if the ectopic pacemaker stops abruptly, the initial automatic firing rate of the sinoatrial node will be low and automaticity will slowly increase to its normal value. This phenomenon, called overdrive suppression, is common to all normal automatic cells. In this manner the normal sinus pacemaker, by overdriving all subsidiary pacemakers, depresses their automaticity so that there is less likelihood that any one of them will escape and cause an ectopic impulse. Disease and the action of many drugs can abolish overdrive suppression. In fact, the action of catecholamines and digitalis may reverse

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the response of an automatic cell to overdrive so that, instead of depression, overdrive actually enhances automaticity and increases the likelihood of escape rhythms.

Since there are many groups of automatic cells in the heart, any factor which decreases the intrinsic rate of the normal sinoatrial nodal pacemaker or which increases the automaticity of other specialized latent pacemakers can result in an arrhythmia. This may appear as a single ectopic impulse, a group of ectopic impulses, or a sustained rhythm originating at an abnormal site. If an increase in vagal activity depresses the automaticity of the sinoatrial node the site of origin of the impulse may shift to other automatic cells proximal to the atrioventricular node (low atrial rhythm) or to cells in the His-Purkinje system which are not strongly influenced by vagal activity. Similarly, there may be an increase in automaticity at an ectopic site due to a local increase in sympathetic efferent activity or to some local change in the condition of the cells such as those caused by ischemia or stretch.2 If cells at the ectopic site attain threshold before they are excited by propagation of an impulse arising in the sinoatrial node, they will serve as pacemaker for one or a series of impulses which may be responsible for activation of all or parts of the heart.

Ectopic automatic rhythms also may result from abnormalities in the propagation of an impulse arising in the sinoatrial node. Sinoatrial block may permit the escape of either subsidiary atrial pacemakers or pacemakers in the lower atrioventricular node and His-Purkinje system. Block of impulse transmission from the atria to the ventricles, either in the atrioventricular node, common bundle, or bundle branches, ordinarily will result in the initiation of an ectopic automatic rhythm distal to the site of block. Finally, when two sites of automaticity, one proximal to and one distal to the atrioventricular node, are firing at almost the same rate, there may be a rhythm commonly designated as isorhythmic dissociation.7 In this case many of the normal and ectopic impulses are blocked in the atrioventricular node. The atria and ventricles will be excited almost simultaneously and at almost the same rate for considerable periods of time. This is usually interrupted periodically by intervals during which the atrial or ventricular pacemaker assumes the role of the primary pacemaker. It is quite likely that a similar relationship may exist between an ectopic focus and the sinoatrial node but with block occurring at the junction between the node and atrium and also between the normal cardiac pacemaker and any parasystolic automatic focus (see below under parasystole).

Effects of Depressed Excitability

We now consider arrhythmias and abnormalities of activation of the heart that result from depressed excitability and abnormal conduction. The discussion is written in terms of the ventricle and of the "normally" depressed A-V node but the basic principles apply to atrial fibers as well.

Abnormalities in Conduction

The presence of localized depression of excitability can explain a variety of electrocardiographic phenomena.5,8 Depression of a bundle of Purkinje fibers can reduce conduction velocity from the normal value of 2–3 m/sec to 0.05–0.1 m/sec (fig. 1). Such depression in a segment of the bundle of His would result in first-degree heart block. First-degree heart block caused in part by slowed conduction in the ventricular conducting system has been documented by His bundle recording.9 Similar delay in a bundle branch could give rise to ventricular aberration or bundle-branch block, even in response to a non premature impulse, whereas aberrancy caused by premature activation or high rate probably results from conduction infringing on the relative refractory period (before complete repolarization of the previous impulse). Similar slowing of conduction of non premature impulses has been shown in fibers depressed by phase 4 depolarization.10

Conduction through depressed fibers also shows increased sensitivity to changes in rate which may result in variable degrees of delay and block (fig. 2). Conduction block may occur without a noticeable increment in conduction delay (second-degree type II block) (fig. 2B) or transmission of the impulse through the depressed cardiac fibers may show the Wenckebach phenomenon (second-degree type I block) (fig. 3). In the normal ventricular conducting system such increases in rate do not cause conduction delay or block unless excitation occurs before completion of repolarization of the previous impulse.

These findings provide an explanation of many electrocardiographic observations. An increase in heart rate can result in a transition from normal intraventricular conduction to bundle-branch block and even to complete heart block.11 Records of the activity of the His bundle in the human heart have shown that many disturbances of atrioventricular
Effects of localized depression on conduction in a bundle of Purkinje fibers. (A) Diagram of the preparation with location of stimulating electrodes $S_1$ and $S_2$, and recording electrodes 1, 2, and 3. The crosshatched area where recording electrode 2 is located has been depressed by local elevation of $K_\theta^+$ to 15 mV. (B) Tracing shows that conduction before depression is rapid; when the bundle is stimulated at $S_1$ the impulse conducted from one end of the bundle to the other in less than 5 msec. In C, after depression of the center segment (note the depressed action potential in trace 2) conduction between electrodes 1 and 3 required 150 msec. Conduction velocity fell in the depressed part of the bundle to about 0.07 m/sec from a normal value of about 3 m/sec. Calibrations: vertical, 100 mV; horizontal, 500 msec.

Depression of excitability may also cause unidirectional block (fig. 4). One-way block located in a peripheral twig of the Purkinje fiber network might produce no obvious changes in the electrocardiogram but obvious changes would occur if one-way

Conduction occur in the bundle of His or the bundle branches rather than in the A-V node. In Mobitz type II A-V block, conduction block apparently occurs in the ventricular conducting system. A progressive increase in the degree of block has been demonstrated with increasing atrial rate (see fig. 2). The Wenckebach phenomenon in the ventricular conducting system may appear as incomplete bundle-branch block progressing in severity to complete bundle-branch block, complete block corresponding to the dropped beat of the Wenckebach period. If Wenckebach periodicity occurs in the common bundle, above its bifurcation, only a progressive prolongation of the P-R interval culminating in A-V block is observed on the electrocardiogram without aberrant activation of the ventricles.

The effects of increasing rate on conduction through a depressed segment in an unbranched bundle of canine Purkinje fibers similar to that shown in figure 1A. Recording electrode 2 was located in the depressed center segment, while electrodes 1 and 3 were at either normal end. (A) At a drive rate of 50/min every impulse is conducted with delay. (B) At 60/min 4:3 conduction block appears (second-degree type II block). (C, D, and E) At rates of 75, 100, and 140/min there is a progressive increase in the degree of conduction block. Calibrations: vertical, 100 mV; horizontal, 350 msec.

Wenckebach cycles in a bundle of canine Purkinje fibers. Recording electrode 2 was located in the depressed center segment, while electrodes 1 and 3 were at either normal end. Note the lengthening of the action potential in trace 2 after the dropped beat of the Wenckebach cycle. As a result, the next impulse reaches the depressed segment during its refractory period and is blocked, resulting in a 2:1 cycle after each Wenckebach cycle. Calibrations: vertical, 100 mV; horizontal, 100 msec.

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Figure 4

Unidirectional conduction block in the segment of a bundle of canine Purkinje fibers depressed with high K⁺ (middle trace). (A) Stimulation at one end of the bundle results in conduction. The recording sites shown in the lower, middle, and top traces were activated in that order. (B) Stimulation at the other end of the bundle results in activation of recording site in top trace (nearest stimulating electrode) but conduction block in the depressed area (middle trace). Calibrations: vertical, 100 mv; horizontal, 500 msec.

block of normal forward conduction were present in the common bundle or in both of the bundle branches. Studies in man have shown that many cases of complete heart block are caused by conduction block in the common bundle or its branches. One-way block at those sites could prevent conduction from the atrium to the ventricle while allowing conduction from the ventricle to the atrium.

Concealed Conduction

A premature impulse of atrial origin that fails to evoke a ventricular contraction may affect propagation of the next atrial impulse, for example by prolonging the P-R interval. Such effects show that apparently nonconducted impulses may conduct part way through the A-V node or even part way into the ventricular conducting system, leaving changes of excitability in their wake. Such impulses are said to have undergone "concealed conduction", what is actually "concealed" is, of course, the exact site at which block occurred. Block of a premature impulse in the A-V nodal area is probably rather common and is detected by the fact that the next atrial impulse is either blocked or reaches the ventricle with delay. If a premature impulse of atrial origin is conducted through the A-V node and blocked in the ventricular conducting system, the next impulse may be conducted normally in the ventricular conducting system because it must undergo normal A-V nodal delay before reaching the point where the previous impulse died out. That delay allows time for recovery of the area where the premature impulse was blocked. In addition, the time needed for recovery is reduced because a premature action potential in the ventricular conducting system is shorter than a normal action potential. The fact that such impulses can propagate into the ventricular conducting system before blocking thus remains "concealed" even from ordinary electrocardiographic techniques and can be shown only by direct records of the activity of the bundle of His or the bundle branches.

The effect of a blocked impulse on the following impulse depends on the site of block, on the time needed for the following impulse to reach the site of block, and on how long it takes the area in which block occurred to recover its excitability. We have found that in depressed Purkinje fibers the time required for complete recovery of excitability far exceeds that needed for complete repolarization, which greatly prolongs the period during which conduction of a subsequent beat may be impaired. In figure 5A, a premature impulse originating in normal tissue blocks within the depressed area and creates refractoriness that blocks the next driven impulse, even though that impulse arose long after complete repolarization in the normal area. In figure 5B, the impulse following the blocked impulse is conducted but with an increased delay of 50 msec. Block of this type in depressed ventricular conducting fibers and its effect on a subsequently conducted atrial impulse within the ventricular conducting system would appear electrocardiographically as A-V block of a premature atrial impulse followed either by block of the next impulse or by aberrant conduction of the next impulse. This effect can be seen even at a normal or low heart rate and has been reported in the human heart.

Figure 5

Concealed conduction in a depressed segment of a bundle of canine Purkinje fibers. Recording electrode 1 was located in the depressed area and electrode 2 in a normal area. The premature impulse arising in the normal area is indicated by an arrow. (See text for discussion.) Calibrations: vertical, 100 mv; horizontal, 500 msec.
Reentrant Excitation

Reentry of excitation in the ventricle requires that the impulse which excites the ventricle somehow finds a separate pathway in which it can travel and from which it can emerge at the end of the refractory period to reenter the ventricle and elicit a second activation. The impulse destined to reenter the ventricle must survive for some 300 msec if it is to outlast the ventricular refractory period. If the impulse is conducted in a short pathway functionally isolated from the heart, conduction velocity in that pathway must be very slow. Since very slow conduction has long been assumed to be present in the atrioventricular (A-V) node, a particular form of arrhythmia, the nodal return systole or echo beat, has long been regarded as reentrant. In nodal return extrasystoles an impulse that arises in the atrium or ventricle and is conducted into the A-V node also “returns” from the node to the chamber in which it originated. Such return extrasystoles are explained by assuming circus movement of excitation in or near the A-V node.

Most models offered to explain such circus movement are essentially identical with those first proposed by Schmitt and Erlanger and shown in figure 6. The upper diagram in figure 6 shows a strand of the ventricular conducting system (D) bifurcating into two branches (B and C), both of which will ventricular muscle. The arrow at D indicates an impulse that travels with normal velocity via C and the ventricular muscle to reach B but does not travel from A to B because of one-way block in that branch (stippled area). Activity can, however, enter the depressed area via its far end at B. If conduction from B to A is very slow, the impulse may not reach A until the fibers at A and D have recovered their excitability. If that occurs, the impulse will continue past A and into D to reexcite the entire heart and give rise to a reentrant extrasystole. Reentry via conduction around such a circuit can occur only if the depressed area is the site of one-way block and if conduction through it is very slow. In the lower diagram in figure 6 the pathways are not discrete separate branches; they could be different fibers or bundles of any type. The lower diagram of figure 6 thus contains the elements necessary for reentry within a syncytial structure, i.e., reentry dependent on longitudinal dissociation of function.

We find that reentry in response to a premature or a nonpremature impulse readily occurs in the presence of slow conduction and unidirectional block in unbranched bundles or in networks of the ventricular conducting system. That circus movement in a loop of depressed ventricular conducting fibers can cause premature beats is demonstrated in figure 7. An impulse traveling down the bundle to the loop can enter the loop in only one direction (branch a) because of unidirectional block in branch c (lower branch) (fig. 7C). Figure 7A and C shows that if the impulse is blocked in both limbs of the loop there is no reentry into the main bundle. If the impulse that enters the upper part of the loop (branch a) is delayed but not blocked at the depressed area, it travels around the loop, reenters the main bundle, and gives rise to an extrasystole or premature beat (fig. 7B and D). A sinus impulse could therefore enter a bundle leading to such a depressed loop; the impulse reentering the bundle from the loop would travel...
Figure 7

Single circus movement in a loop of canine Purkinje fibers depressed by high K+. (A) Action potentials recorded during conduction block in the loop, and (B) single circus movement. (C and D) Diagrams of the preparation and location of the stimulating electrode (S1) and the recording electrodes (1, 2, 3). The branches of the loop are indicated by a, b, and c. The pathway of propagation shown by arrows in C corresponds to the action potentials shown in A. Note only single depolarizations at sites 1 and 2 and the absence of depolarization at site 3 indicating block. The pathway of propagation in D corresponds to the records shown in B. In B the first depolarization at site 1 and the depolarization at 2 are followed by delayed activation at 3 (a site of unidirectional block). This is followed by the reentrant impulse at 1 (second depolarization). Calibrations: vertical, 100 mv; horizontal, 500 msec.

back into the rest of the ventricular conducting system and ventricle as an extrasystole. If this occurred after every sinus impulse a bigeminal rhythm would occur.

In figure 7, the impulse, once past recording site 2, is not subject to further delay and travels around the loop fairly rapidly. It may therefore enter the upper branch again and reach site 2 while it is still refractory. A repetitive circling of excitation around the loop is thus not possible. If there are two sites of delay or slow conduction around the entire loop an impulse might travel around the loop repeatedly, sending impulses out any branch that it passed on its trip around the loop.26 Such continuous circus movement could result in a tachycardia. Not all tachycardias result from reentry but many may, particularly in patients in whom coupled premature ventricular systoles appear and show the same QRS configuration as the systoles of the tachycardia. In those instances the first beat of the paroxysm of tachycardia often appears with fixed coupling to the QRS of the last normal beat.27 Paroxysmal ventricular tachycardia can often be precipitated by an applied ventricular premature stimulus and terminated by an appropriately timed ventricular stimulus.28, 29 Similar findings have been reported for supraventricular tachycardias resulting from continuous reentry within the A-V node.30 These observations can readily be explained in terms of the mechanisms described above; premature stimulation may result in the slow conduction needed for reentry and a single applied stimulus during the tachycardia would cause another impulse to enter the loop, making it refractory to the circulating impulse.

We have also found that depression of a short segment of an unbranched bundle of Purkinje fibers can lead to reentrant excitation of a kind analogous to an A-V nodal return extrasystole.25 The impulse entering the depressed area in the bundle is slowed and, after considerable delay, continues in the forward direction while a reentrant impulse is reflected backward in the direction from which the initiating impulse arrived (fig. 8). In this sort of reentry by “reflection” the impulse need not continue in the forward direction; block in the forward direction combined with reentry in the retrograde direction has been observed.25 A possible mechanism for reflection is shown schematically in figure 8C, in which the model shown in figure 6 is modified by enlarging the area of depression. The conditions shown in this diagram presumably could arise in depressed fibers located anywhere in the heart.

A depressed 8-10-mm segment of unbranched Purkinje fibers capable of giving rise to reentry by reflection could be located anywhere in the conducting system from the His bundle to a distal peripheral twig. The electrocardiographic manifestations of such reentry would vary depending on the location of the depressed area. In the common bundle it could result in various degrees of A-V block associated with return extrasystoles (fig. 9).

Were the depressed segment in a peripheral twig of the conducting system, the electrocardiographic manifestations of the events depicted in figure 9

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Reentry (reflection) in a linear bundle of canine Purkinje fibers. (A) Diagram of preparation showing location of stimulating electrodes \( S_1 \) and \( S_2 \) and recording electrodes \( a, b, c \). The center segment, depressed by high \( K^+ \), is indicated by crosshatched area. The bundle is being stimulated at \( S_1 \) only. (B) In the first group of action potentials \( I \) shows conduction of impulse originating at \( S_1 \) without reentry; conduction from \( a \) to \( c \), through the depressed area, required 100 msec. In the second group of action potentials \( I \) shows conduction of another impulse from \( S_1 \) with a marked increase in the conduction delay between recording sites \( b \) and \( c \) to 250 msec. A reentrant impulse \( II \) returning in the opposite direction is shown at recording sites \( b \) and \( a \). (C) Diagrammatic representation of a possible pathway of impulse propagation during reentry in two parallel fibers. Severely depressed area indicated by crosshatches, moderately depressed area by stipple. Impulse \( I \) is completely blocked in upper fiber at area of unidirectional block but traverses the moderately depressed area in lower fiber, then reenters upper fiber to travel in the reverse direction as impulse \( II \). Calibrations: vertical, 100 mv for traces \( a \) and \( c \) and 50 mv for trace \( b \); horizontal, 250 msec.

would be completely different. Nothing might be seen on the electrocardiogram apart from occasional extrasystoles since the focal ventricular delay, concealed retrograde conduction in the small twig, and focal ventricular block might well not be detected.

**Fixed and Variable Coupling**

During the time between the appearance of the QRS complex evoked by the sinus impulse and the appearance of the reentrant extrasystole the impulse is traveling through the pathway that leads to reentry. This event is not seen on the electrocardiogram because the amount of tissue that comprises this pathway is small and because conduction through it is slow.7 If the pathway that leads to reentry in a loop of Purkinje fiber bundles is always the same and if the impulse always travels through it at the same speed, the interval between the QRS complex of the dominant rhythm and the extrasystole will be fixed and the result will be a bigeminal rhythm with fixed coupling. If the conduction time through the pathway leading to reentry varies, the coupling interval will vary (fig. 10).

Variable or progressive conduction delay in a depressed segment can also result in variable
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Figure 10

Variable coupling intervals of reentrant impulses due to increasing conduction time in a reentrant pathway. The mechanism of reentry and location of recording sites 1, 2, and 3 in the reentrant pathway are shown in figure 7B and D. The first depolarization in trace 1 of each panel is the simulated action potential which propagates to site 2 giving rise to the action potential in trace 2 and then to site 3 (action potential in trace 3), finally reemerging to reexcite at site 1; the second depolarization in 1 is the reentrant impulse. Conduction delay between sites 2 and 3 is variable; in A when conduction between these recording sites was 215 msec the coupling interval between the stimulated beat and the reentrant impulse at recording site 1 was 330 msec. As conduction time between sites 2 and 3 increased to 285 msec (B) to 345 msec (C) to 360 msec (D), the coupling interval at site 1 increased to 400 msec (B) to 450 msec (C) to 490 msec (D). Calibrations: vertical, 100 mv; horizontal, 500 msec.

coupling intervals in reentry resulting from reflection, as in figure 9 in which Wenckebach periods appeared at a constant drive rate. When conduction through the depressed segment required 320 msec, as in impulse A-3, the coupling interval of the reentrant impulse to the previous impulse was 425 msec. Impulse B-5 was delayed only 200 msec in the depressed segment and the coupling interval of the reentrant impulse was decreased to 285 msec.

Wenckebach periods may also occur in the reentrant pathway either in a loop of Purkinje fiber bundles or in the depressed segment of an unbranched bundle of Purkinje fibers. A progressive increase in conduction delay in the reentrant pathway would result in progressive lengthening of the coupling intervals of the extrasystoles. During the blocked beat of the Wenckebach cycle there would be no reentrant extrasystole.

Mack and Langendorf\textsuperscript{31} and Langendorf and Pick\textsuperscript{32} have reported intermittent ventricular bigeminy in which progressive lengthening of the coupling intervals was followed by dropping out of the ectopic impulse causing intermittence of the bigeminy and which therefore may be due to such a Wenckebach cycle in the reentrant pathway.

Since the time required for an impulse to conduct through a depressed segment tends to increase with increasing rate, or decreased preceding cycle length, one would expect the coupling interval of reentrant beats to vary also with the heart rate or changes in preceding cycle length. If the dominant rhythm is irregular, as the ventricular rate may be during atrial fibrillation or during sinus arrhythmia, the coupling interval of reentrant beats may vary with the length of the preceding cycle. If the length of the preceding cycle is short, block may occur in the pathway leading to reentry just as it does at high regular rates. Langendorf et al. postulated this effect to explain intermittent ventricular bigeminy in which ventricular premature beats with fixed coupling occur only after long preceding cycles.\textsuperscript{33}

Effect of Rate on the Frequency of Reentry

An increase in rate of the dominant rhythm may reduce the frequency with which reentrant extrasystoles appear. This is readily understood in terms of the effects of increasing rate on conduction in a depressed segment; 1:1 conduction with delay in a depressed segment at slow rates changes to progressively higher degrees of block as the rate increases (fig. 2). If 2:1 block appears in the pathway that leads to reentry, a bigeminal rhythm would be converted to a rhythm in which every other activation of the ventricle is followed by an extrasystole.

If the dominant rate is high enough to produce total block in the pathway that leads to reentry no reentrant extrasystoles will be seen. Impulses nevertheless may regularly enter the pathway that leads to reentry, their block within that pathway being an example of concealed conduction. Concealed conduction in the pathway that leads to reentry obviously may affect the next impulse that enters that pathway. In a heart in which each impulse of a regular sinus rhythm evokes a bigeminal response of the ventricle due to reentry, a premature sinus impulse might be blocked in the pathway that leads to reentry. The premature sinus impulse would thus evoke a single QRS complex rather than a bigeminal response, and the depression caused by block of the premature impulse in the pathway that leads to reentry might
block the next potentially reentrant impulse and this in turn might block the next. A single premature activation of the ventricle might thus cause the disappearance of one or many extrasystoles that would have appeared had the rhythm remained regular.

If an impulse blocks early in its passage through the pathway that leads to reentry the rest of that pathway is spared an excitation. The result may be more complete recovery in the pathway leading to reentry so that the next impulse entering it is conducted rapidly enough to reach the ventricle during the refractory period, i.e., reentry is converted to concealed reentry. In figure 9 concealed reentry of impulse B-2' blocks forward conduction of impulse B-3; as a result impulse B-4 is conducted more rapidly than would be expected from its position in the Wenckebach cycle and does not give rise to reentry. On the other hand, block of an impulse in the pathway that leads to reentry may delay the conduction of the next impulse through that pathway, slowing it enough to allow it to reenter the ventricle. An example of conversion of concealed reentry to frank reentry by this mechanism is shown in figure 9 in which concealed reentry of impulse A-2' delays conduction of impulse A-3 enough so that impulse A-3' becomes fully reentrant.

The special case in which the impulse is blocked just before it reaches and reenters the ventricle (fig. 11) has been called concealed reentry31, 33 but the term seems an appropriate one to describe any instance of block within the pathway that leads to reentry. We have seen block just prior to reentry both during reentry caused by circus movement and during reentry caused by reflection.25, 26 The phenomenon was postulated by Damato in an ingenious explanation of Wenckebach periods in the A-V node.24

Reentry may occur frequently at a slow heart rate, disappear at a moderate rate, become more frequent at a higher rate, and become less frequent at a still higher rate (see fig. 6 in our earlier article25). Such behavior is understandable in terms of the mechanisms described above. At a low heart rate conduction through the pathway that leads to reentry may be slow enough to permit reentry; the increase in conduction velocity often seen when rate is increased may cause the impulse to conduct so rapidly through the pathway that leads to reentry that it reaches the ventricle while it is refractory, so that no reentry occurs. Such improved conduction may result from postexcitatory hyperpolarization of depressed fibers secondary to the more frequent activation. Reentry reappears at higher rates because of the appearance of rate-dependent delay in the pathway that leads to reentry; and a further fall in the frequency of reentry results as still higher rates lead to complete block in the pathway leading to reentry. The disappearance of reentrant extrasystoles may thus result from either of two quite different mechanisms. In one, reentry vanishes because of improvement in conduction through the pathway leading to reentry; in the other, reentry vanishes because of impairment of conduction in the pathway leading to reentry.

The dependence of the frequency of extrasystoles on rate is of particular significance in myocardial infarction with sinus bradycardia or in advanced degrees of atrioventricular block in which the occurrence of frequent extrasystoles has often been described.25 Such ventricular arrhythmias have successfully been prevented by increasing the ventricular rate either by catecholamines or by

**Figure 11**

Concealed reentry in a depressed loop of canine Purkinje fiber bundles. (A) Recordings of action potentials from sites 1, 2, and 3 in the reentrant pathway, shown diagrammatically in B. The branches of the loop are indicated by a, b, and c. An impulse initiated near recording site 1 may propagate down the main bundle near site 2 and block before traveling around the loop. This occurs for the left group of action potentials in A. The impulse may also enter the loop in branch a (but not branch c due to unidirectional block) and travel around the loop to reexcite site 2, but block before returning to site 1. This is indicated by the right group of impulses in A and constitutes reentry which may be concealed on the electrocardiogram since it would not reexcite the ventricles. Calibrations: vertical, 50 mv; horizontal, 500 msec.

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electrical pacemakers. Either of the two mechanisms described above may operate in the disappearance of the extrasystoles.

**Summation, Inhibition, and Parasystole**

Our recent studies have revealed two important electrophysiologic properties of depressed Purkinje fibers, namely summation and inhibition.\(^8\)\(^9\) If a segment of a bundle of Purkinje fibers is so depressed that bidirectional conduction block occurs, excitation of either normal end of the bundle will give rise to an action potential which will propagate to the depressed area and die out in that region (fig. 12). However, excitation of both ends of the bundle will result in summation of the subthreshold responses in the depressed center segment, giving rise to an action potential in that region. If a branch arises in the center of the depressed segment, activity evoked by summation can travel out the branch (fig. 12). This phenomenon of summation in depressed regions of the ventricular conducting system may result in reentrant extrasystoles as previously discussed.\(^8\)

Interaction between impulses traveling toward a junction of depressed fibers can also result in inhibition.\(^8\) In this situation the action potential from one end of the Purkinje bundle is able to excite the depressed region while the action potential from the other end is not. However, an impulse traveling down the ineffective end of the bundle may die out in the depressed area, altering its excitability and thereby preventing or inhibiting the excitation that would otherwise occur when the effective end of the bundle is excited (fig. 13).

The term parasystole is usually used to describe the occurrence of premature beats which occur at varying coupling intervals after a preceding beat. Such premature systoles may occur early in the basic cycle but they often appear late enough to cause fusion beats. In addition, the intervals between successive parasystolic impulses are either

![Figure 12](image1)

**Figure 12**

Summation in a depressed segment resulting in propagation of activity out a branch arising in that segment. (A) The location of the depressed area (shaded), the branch from the depressed area, the stimulating electrodes (S\(_1\) and S\(_2\)), and the recording electrodes (1, 2, and 3). (B) The left-hand panel shows that excitation of the right end of the bundle (S\(_2\)) evokes an action potential at site 3 which dies out in the depressed area; no response is seen at site 2 in the branch or at recording site 1. The middle panel shows that excitation of the left end of the bundle (S\(_1\)) evokes an action potential at site 1 but no activity at sites 2 and 3. In the right panel, when both ends of the bundle are excited simultaneously (sites 1 and 3) summation occurs in the depressed segment and the summated action potential travels out the branch as indicated by the action potential at site 2. (C) Diagrammatic representation of these events. Calibrations: vertical, 100 mv; horizontal, 1 sec. (B reproduced from Circ Res,\(^8\) by permission.)

![Figure 13](image2)

**Figure 13**

Inhibition in a depressed segment. The records were obtained from a preparation resembling that shown in figure 12A; the arrangement of stimulating and recording electrodes was also similar to that shown in figure 12A. (A) Excitation of the left end of the bundle results in excitation at site 1 and propagation into the depressed segment and out the branch (site 2); conduction to the other end of the main bundle does not occur as indicated by the absence of activity at 3; this is shown diagrammatically below A. (B) An impulse arising at the right-hand end of the bundle results in an action potential at site 3 but travels neither through the bundle nor out the branch and does not excite sites 1 and 2. This is shown in the diagram below B. (C) When the right end of the bundle (site 3) is excited before the left end (site 1) the impulse that arises in the right end and dies out in the depressed segment blocks propagation from the left end of the bundle into the branch. There is no depolarization at site 2. This is shown in the diagram below C. Calibrations: vertical, 100 mv; horizontal, 500 msec.
equal or are multiples of a common denominator.  
Premature systoles with fixed coupling may also 
result from parasystole.  

Parasystole is assumed to result from an automatic focus (parasystolic focus) within the atrium or ventricle that is protected from the basic rhythm of the heart by entrance block that prevents the sinus impulse from entering the parasystolic focus and depolarizing its fibers. Exit block supposedly confines parasystolic impulses to the parasystolic focus. The existence of a focus guarded by both entrance and exit block can become known only if intermittent relief of exit block allows the focus to excite either the atrium or the ventricle. Parasystole is frequently encountered in chronically diseased hearts or in association with myocardial infarction. 
The focus itself, or the necessary conditions of entrance and exit block may therefore be inferred to result from severe depression of cardiac tissue. The appearance of slow conduction, unidirectional block, summation, and inhibition in depressed Purkinje fibers suggests possible mechanisms for the occurrence of certain types of parasystole, including those with fixed coupling.

In the depressed ventricular conducting system, the degree of depression may vary markedly between regions separated by only a few millimeters. A small area may show a resting potential of –70 to –80 mv and display spontaneous activity, while an adjacent area, only slightly more depolarized, may be inexcitable and cause both entrance and exit block between the spontaneously active focus and the rest of the heart. Conduction from the parasystolic focus to the rest of the heart is blocked in the inexcitable region (exit block); conduction of the sinus impulse into the area of the parasystolic focus is also blocked in this region (entrance block). If a sinus impulse penetrated into this depressed area of block at a time when it could summate with the impulse arising from the parasystolic focus, the impulse arising by summation might propagate out a branch and excite the heart (fig. 14; compare with fig. 12). For this to happen, the action potentials of the dominant sinus beat and the parasystolic focus would both have to invade the depressed area during the interval in which summation could occur. If that interval were very short, the summated impulse would arise at a time quite closely determined by the time of the dominant impulse, and the extrasystoles that arose would show fixed coupling to the dominant beat. If the interval in which summation occurs were fairly long, then impulses could arise by summation near the beginning or the end of that interval and their delay with respect to the time of the dominant impulse would be variable so that fixed coupling would not be observed.

Inhibition might also influence the occurrence of premature impulses caused by a parasystolic mechanism. Impulses originating in the sinus node could inhibit conduction from the automatic parasystolic focus by the mechanism shown in figure 13, and thereby prevent emergence of the parasystolic impulse into the ventricles. Inhibition of this type would only occur if both the sinus node and parasystolic focus fired within a certain interval. If the parasystolic focus fired at a time when neither refractoriness of the ventricle nor exit block caused by inhibition were present, then an impulse could emerge from the parasystolic focus and excite the ventricle.
Finally, foci of spontaneous activity that are unable to excite the ventricle because of exit block may be able to do so if the exit block is relieved for reasons that have nothing to do with the previous impulse. Fluctuations of excitability at the site of exit block may, for example, occur in parallel with fluctuations in the level of sympathetic activity.

**Cause of One-Way Block**

One-way block is fairly readily induced in the heart.\(^{24}\) Conduction in one direction through a wholly normal bundle of cardiac fibers often takes slightly longer than conduction in the other direction. In bundles of cardiac fibers the branching and interconnection and the frequency of appearance of tight junctions are not uniform along the length of the fiber; that alone could explain some asymmetry of conduction. Any such preexisting asymmetry might well be greatly exaggerated by depression. More importantly, an asymmetry of depression can create an asymmetry of excitability. If one end of a bundle is less well perfused, for example, conduction velocity will depend on the direction of conduction. If a point where two fibers of a bundle join is severely depressed, conduction in each of the fibers toward the point of junction may result in transmission of the impulse by summation at the point of junction. During conduction in the other direction, the point of convergence becomes a point where one fiber divides into two fibers and at that point block will occur. Asymmetries of conduction up to and including one-way conduction may thus result either from asymmetries of depression of excitability or from asymmetries of an anatomic kind and usually result from both being present.

**Cause of Very Slow Conduction**

It is easier to explain total conduction block than it is to explain depression of conduction severe enough to reduce conduction velocity to 1% of its normal value without producing block. When cardiac Purkinje fibers are depolarized to a membrane potential of about -50 mv the system responsible for the normal rapid upstroke is suppressed, so that the membrane loses its ability to develop an increase in sodium permeability and a normal rapid depolarization.\(^{29}\) What remains is the ability of the membrane to undergo an active depolarization which conducts very slowly and which may depend on Ca\(^{++}\) rather than Na\(^{+}\) to carry membrane current; we have called this the slow response.\(^{21}\) These responses are enhanced by the addition of catecholamines.\(^{40}\) It is thus possible that the reentrant arrhythmias that arise in an area of depressed excitability do so because such areas of depressed excitability respond with an action potential that is different in kind from the action potential of normal cardiac fibers.

The ventricular arrhythmias commonly associated with coronary artery disease might well result from partial depolarization and depression of excitability in focal or extensive areas of the ventricular conducting system secondary to hypoxia and poor perfusion. The most dramatic instance of such poor perfusion is that seen in acute myocardial infarction. Ischemia caused by a sudden coronary occlusion results in the leak of large amounts of K\(^{+}\) from the intracellular to the extracellular space\(^{41}\) and depolarizes cardiac muscle. Ischemia also causes an increased release of catecholamines\(^{42}\) which could produce the enhancement of the slow response that is seen when catecholamines are added to depressed Purkinje fibers in vitro.

Recent observations offer direct support to a role for the slow response in chronic arrhythmias and in the arrhythmias of myocardial infarction. Action potentials of Purkinje fibers taken from the hearts of very old dogs subject to extrasystoles are normal in some areas and have the characteristics of a slow response in other areas (fig. 15 A-C). Similar slow potentials have been found in areas of myocardial infarction produced by ligation of the anterior descending coronary artery in dogs\(^{43, 44}\) (fig. 15 D, E).

Whether the response of depressed fibers is or is not fundamentally different from that of normal fibers, there is no doubt that partial depolarization can cause slow conduction. The arrhythmias seen in disorders that result in chronic hypoxia of cardiac muscle, such as valvular insufficiency or cardiac failure, might result from such depression of excitability. Phase 4 depolarization that fails to reach threshold can profoundly depress excitability and conduction.\(^{10}\) It is also known that some preparations of atrial and ventricular muscle removed from diseased human hearts and studied in vitro can show low maximum diastolic potentials, slow depolarization, and a low conduction velocity.\(^{45}\) Ventricular muscle removed from cats in experimentally induced right heart failure also shows low resting potentials and low rates of depolarization.\(^{46}\)
Depressed action potentials in pathologic hearts. (A) Lead II electrocardiogram from a 15-year-old dog with spontaneous ventricular arrhythmias. (B and C) Action potentials recorded from a bundle of Purkinje fibers removed from the heart of this dog. The lower trace shows normal-appearing action potentials. Action potentials in the upper trace have characteristics of the slow response. Note that an increase in stimulus rate in C results in conduction block in the depressed region. (D and E) Action potentials recorded from subendocardial Purkinje fibers on the anterior papillary muscle of the canine heart, 24 hours after coronary ligation. Action potential in the upper trace recorded from fiber surviving the extensive myocardial infarction. Action potential in the lower trace was recorded from the normal margin of the infarcted area. Again, in E, conduction block in the infarct readily occurs when the rate of stimulation is increased. (Friedman PL, Wit AL: Unpublished observations.)

Oscillatory Depolarizations

There is a large body of evidence to show that the transmembrane potential of cardiac fibers can undergo oscillatory changes. Such changes centered around the baseline of the maximum diastolic potential may wax to the point at which they can generate a tachycardia; yet they appear to differ fundamentally from the phase 4 depolarizations characteristic of the sinoatrial node. Oscillatory changes also arise in partially depolarized fibers. Many oscillatory potentials are "afterpotentials," i.e., they follow or are provoked by a preceding impulse. Oscillatory afterpotentials may arise either during or after repolarization of the previous action potential. Oscillatory afterpotentials provoked by the preceding impulse might cause bigeminal arrhythmias.

Concluding Remarks

Depression of a short segment of cardiac fibers can produce a bewildering variety of arrhythmias. These arrhythmias depend on the occurrence in the depressed area of slow conduction, one-way block, summation, and inhibition which in turn may depend on not yet fully explored properties of the slow response. The sensitivity of many arrhythmias to changes in heart rate or in prematurity of excitation is understandable in terms of the sensitivity to such changes of conduction through a depressed area. The variety of arrhythmias that arises from focal depression is greatly increased by the fact that the same sort of behavior in a depressed area will produce quite different arrhythmias according to where that depressed area is located.

The fact that reentry can account for so many properties of premature systoles by no means proves that all such systoles arise from reentry. Parasystole, phase 4 depolarization, and oscillatory changes in membrane potential are fully capable of causing arrhythmias. Recent studies have, however, provided direct proof for the existence of reentry as a cause for arrhythmias, so that reentry based on slow conduction and one-way block may now be regarded as an established fact rather than as an attractive hypothesis.

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