THE RELATIONSHIP among cardiac pacemakers is characterized by the fact that usually one pacemaker is dominant and all the others are subsidiary. The sinoatrial node acts as the dominant pacemaker and all other pacemaker tissues are discharged by a conducted impulse before their diastolic depolarization can attain threshold. These pacemakers are called subsidiary to emphasize the fact that under normal circumstances they are engaged in conducting impulses but under abnormal circumstances they may become actual pacemakers. Subsidiary in this sense means that one or the other of these pacemaker tissues assumes the function of impulse formation when the dominant pacemaker fails to initiate the activation of the heart. On the basis of these recognized facts, a dominant pacemaker can be defined as the pacemaker tissue which first succeeds in attaining threshold and in initiating a propagated impulse. The other pacemakers are subsidiary because their diastolic depolarization fails to attain the threshold before a propagated impulse initiates local excitation.

Although these concepts are undisputed, certain observations seem to be at variance with the idea that the relationship among pacemakers involves only a successful race to the threshold. This is clearly shown by the fact that a sudden suppression of a dominant pacemaker is followed by a period of quiescence before a subsidiary pacemaker begins to discharge rhythmically. The period of quiescence is far longer than the interval between two beats of the newly established subsidiary rhythm. This suggests that subsidiary pacemakers are somehow kept suppressed. This form of inhibition will be referred to as overdrive suppression.

The Effect of a Sudden Cessation of the Activity of a Dominant Pacemaker

Stannius placed a ligature between the sinus venosus and the auricle of a frog heart and reported a resultant standstill of the auricle and the ventricle. In his words, "Wird genau diejenige Stelle unterbunden, wo der Hohlvenensinus in den rechten Vorhof mündet, so steht das ganze Herz im Zustande der Diastole anhaltend stille" (p. 87). This finding was of great interest for it was the first indication of the relationship between dominant and subsidiary pacemakers. Of course, this was not realized at the time the observation was made, for the emphasis was placed on inhibitory and motor nerves to the heart and Stannius reasonably concluded that it was difficult to offer a meaningful explanation at that time. Some 30 years later, Gaskell approached the problem in the tortoise heart at a time when evidence was accumulating for a myogenic rather than neurogenic theory of cardiac impulse formation. He came to a series of important conclusions which bear on the present topic of the interrelationship of pacemakers. First of all, he showed that automaticity decreases regularly from the sinus node to the ventricles. This is the immediate basis for the sinus node dominance. Second, he emphasized that "the development of the automatic rhythm to its fullest extent is a gradual one, commencing with beats at a slower rate than that subsequently attained, and the preliminary standstill which so often occurs is simply a sign of this gradual development" (p. 60). Third, the stimulation of the vagus suppresses the sinus node and brings "to light the hidden independent ventricular rhythm which it is unable to inhibit" (p. 87). Fourth, he reports that "direct stimulation of that part of the heart from which the rhythmical contractions arise, viz., the sinus venous, is a most certain method of obtaining standstill of the heart..." and "... atropin prevents that standstill from taking place..." (p. 110). In fact, commenting about these experiments, Gaskell adds: "... in all rhythmically contracting portions of the heart any direct stimulation, which is strong enough to cause a series of contractions following each other with greater rapidity than the previous rate of rhythm, is very apt to be followed by a pause..." (p. 111). He adds, however, that "such a pause does not necessarily prove that the rhythm has been inhibited by the stimulation and I therefore prefer for the present to leave it doubtful whether the direct stimulation of a rhythmically contracting tissue can in all cases inhibit the rhythm of that tissue" (p. 111).

Of course, it must be realized that the conclusions re-
ported above were selected with a degree of hindsight. Other results and conclusions are rather puzzling. For example, the standstill was felt to be associated with the development of the automatic rhythm and “not due to the action of any special inhibitory mechanism” (p. 118). Furthermore, the ventricular standstill no longer was present when the heart was provided with blood through the coronary vessels or when atropine was given or when the atrium was cut halfway between sinus and ventricles. It is not surprising then that Gaskell concludes that “the meaning of this preliminary standstill—the standstill of the first Stannius ligature—has always been a difficult problem to solve, and many attempts at an explanation have been given” (p. 118).

Several years later Erlanger proceeded to analyze the problems involved in atrioventricular (AV) block in the mammalian heart. Varying degrees of block were produced by applying graded compression of the His bundle by means of a clamp. On tightening the clamp, on occasion, there was an abrupt cessation of ventricular activity, as expected. As in the experiments of Gaskell, the ventricular standstill was temporary and an idioventricular rhythm developed that accelerated slowly toward a steady rate. Also, Erlanger confirmed that the vagus no longer had control over the ventricles when the AV block is complete. He considered the possibility that if the “marked slowing of the ventricular rate is the result of the sudden withdrawal of the stimuli of auricular origin [at the moment complete AV block is established], then it might be possible to ascribe stoppage of the ventricles when the vagi are stimulated to an absence of stimulation” (p. 30). When the complete block followed a partial block, there was no ventricular stoppage, but Erlanger commented that “it is possible that when the block is slowly established, time is allowed for something to occur which permits the ventricles to assume their maximum inherent rate at once” (p. 30). This possibility was demonstrated several years later. However, uncertainty was produced by the fact that in other experiments there was no ventricular stoppage even if the onset of complete AV block was abrupt. Although the results were not consistent, these experiments of Erlanger clearly proposed the question whether the ventricular stoppage at the beginning of vagal stimulation was in actuality related to the cessation of atrial impulses. This question of ventricular stoppage (or slowing) which occurs on induction of AV block was pursued further by Erlanger and Hirschfelder. They considered whether “the ventricles cease to beat for a time when they are no longer whipped into action by their physiological stimulus” (p. 159) because it takes some time for the inherent automaticity of the ventricle to become established or because the clamp stimulates a region which in turn inhibits the ventricles alone. As reported previously, ventricular standstill was longest when the onset of complete AV block was not preceded by a period of partial block. With sudden block, more time would be required by the ventricles to “develop their maximum inherent rhythm” (p. 161). Increasing the atrial rate could lead to ventricular arrest if the AV node did not follow. In the presence of complete AV block, the ventricles were driven at a rate similar to that of the atria: on cessation of drive, the ventricles slowed or stopped for a time. The stoppage depended on the rate and duration of the preceding period of stimulation. The situation was complicated here by the fact that in a number of instances the cessation of the drive was not followed by stoppage but by ventricular cycles which increased in length over a few beats. The ventricles also were stimulated with constant current: during the flow of the current the ventricles beat, but when the current was interrupted they stopped temporarily. Applying tetanic stimulation to the clamp did not result in stoppage of the ventricles. And the stoppage on complete AV block was not abolished by atropine. They conclude that “stoppage of the ventricles is not the result of inhibition” (p. 165). When the vagus was stimulated, the duration of the ventricular standstill decreased when the degree of AV block was more pronounced. This might have been due to the suppression of atria (so that the ventricles stop until their inherent rhythm develops) or to a direct action of the vagus. Although “... no method of deciding this question beyond doubt” (p. 176) was available, Erlanger and Hirschfelder favored the indirect action on the basis that (1) there was no satisfactory evidence that the vagus slows the ventricles of cold-blooded animals, (2) no nerve trunks could be found in or near the auriculoventricular bundle, and (3) the effect of vagus was related to the degree of block. The last argument was somewhat weakened by the difficulty of obtaining exact data bearing on this relation. The general conclusion was that the stoppage of the ventricles produced in different ways was due to the sudden cessation of the activation of the ventricles by sinus impulses. This allowed “a gradual development of the inherent but dormant rhythm of the ventricles” (p. 180). Thus, the authors held the view that neither the ventricular arrest on sudden AV block nor that on vagal stimulation was inhibitory in nature but instead was caused by the necessity of a ventricular rhythm to develop. It is of interest that Erlanger and Hirschfelder in a footnote (p. 166) report the statement of Hering to the effect that the ventricular standstill which follows the excision of the atria is not due to an inhibitory process but to the sudden cessation of atrial activation (“... scheint der nach dem letzten Schnitt erfolgende vorübergehende Stillstand der Kammern nicht die Folge einer Hemmung, sondern die Folge des plötzlichen Ausfalles der Anregung zu sein”).

A few years later, Cushny, noting that “the development of spontaneous rhythm in a normally passive part of the heart still remains quite obscure” (p. 257), approached the problem of the effect of drive of the mammalian ventricles in the presence of complete AV block. Cushny confirmed that drive of the ventricles was followed by a temporary suppression of ventricular automaticity and the suppression was similar to that obtained on section of the auriculoventricular bundle as Erlanger and Hirschfelder had pointed out. The pauses following drive became longer in the later stages of the experiments, with lower temperatures and in the absence of oxygen. Cushny also confirmed that the rate and duration of the drive influenced the duration of the pause. Whether the electrical impulses were weak or strong did not make any difference. Weak impulses were without effect only if they failed to excite the ventricles and strong impulses were
ineffective only if delivered at the same rate as the normal idioventricular rhythm. These findings and the inability of atropine to block the pause (while blocking the vagus) were taken to indicate that the pause did not result from that inhibitory mechanism. Cushny found that during the pause excitability was normal and contractility above normal. Therefore there was no "exhaustion" of either excitability or contractility to account for the pause. After noting that Gaskell believed that "the pacemaker dominates the heart simply by anticipating the spontaneous development of rhythm in the other parts," Cushny goes on to state: "My results reveal another factor in the process, for they indicate that the pacemaker not only anticipates the ventricular spontaneous beat but actively depresses the ventricular rhythmicity." (p. 269). The ventricle, on section of the His bundle, does not merely develop an "uncustomed function" but recovers from "the state of depression to which it has been reduced by a lifelong series of impulses from above" (p. 269). Such a depression was attributed to fatigue of the ventricular rhythmicity possibly due to an accumulation of waste products arising from the more frequent contractions. This fatigue of all pacemakers except the sinus "is of advantage in preventing spontaneous heterotopic contractions and preserving the regular sequence of the cardiac movements" (p. 270). It also was noted that during some stimulations the ventricles fibrillated and "recovery from this was followed by a very long pause ..." (p. 275). Finally, Cushny reported that "members of the digitalis series" lessened the fatigue from drive since the pause became shorter or disappeared completely.

The clinical applicability of some of these notions and the ability of a spontaneous fast rhythm to inhibit an idioventricular pacemaker were illustrated by a report of Cohn and Lewis in a man with complete AV block: runs of spontaneous tachycardia were followed by periods of ventricular asystole. Cohn and Lewis, in agreement with Erlanger and Hirschfelder, proposed that "the new rhythm takes precedence to the old, and the latter passes into a condition of temporary abeyance" (p. 18).

It is curious that while some of the observations were clear enough, on the whole the relationship among cardiac pacemakers remained far from clarified. There are several reasons for that. Often, an important statement was formulated only as a minor consideration for which no systematic experimentation was carried out (and other minor considerations were not necessarily correct). In other instances, the findings were reported in the context of other problems on which attention was focused. Perhaps more importantly, experimental results often were variable and therefore they might have been confusing. Such variability and contradictions must have hindered the clarification of the problem.

For these and other reasons, the concept that the sinus node suppresses the subsidiary pacemakers by virtue of its faster rate never became a general notion. The lack of an understandable mechanism to account for such action probably contributed to the lapping of this question into the background. Yet, from time to time, reports appeared showing the phenomenon of overdrive suppression in man and in animals. In 1955 Rosenblueth studied the automaticity of the AV node in the dog. Although the rhythm of the AV node (AV junctional rhythm) was in general irregular and unstable, the application of driving stimuli to the atria or ventricles in some experiments resulted in the temporary suppression of such AV junctional rhythm. This suppression was attributed to an inhibitory effect of the impulses going through the AV junctional region. This information added the AV junctional region to the ventricular pacemakers as being subject to overdrive suppression.

The problem received increasing attention in the 1960's possibly as attention was stimulated by the introduction of implanted pacemakers for the treatment of complete AV block.

Linenthal et al. reported that electrical drive and spontaneous tachycardias in dogs with AV block and in patients with Stokes-Adams disease were followed by temporary suppression of the idioventricular pacemakers. They confirmed the dependence of the pause on the rate and duration of the fast rhythm preceding it. Furthermore, the pause was shortened by catecholamines and this shortening was abolished by a β-blocker. The papers of Chardack et al. and of Cammilli et al. were primarily concerned with the problems connected with implanted pacemakers for ventricular drive. Both papers show pictures of progressively longer pauses as the rate of drive was increased. Because of this effect, Chardack et al. advised the use of subnormal rate to avoid long pauses in case of sudden failure of the implanted pacemaker. Cammilli et al. emphasized that when the rate of the imposed drive was close to that of the idioventricular pacemaker no pause followed. Edelist et al. studied three patients with AV block and found that atrial drive depressed sinus node impulse formation just as ventricular drive depressed idioventricular rate. González-Serratos and Alanís, in the course of an investigation on the effect of nerve stimulation on cardiac automaticity, found that overdrive was followed by a decrease of automatic discharge in both ventricles and isolated Purkinje fibers (extracellular recording). The effect of electrical drive on ventricular automaticity in unanesthetized dogs with complete AV block was reported in abstract form by Killip et al. in 1966. They found the usual suppression which was dependent on rate and duration of drive. Maximal suppression was found after 30-60 seconds of drive. Paired stimuli causing contractions at only 90/min resulted in suppression similar to that of regular stimuli at 180/min. Also, the suppression was longer the slower the control idioventricular rate. The pause was lengthened by propranolol and shortened by atropine and isoproterenol. It was concluded that repetitive stimulation depresses ventricular automaticity and this depression gradually disappears after drive.

The Mechanism of Overdrive Suppression of Atrial Pacemakers

The experimental evidence so far reported makes it clear that cardiac pacemakers are suppressed temporarily when driven at a fast rate by a faster pacemaker or by applied stimuli. As to the nature of such suppression, little was known and the available information was not exempt from contradictions. For example, Gaskell had reported...
that atrial drive resulted in subsequent suppression and this suppression was abolished by atropine. This clearly pointed to a role for vagal fibers in the suppression. Yet, overdrive inhibits the ventricular as well as the atrial pacemakers and the control by the vagus of idioventricular pacemakers was far less conclusive.3,6 One possibility was that there were different forms of inhibition. The clarification of this problem began with the experiments of West and collaborators15-17 on the release of neuromediators by electrical stimuli applied to cardiac tissues, notably the sinus node. A short stimulation at high frequency (10-100 impulses/sec) applied directly to the sinus node led to hyperpolarization, temporary suppression of pacemaker activity, and a late increase in the rate above the control value. Atropine abolished and physostigmine potentiated the hyperpolarization and the suppression.15 Thus, it was shown that electrical stimuli suppressed the sinus node because they liberated endogenous acetylcholine and the ensuing hyperpolarization accounted for the temporary suppression of pacemaker activity.15 Amory and West16 studied the electrical release of neuromediators by employing several pharmacological agents. Experiments with atropine, physostigmine, and hemicholinium confirmed the role of released acetylcholine in the hyperpolarization and suppression. Experiments with dichloroisoproterenol, reserpine, pyrogallol, cocaine, guanethidine, bretylium, and nicotine proved that late acceleration resulted from release of norepinephrine from sympathetic fibers in the sinus node. The importance of the release of neuromediators (rather than the excitation of the sinus cells) for the negative and positive chronotropic effects of electrical stimulation was demonstrated by Vincenzi and West.15 Thus, on the one hand, intracellular stimulation (100 impulses/sec) did not elicit chronotropic effects and, on the other, stimuli which were subthreshold for the sinus cells (but not for the nerve fibers) still caused sinus suppression followed by acceleration. Similar results were obtained with subthreshold stimulation of the AV nodal area. When tested, some of the drugs listed above affected the chronotropic responses to subthreshold stimulation in the same way as those to suprathreshold stimulation. As Vincenzi and West point out, the intensity of stimuli needed to excite cardiac cells is large enough to release neuromediators from nerve fibers.

Shortly thereafter, Lange18 directed her attention to the effect of electrical stimulation at frequencies that the cardiac cells could follow in the canine heart in situ. She showed that the effect of drive varied depending on the rate imposed. If the drive was at a rate only slightly above that of the sinus node, the sinus accelerated; if the drive was at a rate identical to or slightly below that of the sinus node, arrhythmias appeared. Drive at a rate greater than 20% above that of the sinus node was followed by a temporary sinus suppression. Bouts of atrial flutter and fibrillation also were followed by suppression. Both the suppression and the subsequent acceleration depended on the rate and duration of drive. The suppression was greatest when the driving electrode was placed on the sinus node. With the sinus node crushed, overdrive suppression of other atrial pacemakers was more pronounced. Vagotomy did not influence overdrive suppression and acceleration, but sympathetic enhancement of the suppression. If, during the last part of the drive, the vagus or the sympathetic nerves were stimulated, the suppression was lengthened or shortened, respectively. Overdrive suppression was reduced by norepinephrine, cocaine, and atropine and increased by neostigmine. The subsequent acceleration was increased by cocaine and reduced by reserpine and guanethidine. These results showed that atrial pacemakers are suppressed by drives that the cardiac cells can follow and that the sinus node was the least sensitive of cardiac pacemakers to overdrive suppression. The mechanism of the chronotropic changes was a liberation of neuromediators by the electrical stimuli and, presumably, by propagated action potentials. The residual overdrive suppression after atropine was ascribed to a possible potassium accumulation.

In a companion paper on the effect of drive on the cat sinus node perfused in vitro, Lu et al.19 found that dominant pacemakers did not follow a fast drive as well as the subsidiary pacemakers within the sinus node. During the drive the cells hyperpolarized to a steady value within 3-5 seconds and returned to the original potential within a few beats after the termination of the drive. Although suppression and acceleration were proportional to the rate and duration of the drive, longer drives (>5 minutes) were followed by shorter suppression or actual acceleration. Prostigmin increased both hyperpolarization and suppression and atropine reduced but did not abolish the suppression. Increasing [K+]o decreased the suppression. Lu et al. concluded that subsidiary pacemakers within the sinus are more readily suppressed than the dominant pacemakers. The resumption of activity after drive may involve a shift in pacemakers. The mechanism of suppression certainly involves acetylcholine release but the residual suppression after atropine may be due to ionic shifts such as a loss of potassium. In some cells, overdrive suppression was in part due to conduction block. These experiments establish that overdrive suppression of atrial pacemakers involves the release of acetylcholine, although a residual factor, possibly K accumulation outside the cell membrane, may play a role. The suppression of the sinus node by drive applied to distant parts of the heart (such as the ventricles) suggested to Lu et al.19 the interesting concept that propagated action potentials themselves can liberate neuromediators.

It should be pointed out that recent work of Urthaler and James and their colleagues20-21 recognizes only two major centers of automaticity in the heart: the sinus node and the AV junctional region. The AV junctional region in turn can produce two different rhythms: one rhythm appears when the sinus node is suppressed selectively (AVJ-1) and the other when the AV junction is maximally depressed by acetylcholine (AVJ-2). In the steady state, there is a fixed mathematical relationship between the sinus rhythm, the escape AV junctional rhythm (AVJ-1) and the slow rhythm (AVJ-2). Whether or not other pacemaker areas are present in the atria and in the ventricles under different experimental conditions matters little in the present context, since Urthaler et al.21 have shown that both AVJ-1 and AVJ-2 are subject to overdrive suppression. In the present context, therefore, the term...
“atrial pacemakers” is meant to indicate all possible pacemaker tissues in the atria which can generate impulses, and the term “idioventricular pacemakers” is meant to indicate all possible pacemaker tissues in the ventricles which can generate impulses. A knowledge of the precise location of these pacemakers under normal conditions is not strictly required for the present discussion and will have to await an experimental reevaluation of this problem.

The Mechanism of Overdrive Suppression of Idioventricular Pacemakers

In the atria, the suppression of pacemakers by drive is similar to that caused by vagal stimulation in that both procedures lead to liberation of acetylcholine. The question therefore should be considered whether a similar mechanism applies to the suppression of idioventricular pacemakers, for, after all, a ventricular standstill follows both a fast drive and the initiation of vagal stimulation. There are several other reasons that require an examination of the role of vagal fibers in overdrive suppression of idioventricular pacemakers. Thus, overdrive suppression of the ventricles was reported to be shorter after atropine administration, and acetylcholine has been shown (at least under certain circumstances) to have an inhibitory action on idioventricular pacemakers. Furthermore, histological reports indicate that the conducting system of the ventricle is innervated by cholinergic fibers. Of course, there are other findings that militate against such interpretations. It is a common experience that atropine has little effect on idioventricular rate in acquired complete AV block. Further, stimulation of the vagus in animals with complete AV block has very little inhibitory effect. Therefore, the opposite possibility should be considered: rather than overdrive suppression being an instance of vagal inhibition, vagally induced ventricular standstill could be but one instance of overdrive suppression.

THE ROLE OF THE VAGUS

The ventricular standstill on stimulation of the vagus or after the cessation of ventricular overdrive could be due to the excitation of vagal fibers by the electrical stimuli applied to the vagal trunk or directly to the ventricles to drive them. Alternatively, the vagus could inhibit only the atrial pacemakers and merely reveal the suppression of the idioventricular pacemakers by the sinus. In many species, the sinus node discharges the ventricles at a rate which is about double that of spontaneous firing idioventricular pacemakers. Therefore, the sinus node overdrives the idioventricular pacemakers and merely reveals the suppression of the ventricles. A knowledge of the precise location of the pacemakers under normal conditions is not strictly required for the present discussion and will have to await an experimental reevaluation of this problem.

The resumption of the idioventricular rhythm during vagal stimulation does not depend on the distention of the ventricles during the arrest or on the reflex release of catecholamine due to the fall in blood pressure. This was demonstrated by experiments with animals placed on total cardiopulmonary bypass: the “escape” occurred whether or not ventricular distention and the fall in blood pressure were prevented. These two variables may influence the resumption of idioventricular activity, but are not essen-
The experiments with drive during vagal stimulation (see above) show that resumption of idioventricular activity is not due to an exhaustion of acetylcholine stores in the ventricles or to a release of catecholamine by the vagus.28

THE ROLE OF POTASSIUM

The mechanism of overdrive suppression is a decrease in the slope of diastolic depolarization. This is true for the pacemakers located in the atria19 and for Purkinje fibers.26,29,31 Furthermore, the threshold potential appears to be shifted to less negative values.31 In Purkinje fibers, the diastolic depolarization after the last driven action potential initially is little affected and, in fact, it may be somewhat accelerated. Once this initial depolarization is completed, however, the subsequent depolarizations proceed at a remarkably slow rate. In atrial pacemakers, the flattening of diastolic depolarization is mostly due to a release of acetylcholine (see above). In ventricular Purkinje fibers, the question of the events responsible for the time course of diastolic depolarization after drive has been given different answers.

Alanis and Benitez29 increased and decreased the external sodium and potassium concentrations. Overdrive suppression in Purkinje fibers became longer when [K+]o was increased or [Na+]o was decreased. Overdrive suppression became shorter when [K+]o was decreased. In spontaneously firing Purkinje fibers, the rate decrease when [K+]o was increased or [Na+]o was decreased, as expected. Alanis and Benitez concluded that the suppression might be due to an increased efflux of K ions and a consequent increase in potassium conductance coupled with a diminution of the electrochemical gradient for sodium resulting from an intracellular accumulation of this ion. A role of chloride was considered but was rejected on the basis that the same results were obtained when changing K+ or Na+ whether chloride was increased or decreased. In the light of reported findings,24 the longer suppression with high K+ or low Na+ would not be unexpected since the spontaneous rate of discharge prior to drive becomes slower in high K+ or low Na+ and therefore the drive rate (even if unaltered) becomes relatively higher. Vassalle et al.26 also proposed that an accumulation of potassium outside the cell membrane and the consequent increase in potassium conductance might contribute to the inhibition. However, in view of the fact that K+ loss with overdrive is transitory, they considered the possibility that during prolonged drive a new steady state is attained which is characterized by a decrease in [K+]i, and an increase in [Na+]i, whereby the inward driving force for Na+ is decreased more than the outward driving force for K+. As the concentration in coronary sinus potassium fell during vagal stimulation, it was postulated that during the standstill there was a net K+ uptake due to an increased passive and active K+ influx. A decrease in [K+]o due to an increased K+ influx would contribute to the resumption of idioventricular automaticity. That the fall in coronary sinus K+ was rate-dependent was demonstrated by the fact that the fall was abolished by driving the ventricles during vagal stimulation. In the presence of AV block,27 it was shown that ventricular overdrive led to an increase in coronary sinus potassium and this was correlated with the duration of the subsequent pause. Again, it was possible to show that the change in coronary sinus potassium concentration was a rate-dependent phenomenon and not due to vagal stimulation, because stimulation of the vagus in the presence of complete AV block changed neither the idioventricular rate (except for a few beats) nor the concentration of coronary sinus potassium.27 Since Purkinje fiber automaticity is particularly sensitive to small increases in [K+]o,25 it is conceivable that an increase in [K+]o contributes to the inhibition, at least for short drives. This proposal is in agreement with the finding that during drive the maximal diastolic potential initially decreases.31 A role for potassium in overdrive suppression is also suggested by the following finding. The coronary sinus perfusate of isolated hearts was collected prior to, during, and after ventricular drive. Purkinje fibers were then isolated from the same heart and perfused in vitro: when the fibers were exposed to the perfusate collected previously, their spontaneous rate decreased only when the potassium concentration of the coronary sinus effluent was higher. Adding atropine to the perfusate samples did not change the results. The same decrease was obtained by increasing the K+ of Tyrode’s solution to levels similar to those of the coronary sinus effluent.23

If the increase in extracellular potassium concentration plays a role, it is clear that it is not the only factor. This conclusion is based on the fact that K+ loss is transient and coronary sinus potassium returns to control values when overdrive is prolonged. Yet, the duration of the pause continues to increase. Furthermore, it is possible to dissociate the increase in coronary sinus potassium from the subsequent pause by predriving the ventricles at a given rate for a few minutes and then overdriving them at a higher rate for 1 minute. Because of the predrive, the final overdrive causes a smaller coronary potassium increase than that caused by the same overdrive in the absence of predrive. In spite of the different increase in coronary potassium concentration, the pause is not much affected.29 Vick28 suggested that an increase in potassium permeability independent of a change in [K+]o might be responsible for the suppression in Purkinje fibers. Other contributing factors might have been changes in sodium and chloride permeability and active inward pumping of chloride. Vick points out that there was no direct evidence for these changes.

In view of these considerations, other factors must be considered.

THE ROLE OF AN ELECTROGENIC SODIUM EXTRUSION

As a consequence of drive, more sodium enters the cells because there are more action potentials per unit of time. If sodium initially accumulates inside the fiber (and potassium is lost) the sodium-potassium pump ought to be stimulated. There are several reports24-27 which show that in cardiac tissues the sodium-potassium pump is electrogenic: more sodium is extruded from the fiber than potassium is taken up. An electrogenic pump of this kind causes hyperpolarization. During drive, the initial decrease in maximum diastolic potential is followed by an increase above control value.26,27 When the drive is terminated, the
pump does not cease its activity abruptly and therefore keeps the diastolic depolarization negative to the threshold. As sodium is pumped out, [Na+] returns to control values and the pump slowly decreases its activity. The reduction of the electrogenic sodium extrusion and a possible fall in [K+] allow the fibers to depolarize to the threshold and activity resumes. The maximum diastolic potential (E_{max}) still is higher than control and returns slowly to its original value over a period of several minutes. A role for an electrogenic sodium extrusion in overdrive suppression is suggested by a number of findings. Thus, the hyperpolarization during drive is reduced or abolished by (1) substitution of sodium by the poorly extruded lithium, (2) poisoning of the pump with diinitrophenol or strophantin, and (3) interfering with the metabolic supply to the pump by means of 2-deoxy-D-glucose. The hyperpolarization during drive is increased by norepinephrine. Since norepinephrine has been shown to stimulate the (Na+ + K+)-activated ATPase in cardiac tissues, the enhancement of overdrive hyperpolarization is presumably due to such an action. This interpretation is supported by the fact that with very prolonged overdrive when maximum diastolic potential stabilizes at a new value and the pump is presumably maximally stimulated, norepinephrine fails to increase E_{max}. In hypothermia, the sodium influx should be little affected but the active sodium extrusion markedly prolonged. In fact, overdrive suppression is enhanced at lower temperatures.

An electroneutral sodium-potassium pump also could cause hyperpolarization if it were to decrease [K+], and thus shift the potassium equilibrium potential to more negative values. However, a decrease in [K+] would not be expected to account for the suppression which follows overdrive. In fact, in a Tyrode’s solution containing a low K+ concentration, overdrive may not cause suppression and the coronary sinus potassium during prolonged drive returns to the control value but never decreases below it. It should be added also that the overdrive suppression in Purkinje fibers is not affected by atropine.

THE ROLE OF CALCIUM

During a fast drive, the influx of calcium must be increased because the number of action potentials is higher. In atrial tissue, calcium exchange increases as a function of the rate of stimulation. Since calcium has been shown to increase the membrane conductance to potassium, it is possible that an accumulation of calcium inside the fiber might contribute to overdrive suppression. That [Ca^{2+}] may be increased by drive is suggested by recording of the contractile force of Purkinje fibers: the tension developed by a Purkinje fiber decreases at the beginning of drive as a result of shorter diastolic intervals but then it increases during the drive. When the fiber is driven after the drive at the same rate as control, the contractile tension is maximal (M. Vassalle, unpublished experiments). This finding may indicate that [Ca^{2+}] is increased. In fact, it has been reported that overdrive suppression in Purkinje fibers is reduced by verapamil. Since calcium modifies the control rate and shifts the threshold for excitation, these two factors must be considered as a possible cause of the changes in overdrive suppression. Experiments from this laboratory (E. Musso and M. Vassalle, unpublished) show that even if the drive rate is kept a constant multiple of the predrive control rate in different calcium solutions, still the duration of overdrive suppression varies markedly with external calcium concentration. However, this does not necessarily result from changes in potassium conductance, for two reasons. The first is that the increase in E_{max} occurs also in low [Ca^{2+}]_. The second is that the initial diastolic depolarization is actually slowed in low calcium and enhanced in high calcium. Instead, the results show that the threshold is shifted to more negative values in low calcium and in the opposite direction in high calcium. This factor seems to be the important variable in accounting for the changes in duration of the pause.

Factors Influencing Overdrive Suppression

During ventricular overdrive, the blood pressure usually increases and, after overdrive, it falls to low values during the pause. This must elicit sympathetic reflexes which could play a role both in the induction and in the termination of the suppression after drive. That catecholamines influence ventricular pacemaker activity and that catecholamine depletion by reserpine prolongs the ventricular standstill during vagal stimulation was demonstrated some time ago. An analysis of the role of catecholamines and the sympathetic nerves in overdrive suppression also has been carried out and several agents, including β-blockers and reserpine, have been used. The results indicate that when the influence of the sympathetic nerves is removed, overdrive suppression is of longer duration. By stimulating the stellate ganglion or initiating a sympathetic reflex during the drive, the pause was shortened markedly. This procedure is of interest in that the effect of the sympathetic nerves on the control idioventricular rate is avoided. Acute sympathetic denervation, instead, prolongs the pause. The administration of catecholamines also shortens the pause and in a dose-dependent manner even if the change in control rate is taken into account. The effect of catecholamines is removed by β-blockade. In no instance is the pause or the resumption of activity abolished by manipulation of the sympathetic system. This strongly suggests that the sympathetic system conditions but does not determine the events after drive. The correctness of this conclusion is suggested by the fact that the suppression and resumption of activity after drive occur also in reserpine-treated isolated ventricles and in isolated Purkinje fibers.

Overdrive Suppression in Man and Clinical Applications

Overdrive of the sinus node has been carried out in man with the object of testing normal and abnormal sinus node function. Mandel et al. applied fast atrial driving (up to 150/min) for varying periods of time (50–180 seconds) to unanesthetized patients. They found that the duration of the drive had little effect on the subsequent pause but, as the rate of drive was increased, the pause duration became maximal at 130/min. The pause after a drive of 150/min was shorter than that at slower rates and sometimes was followed by secondary slowing. As expected, the pause was longer when the sinus rate was slower. These results
showed that, at least in part, results obtained in the experimental animal could be reproduced in man in the absence of anesthesia and surgical trauma. Furthermore, Mandel et al. tested the effect of overdrive in three patients with “sick sinus syndrome” and found that the pause was much longer in this condition even if the lower sinus rate in these patients was taken into account. As in the experimental animal, atropine reduced but did not abolish the pause and the reduction was most marked in two of the patients with sick sinus syndrome. Interestingly, subthreshold stimulation did not result in any reduction of sinus rate; the possible explanation offered was that the precise location of the driving catheter electrode was uncertain. The termination of an episode of tachycardia is frequently associated with a sinus node depression which is likely to be longer in duration in patients with the sick sinus syndrome. The overdrive procedure thus provided a valuable test to explore the automatic function of the sinus node. Similar results were reported independently by Rosen et al. who found that in a series of 10 subjects with symptomatic sinus node disease atrial pacing resulted in a prolonged asystole in four patients.

In a subsequent communication, Mandel et al. studied a group of 31 patients with sick sinus syndrome by several methods including overdrive. In 29 patients there was an enhanced overdrive suppression (increased sinus node recovery time). Overdrive from the ventricles also resulted in suppression of the sinus node but the suppression was less marked than with atrial drive, possibly because not all the impulses from the ventricles succeeded in discharging the sinus node. Because atropine markedly shortened the pause, it was proposed that the excessive prolongation of the pause in patients with sick sinus syndrome was vagal in nature and might be due to hyperresponsiveness to acetylcholine. The overdrive of the sinus node was recommended as a testing procedure in the case of sinus node dysfunction.

Whenever this test was applied, longer pauses often were found in patients with sinus dysfunction. However, it is becoming clear that the test may give normal results even in patients with sinus node disease. One possible reason for this apparent discrepancy has been stressed by Strauss et al. namely, not all the driven atrial impulses may invade the sinus node because of varying degree of retrograde block between atria and sinus node. In addition the duration of the pause may be affected by antegrade block from the sinus node to the atria. In fact, Strauss et al. pointed out that block is more likely to occur at a faster driving rate and this could be the explanation for the fact that in the studies of Mandel et al. the pause was shorter at a rate of 150/min than at a slower driving rate. Steinbeck and Luderitz provided evidence for antegrade block between the sinus node and the atria in patients with sinus node disease. Thus, after overdrive, there were abrupt changes of the atrial cycle length which differed by one basic interval.

The present status of clinical application of overdrive suppression suggests that the procedure yields useful information about the function of the sinus node, but the results need to be interpreted in the light of the fact that the dysfunction is unlikely to be limited only to the automatic process.

Concluding Remarks

It is apparent that the sinus node dominance over subsidiary pacemakers is due to its faster diastolic depolarization. Such dominance is enhanced by the inhibition that the sinus node exerts by virtue of its faster rate. This inhibition may be viewed as a safety factor which makes it more difficult for subsidiary pacemakers to emerge and compete with the sinus node under normal conditions. This type of interpacemaker organization is useful also for the control of cardiac automaticity. Increased sympathetic discharge reduces overdrive suppression but also increases the rate of the sinus node far in excess of that of Purkinje fiber. Increased vagal discharge decreases the rate of the sinus node and, because of the sinus bradycardia, the rate-dependent inhibition of the idioventricular pacemaker tissues is removed. Thus, these subsidiary pacemaker tissues (being insensitive to vagal inhibition) become ready to activate the ventricles. As the sinus node becomes excessively slow or is arrested completely, the subsidiary ventricular pacemakers become actual pacemakers for the heart without delay. If the suppression of the sinus node (or the onset of complete AV block) is abrupt, however, several seconds will be needed for the rate-dependent inhibition to subside. Thus, while the stimulatory action of the sympathetic system involves the whole heart, the inhibitory action of vagus involves only the atria and, in actuality, leads to the removal of another type of inhibition, the rate-dependent inhibition of the ventricles.

Another advantage of this functional organization among pacemakers is that the sinus node exerts its rate-dependent inhibition on all other pacemaker tissues of the heart as long as they are discharged by impulses of sinus origin.

Finally, the different degree of intrinsic automaticity of subsidiary pacemaker tissues in the atria and ventricles provides for a fine regulation of overdrive suppression. If the sinus node were to fail in its function because of disease, the subsidiary pacemaker tissues would not be released en bloc from inhibition. On the contrary, the subsidiary pacemaker tissues in the atria would assume dominance. This would be expected because the atrial pacemakers have a faster intrinsic rate than the idioventricular pacemakers and therefore are less suppressed by the sinus node. The location of a new dominant pacemaker in the atria allows for the maintenance of vagal and sympathetic control over pacemaker function. At the same time, the idioventricular pacemakers are still overdriven, albeit to a lesser degree.

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