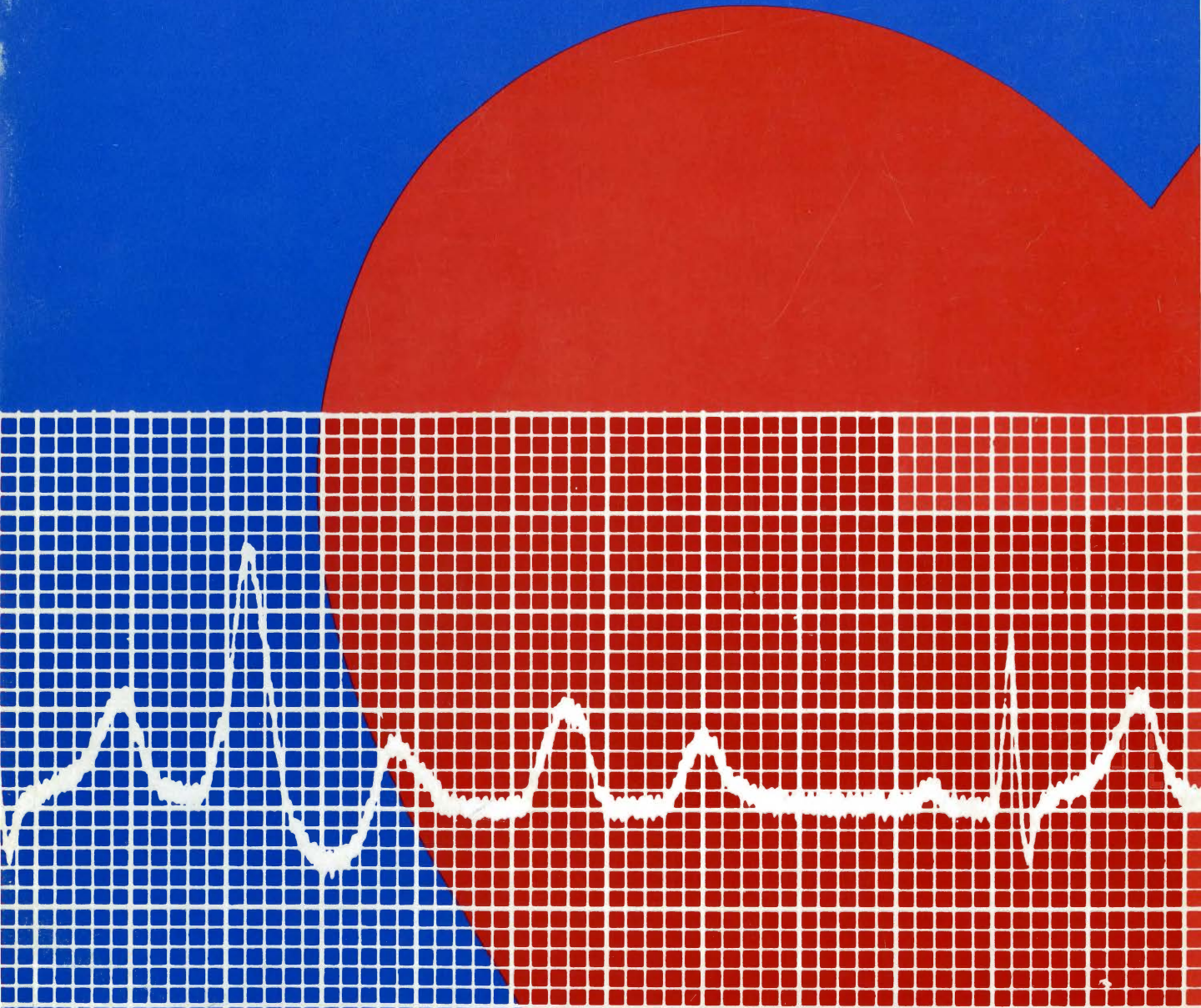


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VOLUME NINE • NUMBER ONE • 1973



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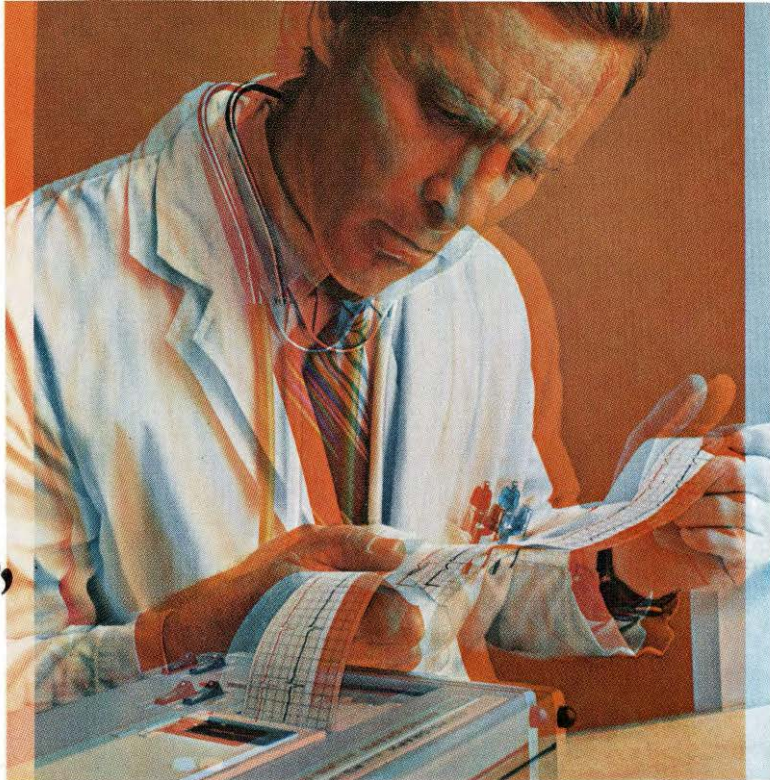
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MEDICAL COLLEGE OF VIRGINIA QUARTERLY

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Cardiac Arrhythmias

Sponsored by the Council on Clinical Cardiology, the American Heart Association, the Tidewater Heart Association, and the Virginia Heart Association

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Introduction

This issue of the MEDICAL COLLEGE OF VIRGINIA QUARTERLY is devoted to the publication of the proceedings of the Cardiac Arrhythmias Symposium held at the Cavalier Hotel in Virginia Beach, Virginia from June 8-10, 1972. The meeting was co-sponsored by the Council on Clinical Cardiology of the American Heart Association and the Tidewater Heart Association. This was the second cardiovascular program to be held within a year in which Medical College of Virginia faculty members, teamed with a guest faculty of national recognition, provided a review of basic and clinical aspects in the field of cardiac arrhythmias. Approximately three hundred persons, including physicians and nurses, attended the meeting which utilized a format of formal presentations, panel discussions, and evening workshops. The first meeting, a Cardiac Pacing Symposium, was held in Williamsburg, Virginia on April 16 and 17, 1971. The proceedings of this program were published by the MEDICAL COLLEGE OF VIRGINIA QUARTERLY in Volume Seven, Number Four, 1971.

The reason for such emphasis upon the field of cardiac arrhythmias is primarily due to the fact that there has been an awakened interest in recent years in the problem of sudden death. It is now being appreciated that a significant number of

deaths attributed to cardiovascular disease are due to cardiac arrhythmias, a potentially correctable disorder.

The success of the meeting would not have been possible without the able support of Mr. Melvin Shaffer and his Audio-Visual Department. I would also like to express my appreciation to the co-directors, Dr. Eugene M. Wyso, Dr. William A. Dickinson, Jr., and Dr. Robley D. Bates, for their assistance in the development of the program. The electrocardiographic materials were provided by cardiovascular fellows of the Cardiovascular Division of the Department of Medicine and the coronary care unit nursing staffs of both the Medical College of Virginia Hospital and St. Mary's Hospital. In addition, I would like to thank the editorial staff of the MEDICAL COLLEGE OF VIRGINIA QUARTERLY, which included Miss Mary Parke Johnson, Mrs. Nancy Varmette, and Miss Stuart Gravatt, as well as my own secretaries, Mrs. Barbara Hendrick and Mrs. Marty Eagle, whose efforts will never be forgotten.

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Conducting Pathways of the Human Heart*

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For over a century the cardiac beat has been experimentally observed and analyzed. To a surprising degree the relevancy of the early researches persists, and the views of the 19th century investigators though modified, have not been eclipsed by time. It may, therefore, be appropriate to preface this clinicopharmacological seminar on arrhythmias by a brief review of the cardiac conducting pathways whose existence is generally accepted today and to retrace the concepts which led to their discovery.

The phenomenon was already so familiar that by 1882 the Cambridge physiologist W. H. Gaskell (fig. 1) could neglect specific citations in his reference to the ease with which cardiac contractions in cold blooded animals are seen to commence in the sinus venosus and with distinct pauses, sequentially pass to the auricles and ventricles (3). From his writings and those of several contemporaries, it is clear that basic questions regarding cardiac conduction were not only well defined but could already be physiologically explored against a formidable background of embryology, comparative anatomy, and histology. The continuous tubal structure of the primitive heart permitting a wave of contracture was well known. In contrast were the obstacles to be circumvented when hearts evolved with interposing rings of fibrous (fig. 3) tissue which appeared to

separate the muscular continuity of the atria and ventricles.

Simple notions that contractions resulted from "direct stimulation of the blood on cardiac muscle" had long since been abandoned. In particular, the discovery of both cardiac nerves and the ganglionic masses of Remak (23), Bidder (2), and Ludwig (21) introduced the possibility of a much more plausible neurological explanation for the transmission of cardiac impulses. It was inferred that cardiac muscle contracted in response to a stimulus initiated at central nervous system or peripheral ganglionic level. Since neural connections between atria and ventricles could be demonstrated, the apparent muscular dissociation between these chambers could be disregarded.

The attraction of a neurological mechanism in explaining cardiac rhythm and contraction waves was further enhanced by the earlier experiments which purported to show that isolated portions of heart would contract only if they contained elements of neural ganglia. This comfortable situation was soon to be disturbed by Gaskell's instinct to challenge the accepted. Though his meager illustrations are poor quality woodcuts and his argument sometimes diffuse, two essential advances emerge from his research: 1) a recognition of inherent excitability in cardiac muscle independent of ganglia and 2) demonstration in a tortoise heart that a bridge of muscle tissue exists between the atria and ventricles (3).

* Presented by Dr. Shiel at the Symposium on Cardiac Arrhythmias, June 8, 1972, at Virginia Beach, Virginia.



Fig. 1—Walter H. Gaskell. 1847–1914.

With the identification of the fasciculus atrioventricularis, or “Gaskell’s Bridge,” the myogenic concept of cardiac conduction was established. It remained to show that the structure observed in poikilothermic animals had an analogous counterpart in mammals. This was accomplished by W. His, Jr. (fig. 2) in 1893 (7, 8, 9), and almost simultaneously by the independently working A. F. Stanley Kent (16). Predictably, the ensuing years were occupied in successful search and survey of alternate pathways. These major systems are depicted in the diagrams and discussed in the order of their discovery (figs. 3, 4, 5, and 6).

Following the identification of the atrioventricular fasciculus, the attached A-V node and the bundle branches curiously remained undescribed until the appearance of Tawara’s monograph in 1906 (24). In this year also, the sinoatrial node was dis-



Fig. 2—Wilhelm His, Jr. 1863–1934.

covered by Keith and Flack (13, 14, 15), an event which stimulated search for internodal tracts. Three bundles of Purkinje-like tissue associated with the names of Wenckebach, Thorel, and Bachmann (27, 25, 1) have been described. They are represented in figures 3, 4, and 5, and have been reidentified by James (11) as the middle, posterior, and anterior internodal tracts.

Though the bundle of His is apparently the sole atrioventricular muscular connection in normal human hearts, a number of accessory pathways have been found in fetal, infant, and pathological hearts. They are of particular interest and significance in explaining arrhythmias associated with the Wolff-Parkinson-White syndrome. Notably these tracts include the connections described by Kent (18, 19, 20) between the lateral walls of the right atrium ventricle, the paraspecific fibers of Mahaim

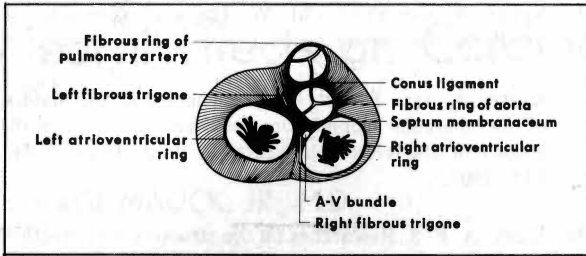


Fig. 3—The interatrioventricular fibrous skeleton: Note A-V bundle penetrating right fibrous trigone.

(22) which run from the left bundle branch to the upper interventricular septum, and the accessory fibers described by James (10). The vast and fastidious labors on the conducting system have even in modern times not deterred some investigators, notably, though not uniquely, Glomset and his associates (4, 5, 6) from denying the existence in man of a myogenic conduction system and attempting to reincarnate the supremacy of the neurogenic theory. Perusal of their papers will reassure the reader that, however he receives them, their views are not unsupported by much careful investigation. There are indeed many reasons for the doubts and discrepancies of various investigations. Anatomic certainty comes only from meticulous serial sectioning, and the tedium and labor involved have perhaps tempted some conclusions whose validity has been impaired by faulty techniques. On physiological grounds alone, the presence of conducting systems is incontrovertible, and there is abundant anatomical data testifying not only to specialized muscle paths but also to their intimate association with neural elements. Whether the situation of nerve and muscle indicates mere anatomic proximity or bespeaks a close functional connection, is, however,

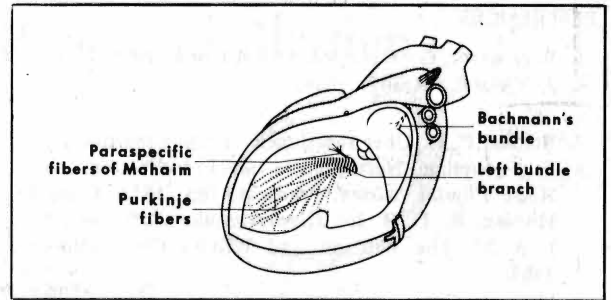


Fig. 5—Scheme of the conducting pathways viewed from the left atrioventricular aspect.

a question still unsettled. Though the long and current ascendancy of the myogenic theory reflects the accumulated evidence in its favor, this review of the discovery of the conducting system may bear witness to the dangers of facile acceptance. The myogenic theory was conceived in dissatisfaction with the neurogenic explanation and born in the labors of Gaskell, His, and Kent. Not all discoveries have survived attempts at confirmation, and in particular, the existence of the lateral A-V fibers described by Kent (fig. 3) have been successively accepted, rejected, and later reinstated as present in fetal and certain pathological hearts. Again, so far from excluding the possible contribution of neural elements to conduction, modern ultrastructural and histochemical studies of the S-A and A-V nodes have strengthened the evidence of autonomic nerves (26) and cholinesterase activity at these sites (12). Clearly, therefore, the identification of both neural and muscular components in no way abates the potential importance of either. On the contrary, continued exploration of the neuromuscular relationships is required, and it remains the task to solve the contribution of each before today's discordant views can harmonize.

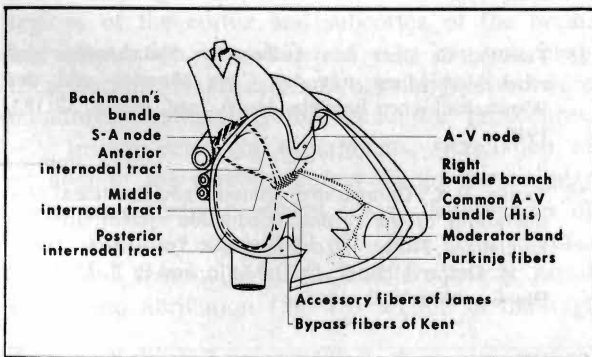


Fig. 4—Scheme of the conducting pathways viewed from the right atrioventricular aspect.

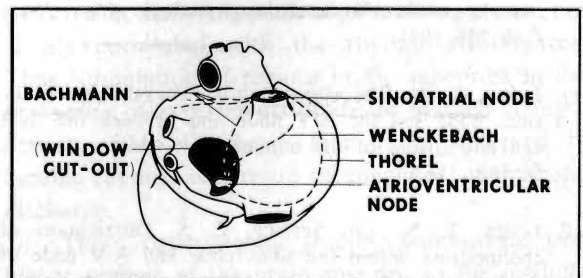


Fig. 6—Heart viewed from above showing the Wenckebach, Thorel, and Bachmann bundles (middle, posterior, and anterior internodal tracts of James).

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Neural Effects on Cardiac Rate and Rhythm*

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The importance of autonomic discharge emanating from high neural regions rostral to the medulla oblongata on heart rhythm was first recognized in the classical studies by Schiff (5) and Danilewsky (1) during the late nineteenth century. Only in the last two decades, however, has a precise description of these neural effects on heart rhythm become possible. Crucial to these more recent advances have been improvements in technology which have permitted application of discrete electrical stimuli to various regions of the brain as well as continuous monitoring of heart rate and arterial pressure. These studies, reported here, represent a portion of a broader research project carried out in the neurophysiological laboratory of the Medical College of Virginia for a number of years and aimed at clarification of the role of autonomic discharge from higher neural centers on organ function (2, 4).

Briefly, the experiments were performed in anesthetized dogs, cats, and monkeys. Steel electrodes were guided under stereotaxic control into regions of the cortex and subcortex of the brain, and stimulation was delivered at a constant electrical current. Heart rate and arterial pressure were monitored continuously throughout the procedures.

In one series of experiments, stimulation of an area of the cerebral cortex within the cingular gyrus consistently produced severe disturbances of heart rhythm consisting of sinus bradycardia, sinus and ventricular arrest, and, frequently, atrial flutter and fibrillation (fig. 1). Section of the vagi

bilaterally abolished these arrhythmias. Thus, it was clearly demonstrated that certain regions of the brain were capable of exerting considerable control on parasympathetic function.

In a second group of experiments, electrodes were similarly placed more deeply into the subcortex in a region within the mesencephalic reticular formation. Stimulation of this region evoked striking increases in sympathetic efferent discharge which produced all of the ventricular arrhythmias observed in the clinical ECG. Furthermore, the arrhythmias were always evoked in a sequence; for example, sinus tachycardia was followed by ventricular fusion contractions, ventricular premature contractions, ventricular tachycardia, and rarely, ventricular fibrillation (3). It is particularly noteworthy that a graded increase in stimulus intensity was also capable of producing this spectrum of ventricular rhythm disturbances (fig. 2). If we sectioned the vagus nerves bilaterally, no change occurred in the responses observed. Administration of propranolol in small doses totally abolished all of the effects. Although alterations in arterial pressure occurred in many experiments, the changes were not closely correlated with the rhythm disturbances. Thus, stimulation of regions in the subcortex in the first series of experiments produced marked changes deeper within the brain than those observed in cardiac rhythm as a result of enhanced sympathetic discharge.

These experimental studies demonstrate that higher regions of the brain superior to the medulla may produce significant changes in cardiac rhythm as a result of alterations in autonomic discharge. Furthermore, in various regions of the brain, either

* Summary of a lecture delivered by Dr. Mauck at the Symposium on Cardiac Arrhythmias, June 8, 1972, at Virginia Beach, Virginia.

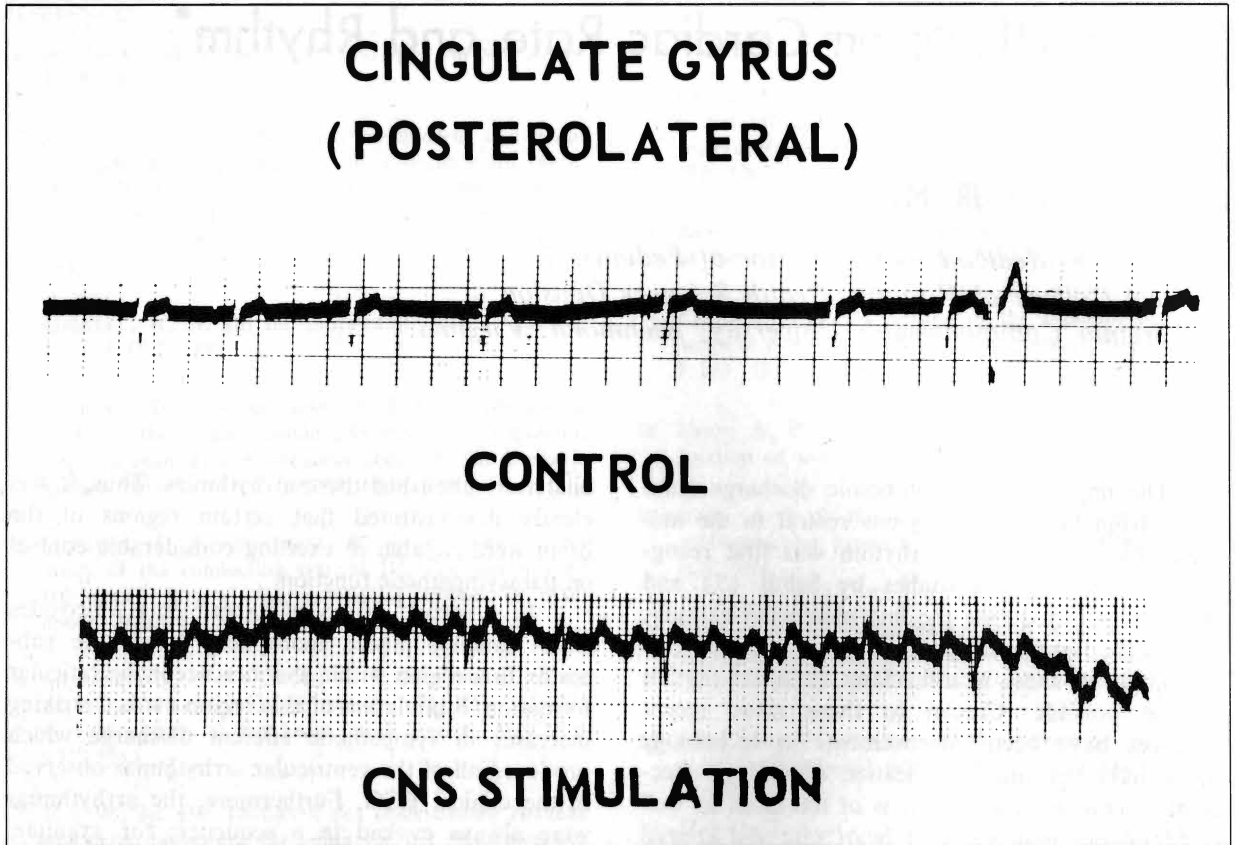


Fig. 1—The effect of stimulation of the cingulate gyrus on heart rhythm.

dominantly parasympathetic or sympathetic responses are produced. It is possible through these alterations in neural discharge to produce essen-

tially all of the arrhythmias observed by electrocardiography in the clinical setting.

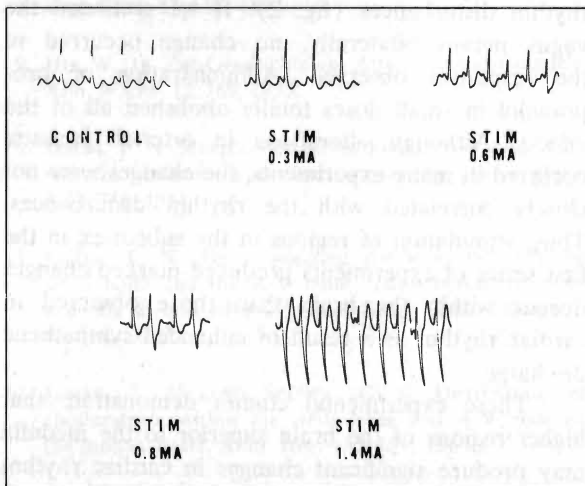


Fig. 2—The effect of graded increments in electrical stimulation of the mesencephalon on heart rhythm.

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Introduction to the Phasic Effects of the Vagus on Sinoatrial and Atrioventricular Nodes*

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I want to emphasize that the vagus has effects upon both the sinus node and the A-V node. It slows sinus discharge, and it depresses, delays, or blocks atrioventricular transmission. It is also known that under certain conditions the discharge of vagal fibers to the heart may be phasic. From the physiological standpoint, it ought to be phasic, particularly at slow heart rates. The reason it should be phasic is that when the systolic pulse wave arrives at the baroreceptor regions of the aorta and of the carotid sinuses, it elicits a discharge of afferent fibers in those regions which goes to the central nervous system and leads to enhancement of vagal activity. By enhancement I mean an increase in the frequency of discharge. An increase in pressure in the pressure-sensitive regions of the arterial tree leads to an increase of vagal impulses to the heart. Since the systolic pulse rate is phasic, the changes in pressure in these baroreceptor areas are also phasic. One might reasonably expect that this is a closely coupled reflex arc; the discharge from the vagus nerve fibers would also be phasic and more or less locked to the systolic pressure cycle.

This has been recognized for a long time, particularly in one of the clinical situations that has aroused the curiosity of electrocardiographers through the years. When there is atrioventricular block so that the atria and the ventricles respond separately and independently, the condition known as ventriculophasic sinus arrhythmia has been ob-

served. That is, if the basic rate of the ventricle following the development of A-V block is very slow, perhaps 30 beats per minute, and if the sinus rate is considerably faster, then it can be observed that the sinus discharge which follows a ventricular contraction is somewhat delayed. When the ventricle is beating once every two seconds, it will eject a large stroke volume with a wide pulse pressure, and there will be a sharp rise in systolic pressure. Thus, there will be a discrete stimulation to the baroreceptors, a resulting reflex discharge of vagus fibers to the heart, and a decrease in sinoatrial frequency. There are many possible ways of explaining ventriculophasic sinus arrhythmia, but the reflex vagal explanation makes the most sense and almost certainly is responsible. It has not been generally recognized that there might also be time-locked phasic changes in vagal activity to the atrioventricular conduction system; yet, this is also a possibility. Changes in conduction time or intermittent block, as in Wenckebach periodicity, could be reflexively induced through this baroreceptive mechanism, but the possibility of vagal activity has been rejected because there is often not a corresponding change in the sinoatrial cycle. In the process of another investigation, we discovered that the time course of vagal effects upon the sinus node and upon the A-V node are distinctly and discretely separate. These effects occur out of phase with one another, depending upon the heart rate. If the baroreceptor reflex produces alterations in sinus nodal activity which are out of phase with effects on A-V nodal activity, then one might expect that at one heart rate effects upon one system would

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predominate, and that at another heart rate effects upon the other might predominate. This is precisely what happens. Therefore, in the analysis of complex arrhythmias it is necessary to consider the time intervals between the possible phasic discharge in the vagus and the next event in the cardiac cycle. Experimentally, the overall time from a QRS complex to the expected effect upon sinus discharge is

approximately 600 msec; the latency for effects on A-V transmission is approximately 400 msec.

Analysis of complex arrhythmias could very often be made much simpler if the electrocardiograms were recorded with a simultaneous record of arterial pressure, so that it would be possible to time the electrical events relative to the time and amplitude of the systolic pulse wave.

CONTROL

... of the heart rate... the vagus... the cardiac cycle... the QRS complex... the sinus discharge... the expected effect... the overall time... the latency for effects... the time and amplitude... the systolic pulse wave...

... approximately 600 msec... the latency for effects on A-V transmission... approximately 400 msec... Analysis of complex arrhythmias... could very often be made much simpler... if the electrocardiograms were recorded with a simultaneous record of arterial pressure... so that it would be possible to time the electrical events relative to the time and amplitude of the systolic pulse wave.

The Critical Use of the His Bundle Electrogram*

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The technique for electrode catheter recording of consistent and stable His bundle activity presently used in the clinical laboratory was initially developed as an investigational tool (10, 11). In the clinical laboratory, the His bundle electrogram, in conjunction with the surface electrocardiogram—a technique that has been termed His bundle-electrocardiography by Castellanos (2)—has provided a more accurate means of localizing the site of conduction abnormality in patients with various forms of heart block. In addition, this technique has been utilized to study various physiological and pharmacological interventions (6, 12), arrhythmias (7), and the Wolff-Parkinson-White syndrome (3, 4).

Unfortunately, published reports have contained a variety of terms applied to the various intervals representing conduction through the atrioventricular transmission system. Moreover, the procedures for quantitating critical conduction measurements made with the use of His bundle-electrocardiography have relied heavily upon the shape of a recorded deflection during the P-R segment and its temporal relationships to atrial or ventricular activity. In view of the numerous reports using His bundle recordings that are presently appearing in the literature, a critical evaluation of the His bundle electrogram and some of its applications seems appropriate.

Figure 1 shows an anterior-posterior view of the heart and the position of an electrode catheter during the recording of His bundle electrograms.

* Presented by Dr. Scherlag at the Symposium on Cardiac Arrhythmias, June 8, 1972, at Virginia Beach, Virginia. Please send requests for reprints to: Dr. B. Scherlag, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, Florida 33140.

In general, the His bundle electrogram is recorded by the use of a standard bipolar pacing catheter with ring electrodes 5 mm or 10 mm apart. The catheter is introduced from the femoral vein into the right heart and stabilized at the A-V ring at the base of the posterior tricuspid leaflet.

In figure 2A, electrograms from the high right atrium and from the His bundle area are shown with simultaneously recorded ECG leads. As opposed to standard electrocardiographic recordings which are usually made with relatively wide frequency response settings, that is, 0.1 to 200 Hz, the His bundle electrogram is commonly recorded with narrower band width limits to accentuate rapid deflections and attenuate slower waves, that is, 40 to 200 or 40 to 500 Hz. For this illustration, another bipolar catheter in the right atrium near the sinus node recorded atrial activity at the onset of the P wave. The His bundle electrogram, in conjunction with the three standard ECG leads, allows a division of the P-R interval into three components. The first is the P-A interval. This is the time from the earliest onset of the P wave (atrial activation in the area of the sinus node), as seen in any of the surface electrocardiograms, to the onset of atrial activity in the area of the A-V junction, as seen in the His bundle electrogram. This interval is taken as a measure of a representative portion of intra-atrial conduction, specifically the conduction time from the area of the sinus node to the area of the A-V node during normal sinus rhythm.

The A-H interval is the time from the beginning of the A wave to the onset of His bundle activity. This interval is taken as a measure of A-V nodal conduction. In our initial study, the term P-H interval was used as a measure of A-V nodal con-

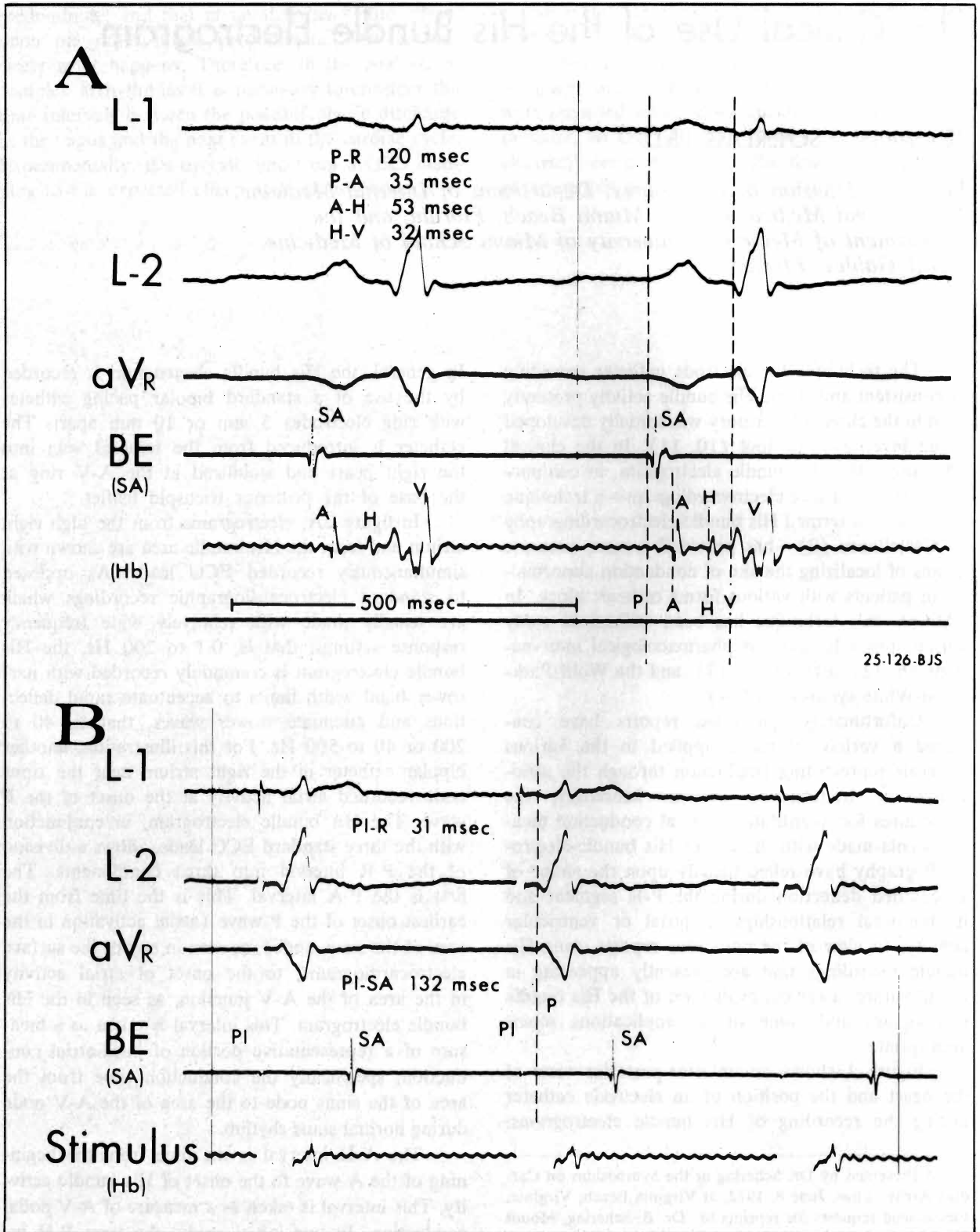


Fig. 1—Recording of His bundle bipolar electrogram (Hb) and simultaneously recorded bipolar electrogram from the sinus node area (BE, SA) with 3 standard ECG leads (L-1, L-2, and AVR). A. The P-R interval (120 msec) is divided into intra-atrial conduc-

tion time (P-A = 35 msec); A-V nodal conduction time (A-H = 53 msec); and His-Purkinje system conduction time (H-V = 32 msec). B. Pacing at a faster rate than the sinus rate, from the recording electrodes (stimulus, Hb), produces an unchanged QRS complex in all leads with a pacer impulse (PI) to R wave interval (PI-R) of 31 msec, directly comparable to the previously measured H-V time, 32 msec (panel A). Pacing the His bundle from the aortic root allowed retrograde activation of the atrium (PI-SA = 132 msec). The interval between time lines equals 1 second. (Reproduced by permission of The American Heart Association, Inc., from B. J. Scherlag, *et al.*, "His Bundle Electrogram," *Circulation* 46:602, 1972.)

duction. Unfortunately, this term has persisted although we now use the term A-H interval since it represents a more accurate measure of transmission through the A-V node. Ordinarily, the A wave of the His bundle electrogram represents local

atrial activity in the immediate vicinity of the A-V node and therefore, eliminates the intra-atrial conduction between the sinus node and the low right atrium. In addition, the A-H interval allows a comparison of A-V nodal conduction during both sinus

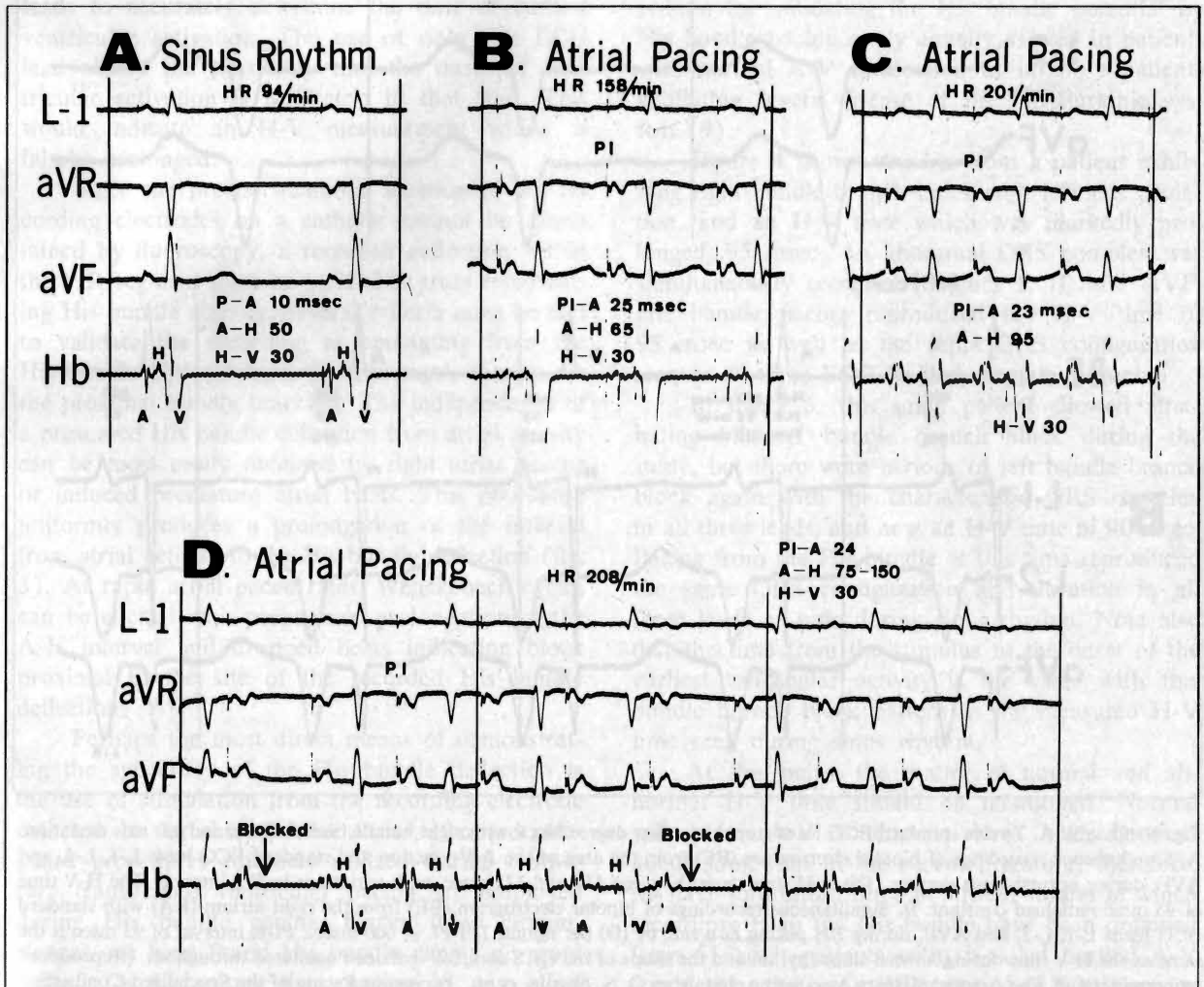


Fig. 2—The effect of atrial pacing on intra-atrial (P-A or PI-A), A-V nodal (A-H), and His-Purkinje (H-V) intervals in the dog. A. During sinus rhythm at a heart rate of 94 beats per minute, the P-A, A-H, and H-V time measured from the His bundle electrogram (Hb) and the simultaneously recorded ECG leads I, AVR, and AVF, are 10, 50, and 30 msec respectively. B and C. Atrial pacing up to a rate of 201 beats per minute produces a progressive increase in the A-H interval to 95 msec while the H-V interval remains constant at 30 msec. The pacer impulse to atrial activity (PI-A) is essentially the same at 23 to 25 msec during atrial pacing. D. At a heart rate of 208 beats per minute, a 5:4 Wenckebach cycle is seen with A-H variation from 75 to 150 msec. PI-A and H-V remain the same at 24 and 30 msec, respectively. Note that in the blocked beat the H and V deflections do not appear after the stimulus and atrial activity.

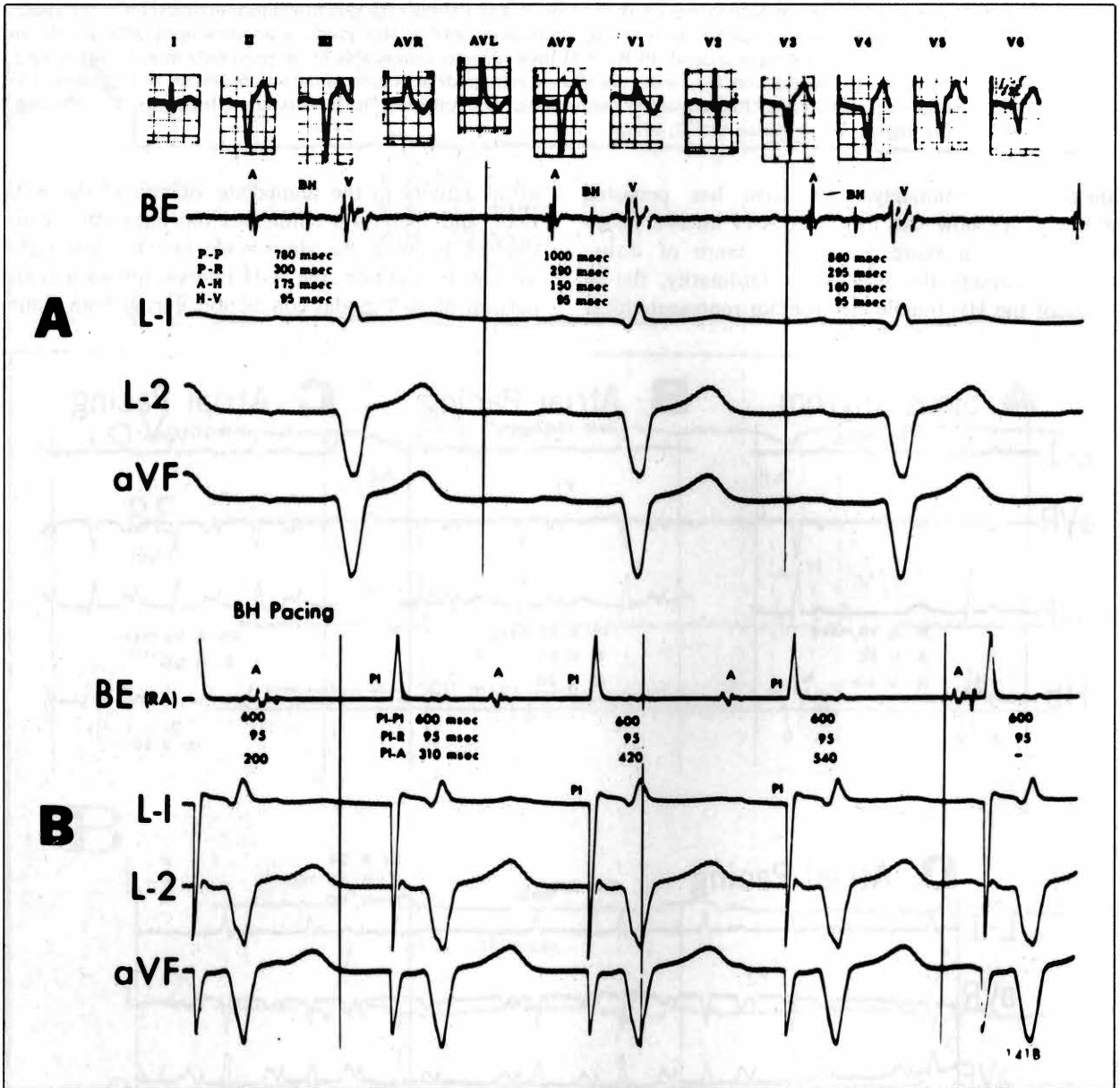


Fig. 3—Case W.A. Twelve standard ECG leads (top) show first degree block with right bundle branch block and left axis deviation. A. Simultaneous recordings of bipolar electrogram (BE) from the area of the A-V junction and standard ECG leads L-1, L-2, and AVF, during normal sinus rhythm. The A-H time varies between 150 and 175 msec, with variations in P-P interval. The H-V time of 95 msec remained constant. B. Simultaneous recordings of bipolar electrogram (BE) from the right atrium (RA) with standard ECG leads L-1, L-2, and AVF, during BH pacing at a rate of 100 per minute (PI-PI = 600 msec). PI-R interval of 95 msec is the same as the H-V time during normal sinus rhythm and the shape of the QRS complex remained unaltered throughout. (Reproduced by permission of The American Heart Association, Inc. from O. S. Narula, *et al.* "Pervenous Pacing of the Specialized Conducting System in Man: His Bundle and A-V Nodal Stimulation." *Circulation* 41:77, 1970.)

rhythm and atrial pacing because the atrial deflection used in the measurement is not ordinarily altered by the pacing site (fig. 3). This is in contrast to the P-H measurement which cannot be accurately

compared during spontaneous rhythm and atrial pacing since the pacer impulse is not usually applied in the area of the sinus node (compare figs. 3A and 2B,C,D).

The H-V interval is the time required for the impulse to traverse the His-Purkinje system, that is, from the onset of His bundle activity to the earliest onset of regular ventricular muscle activity as seen on any of the ECG leads or the His bundle electrogram. The term H-Q interval has been used to describe the conduction time through the His-Purkinje system in several reports. We prefer the term H-V on the basis of the fact that a Q wave may not be present in the ventricular deflection utilized for the measurement. In addition, we have stressed the use of at least three standard ECG leads to accurately determine the time of earliest ventricular activation. The use of only one ECG lead allows the possibility that the onset of ventricular activation is isoelectric in that lead. This would indicate an H-V measurement which is falsely prolonged.

Since the precise anatomic location of the recording electrodes on a catheter cannot be ascertained by fluoroscopy, a recorded deflection within the P-R segment must be verified as truly representing His bundle activity. Several criteria must be met to validate the recording as emanating from the His bundle and not from the atrium, A-V node, or the proximal bundle branches. The independence of a presumed His bundle deflection from atrial activity can be most easily obtained by right atrial pacing or induced premature atrial beats. This procedure uniformly produces a prolongation of the interval from atrial activity to the His bundle deflection (fig. 3). At rapid atrial paced rates, Wenckebach cycles can be elicited with progressive prolongation of the A-H interval and dropped beats indicating block proximal to the site of the recorded His bundle deflection.

Perhaps the most direct means of demonstrating the specificity of the His bundle deflection is the use of stimulation from the recording electrode catheter. In our clinical laboratories, standard safeguard procedures routinely utilized during temporary transvenous ventricular pacing are employed during His bundle pacing. Under these circumstances, we have found His bundle pacing no more difficult or hazardous than pacing in any other portion of the right or left ventricle. Pacing of the His bundle produces capture of the ventricles with the same QRS morphology in all ECG leads as that seen during sinus rhythm or atrial pacing (fig. 2B). This indicates that the point of stimulation was proximal to the right or left bundle branch and must

therefore be located in the His bundle or A-V node. Note also that the interval from the pacer impulse to the onset of ventricular activity is the same as the interval from the recorded His bundle potential to ventricular activation during sinus rhythm or paced atrial rhythm. If this interval is constant over a wide range of heart rates, a pacing site in the A-V node can be eliminated since conduction velocity in any part of the A-V node decreases with increasing rate. On the other hand, conduction in the His-Purkinje system is virtually unaffected by heart rate. We have found that these criteria for validating the His bundle potential by His bundle pacing apply equally as well in patients with normal A-V conduction as in those patients exhibiting severe disease of the His-Purkinje system (9).

Figure 4 shows tracings from a patient exhibiting right bundle branch block with left axis deviation, and an H-V time which was markedly prolonged, 95 msec. An abnormal QRS complex was simultaneously recorded in leads I, II, and AVF. His bundle pacing reproduced the H-V time of 95 msec as well as the same QRS configuration seen in all three ECG leads during sinus rhythm.

In figure 5, this same patient showed alternating bilateral bundle branch block during the study, but there were periods of left bundle branch block again with the characteristic QRS complex in all three leads, and now an H-V time of 90 msec. Pacing from the His bundle at this time reproduced the same QRS configuration and duration in all three leads as seen during sinus rhythm. Note also that the time from the stimulus to the onset of the earliest ventricular activity is the same with this bundle branch block pattern as the measured H-V time seen during sinus rhythm.

At this point, the matter of normal and abnormal H-V time should be mentioned. Normal values for A-V conduction have been battered about somewhat in the recent literature; therefore, we have scrutinized three published studies in which recordings from the His bundle have been obtained from 51 adult patients with so-called normal A-V conduction, that is, a P-R interval of 200 msec or less. Table I is a statistical analysis of the values from these various studies. It can be seen that the values in the study by Narula *et al.* (8) as well as from the study of Bekheit *et al.* (1) from Great Britain are closely comparable. In addition, if one assumes an average P-A time of 40 msec, the data

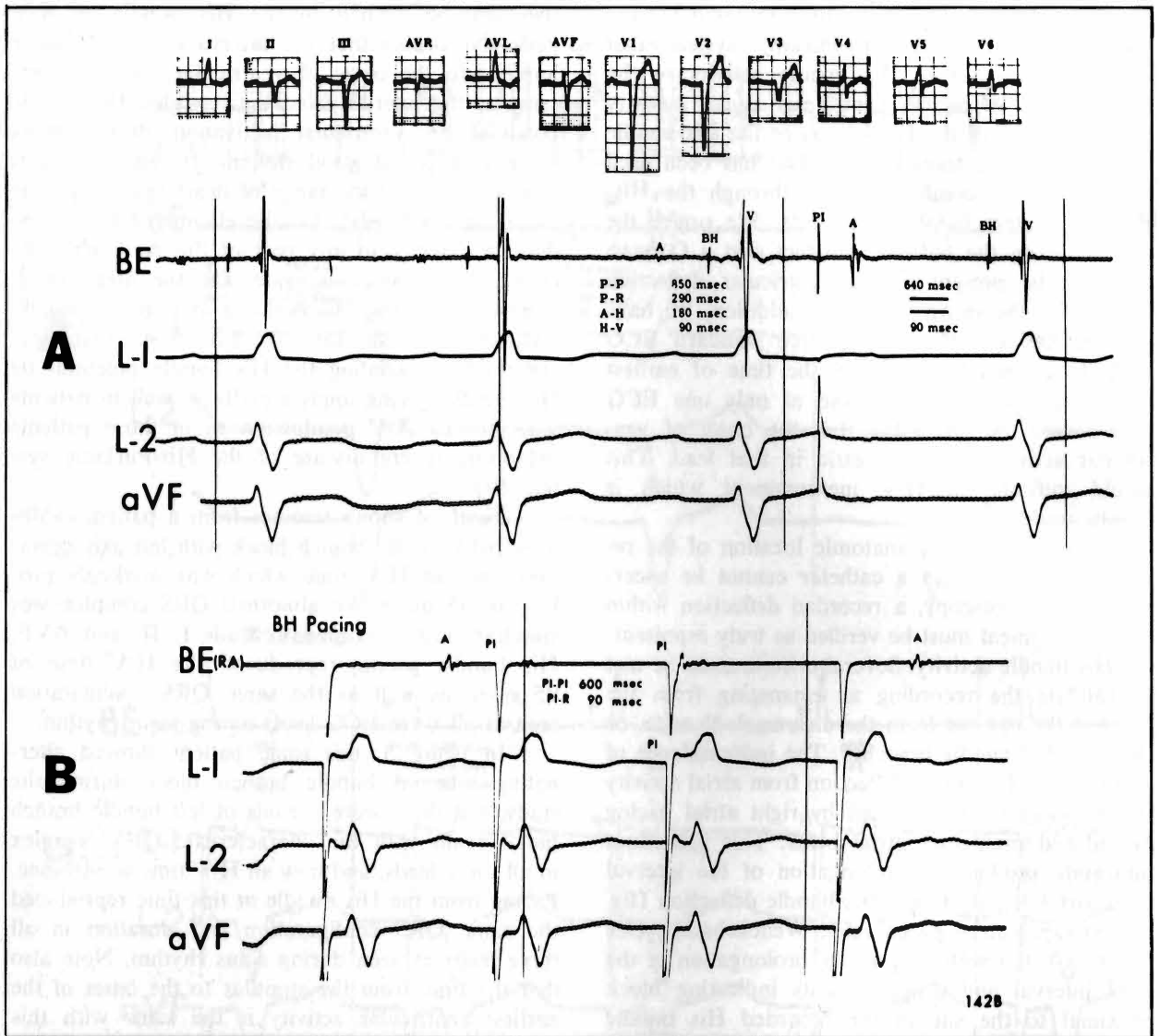


Fig. 4—Case W.A. Twelve standard ECG leads (top) from the same patient as in figure 3, whose pattern changed during study from right bundle branch block to left bundle branch block. A. Simultaneous bipolar electrograms (BE) recorded from the area of the A-V junction and standard ECG leads L-1, L-2, and AVF. The A-H time at P-P interval of 850 msec was 180 msec. The induced (PI) premature atrial systole (A) at P-P interval of 640 msec either blocked and was followed by an A-V junctional escape beat or conducted with an extremely prolonged A-H time. The H-V time of 90 msec was constant throughout. B. Bundle of His pacing at a rate of 100 per minute (PI-PI = 600 msec). The PI-R interval of 90 msec is equal to the H-V time during normal sinus rhythm. The shape of the QRS complex remains unaltered throughout. (Reproduced by permission of The American Heart Association, Inc. from O. S. Narula, *et al.* "Pervious Pacing of the Specialized Conducting System in Man: His Bundle and A-V Nodal Stimulation." *Circulation* 41:77, 1970.)

for heart rate P-R, P-A, A-H intervals in all three studies show good agreement. The lower and upper limits for the H-V interval, that is ± 2 standard deviations, in the last two studies are also in close accord, giving a range of 33 to 49 msec and 27 to 47 msec, respectively. In the study by Damato

et al. (5), the H-V intervals averaged 51 ± 12 with a range of 39 to 63 msec. Other laboratories have reported normal values of 35 to 55 msec, and in a more recent report, Damato and his group have indicated an average value of 45 msec for the normal H-V time in patients. Unfortunately, no tabulated

TABLE 1. "Normal" Values of A-V Conduction Intervals in Man (mean and standard deviation)

REFERENCE	BASAL HR (beats/min)	CONDUCTION TIME (msec)			
		P-R	P-A	A-H	H-V
Narula <i>et al.</i> (8)	67 ± 10	172 ± 11	43 ± 14	88 ± 21	41 ± 4
Damato <i>et al.</i> (5)	71 ± 8	167 ± 16	116 ± 14*		51 ± 6
Bekheit <i>et al.</i> (1)	64 ± 15	154 ± 19	37 ± 11	78 ± 18	37 ± 5

Basal HR = normal sinus rate; P-R = intra-atrial, A-V nodal and His-Purkinje conduction time; P-A, A-H, H-V. See text for discussion.

* This value represents the P-H interval consisting of P-A + A-H. See text for discussion.

(Reproduced by permission of The American Heart Association, Inc. from B. J. Scherlag, *et al.*, "His Bundle Electrogram," *Circulation* 46:606, 1972.)

data have been published to substantiate these ranges and average values. It should be emphasized that the determination of normal limits is of more than academic interest. Basic studies as well as recent clinical reports indicate a close association between prolongation of the H-V time and the existence of partial or complete bilateral bundle branch block. Other reports have shown a correspondence between an abbreviated A-H or H-V interval and anomalous A-V conduction.

It is generally considered that His bundle-electrocardiography has provided a more direct means for electrophysiological and diagnostic study of various clinical problems. However, these interpretations and diagnoses based on His bundle recordings must stand up to critical quantitative verification of the presumed His bundle deflection. Quantitative determinations of the interpretations based on His bundle-electrocardiographic measurements are critical, and in order to facilitate such determinations, greater standardization of measurements and terminology is required.

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Electrophysiology of Concealed Conduction*

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The phenomenon of cardiac excitation penetrating conducting tissue but failing to traverse it completely was called "concealed conduction" by Langendorf in 1948 (1). Earlier electrocardiographers had clearly demonstrated its occurrence. Since the introduction of this term in 1948, the concept of concealed atrioventricular (A-V) conduction has been invoked to explain many complex arrhythmias and has found wide application in clinical electrocardiography. In the clinical electrocardiogram, penetration of impulses that do not emerge from the A-V conduction system (concealed conduction) can be inferred from their influence on subsequent events such as 1) delay of conduction of a succeeding propagated response, 2) block of a succeeding atrial impulse which occurs at a time when the transmission system should have been excitable, 3) delay of the expected discharge of a junctional pacemaker, or 4) in some cases, facilitation or acceleration of a succeeding impulse.

In many early experimental, and most clinical investigations, the A-V node was thought to be the location in which antegrade as well as retrograde incomplete penetration of an impulse resulted in an effect on subsequent events. This was largely based upon the fact that the ECG only permits analysis of atrial and ventricular activity; electrocardiographers, therefore, considered the A-V node as the location where the atrial input was modulated to produce the resultant ventricular response pattern. Further refinements in microelectrode tech-

niques have allowed more precise localization of the area of concealed conduction as well as some insight into the mechanisms by which a nonpropagated impulse can block, delay, or accelerate subsequent conduction within the A-V node or His-Purkinje conduction systems, or both.

Several figures are presented here to demonstrate the different mechanisms of concealed conduction in which microelectrodes were used to record from the A-V node and His-Purkinje system together with simultaneously recorded atrial and ventricular electrograms. Of course, in a standard ECG, one would not be able to determine what was occurring within the specialized A-V conduction system, since only the information provided by the atrial and ventricular electrograms (P wave and QRS complex) would be available for interpretation.

Delays and block of antegrade conduction by premature beats are the most common examples of concealed conduction in man. The first illustration, recorded in an isolated rabbit atrioventricular preparation, shows an example of a premature ventricular contraction (PVC) causing complete A-V block of the subsequent sinus beat. This is due to the PVC partially penetrating the A-V conduction system. In figure 1, the upper trace is an electrogram recorded from the right atrium (RA), and the lower trace (RV) is an electrogram recorded from the right ventricular muscle. Simultaneously, transmembrane action potentials were recorded from a single A-V nodal fiber (AVN, second trace) and a single right bundle branch fiber (RBB, third trace). Time dots denote 100 msec intervals. The first atrial response was propagated from the atrium, through the A-V node, bundle of His (not recorded from), right bundle branch fibers and then to the

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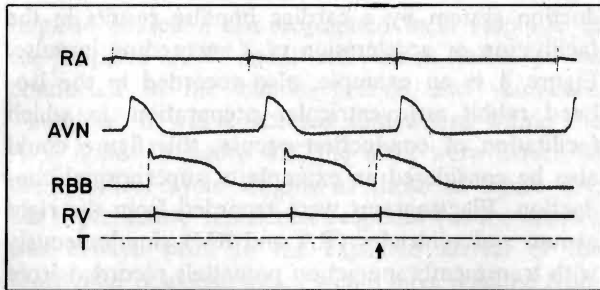


Fig. 1—A concealed ventricular premature response causing block of a normally conducted atrial activation. Bipolar electrograms were recorded in the isolated rabbit heart from the right atrium (RA) and right ventricles (RV), together with transmembrane potentials from the A-V node (AVN) and right bundle branch (RBB). The timing pulses (T) denote 100 msec. At the arrow, the preparation was prematurely activated by electrical stimulation through electrodes placed over the region of the right bundle branch. The third sinus response was blocked as a result of the premature ventricular response prematurely invading the A-V node. (Reproduced, with modifications, by permission of the *American Journal of Cardiology*, 28:409, 1971.)

ventricular myocardium. Following the first two normally conducted atrial beats, a premature ventricular contraction develops (third ventricular electrogram in the RV tracing). Retrograde conduction of this PVC is blocked as clearly shown by the failure of the third atrial response resulting in a ventricular response at the expected time. In this instance, the PVC was conducted retrograde and excited the A-V nodal fiber earlier than conduction from the atrium would have been expected to excite the impaled A-V nodal fiber. Note that the time between the third atrial to A-V nodal response is clearly shorter than either the normally conducted first or second beats.

Another important and commonly observed clinical example of the role that atrial rate plays in determining the occurrence and frequency of concealment is the fact that the ventricular response is more rapid during atrial flutter than during atrial fibrillation. In figure 2, extracellular atrial (RA) and ventricular electrograms (RV) were recorded simultaneously with transmembrane action potentials from a bundle of His fiber (BH) and right bundle branch fiber (RBB) in an isolated rabbit atrioventricular preparation during atrial flutter (fig. 2A) and during atrial fibrillation (fig. 2B). During atrial flutter, every other atrial response is blocked within the A-V node, as demonstrated by the absence of all-or-none bundle of His, right bundle branch, and

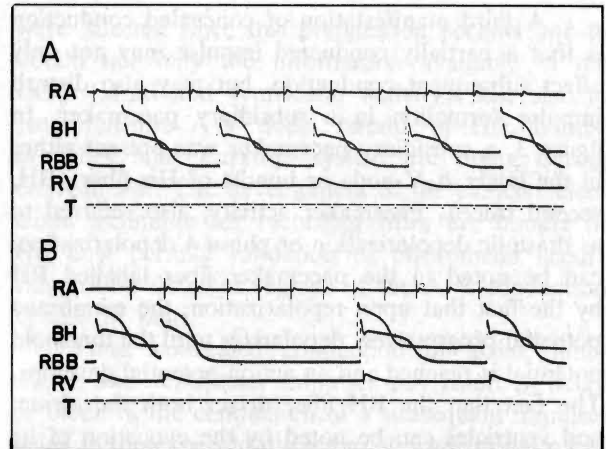


Fig. 2—Atrioventricular conduction during atrial flutter and fibrillation in the isolated rabbit heart. Bipolar electrograms were recorded from the right atrium (RA) and right ventricle (RV) together with transmembrane potentials from the bundle of His (BH) and right bundle branch (RBB). The timing pulses (T) denote 100 msec. A: the isolated atrioventricular preparation is driven from the atria at a cycle length of 300 msec. B: the atria are stimulated rapidly to simulate atrial fibrillation. (Reproduced, with modifications, by permission of the *American Journal of Cardiology*, 28:408, 1971.)

ventricular responses. During atrial fibrillation provoked by very rapid electrical stimulation of the atria, the ventricular response interval in the RV electrogram is slower and more irregular than during atrial flutter. During the long interval between the second and third ventricular responses (RV-RV), 5 atrial responses occur in the atrial electrogram which are not conducted to the bundle of His and the right bundle branch. All of the ventricular responses are delayed to various degrees within the A-V node. The degree of consecutive concealment governs the irregularity of the ventricular rate during atrial fibrillation.

Occasionally during atrial fibrillation, aberrant QRS complexes are recorded. This has been thought to result in some instances from escape of subsidiary pacemaker. However, we have observed that aberrant QRS complexes may result from block or concealed conduction within the right bundle branch. Similar findings have been reported in man during His bundle recordings. We believe, therefore, that variation in degree of concealed conduction within the A-V node is the most common cause of the irregular, slow R-R periods observed during atrial fibrillation.

A third manifestation of concealed conduction is that a partially conducted impulse may not only affect subsequent conduction, but may also disturb impulse formation in a subsidiary pacemaker. In figure 3, a subsidiary pacemaker was present either in the lower A-V node or bundle of His fiber (BH, second trace). Pacemaker activity, also referred to as diastolic depolarization or phase 4 depolarization, can be noted in the pacemaker fiber labelled BH by the fact that upon repolarization, the membrane potential progressively depolarizes until the threshold potential is reached and an action potential develops. The fact that the BH fiber drives both the atrium and ventricles can be noted by the evocation of its action potential prior to atrial, right bundle branch, or ventricular activity. Thus retrograde conduction to the atria and antegrade conduction to the ventricles occurs in the first two beats. Following the second atrial response, a premature atrial beat develops (third RA electrograms). This atrial response is conducted antegrade to the impaled BH fiber and prematurely fires a subsidiary pacemaker. Concealment is complete since the premature atrial beat fails to be propagated beyond the subsidiary pacemaker, that is, no action potentials occur at either the RBB or RV recording sites. In this instance, the development of the next expected discharge of the subsidiary BH pacemaker was delayed by 58 msec due to the premature discharge of the BH pacemaker.

The fourth example of concealed conduction is one where partial penetration of the A-V con-

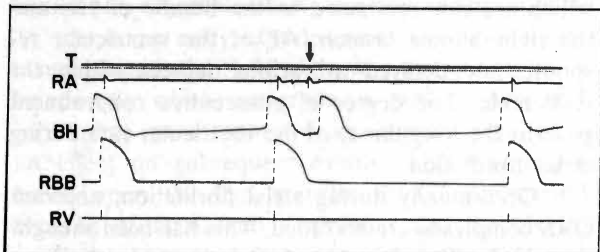


Fig. 3—Premature atrial activation causing “resetting” of a junctional pacemaker. Bipolar electrograms were recorded in the isolated rabbit heart from the right atrium (RA) and right ventricle (RV), together with transmembrane potentials from the bundle of His (BH) and right bundle branch (RBB). The timing pulses (T) denote 10 msec. At the arrow, the preparation was prematurely activated by electrical stimulation through electrodes placed on the right atrium. (Reproduced, with modifications, by permission of the *American Journal of Cardiology*, 28:410, 1971.)

duction system by a cardiac impulse results in the facilitation or acceleration of a succeeding impulse. Figure 4 is an example, also recorded in the isolated rabbit atrioventricular preparation, in which facilitation of conduction occurs; this figure could also be considered an example of supernormal conduction. Electrograms were recorded from the right atrium and ventricles (RA and RV) simultaneously with transmembrane action potentials recorded from the A-V node (AVN) and right bundle branch (RBB). In figure 4A, the atria were driven at a constant rate, and basic atrial responses were conducted antegrade to the ventricles as shown by the first 2 atrial beats. The third atrial response was evoked prematurely, and it can be seen that the

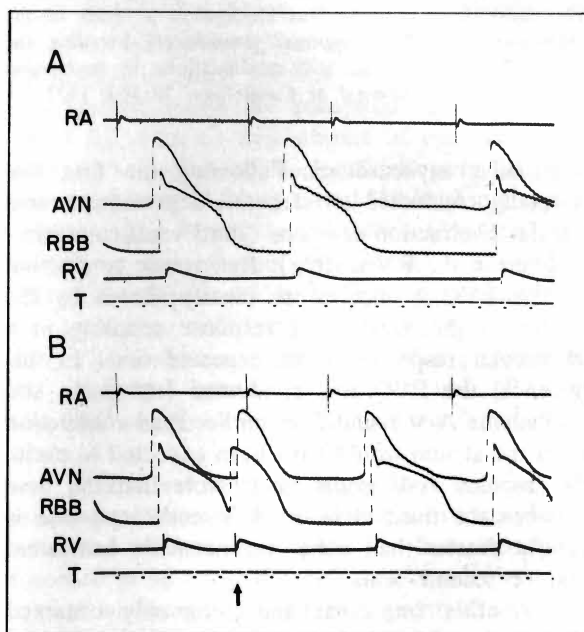


Fig. 4—A concealed ventricular premature activation causing conduction of a previously blocked atrial activation. Bipolar electrograms were recorded in the isolated rabbit heart from the right atrium (RA) and right ventricle (RV), together with transmembrane potentials from the A-V node (AVN) and right bundle branch (RBB). The timing pulses (T) denote 100 msec. The sequence of atrial activation was identical in A and B. In A, note that the third atrial response was not conducted to the ventricles but was blocked within the A-V node with only a local nonpropagated response occurring (unpublished data, Moore and Spear). At the arrow in B, the preparation was prematurely activated by electrical stimulation through electrodes placed over the region of the right bundle branch. (Reproduced, with modifications, by permission of the *American Journal of Cardiology*, 28:412, 1971.)

impulse caused a nonpropagated local response in the impaled A-V nodal cell which failed to be conducted to the bundle branch and ventricles. Therefore, it was concealed somewhere within the A-V node. In figure 4B, the atria were driven at the identical cycle lengths as those in figure 4A, but a premature ventricular response (at the arrow) was evoked prior to the expected arrival of the ventricular response which would have resulted from antegrade conduction of the second atrial response. This ectopic ventricular response was conducted retrograde to the impaled A-V nodal cell. The second atrial complex was evoked at precisely the same time as in figure 4A; however, conduction of this atrial response to the impaled A-V nodal cell was blocked since the impaled A-V nodal fiber was excited by the premature ventricular response. Therefore, bidirectional collision occurred somewhere above the impaled A-V nodal fiber. The premature atrial response (third atrial RA response) occurred at identical times in panels A and B. However, the response in figure 4B, unlike that in 4A, was conducted to the ventricles because the concealed premature ventricular response facilitated conduction of the premature atrial response by peeling back a refractory barrier within the A-V node. Figure 4B, then, is an example of concealed conduction which resulted in the development of facilitated or "supernormal" conduction.

In summary, I have tried to present examples and mechanisms for concealed conduction. Illustrations recorded in the isolated rabbit A-V preparation

were selected since this preparation permits one to obtain not only the information available in the ECG (atrial and ventricular activity), but also to see what the A-V node, bundle of His, bundle branches, and Purkinje system are doing during concealment. The development of the catheter electrode technique for recording from the bundle of His now permits validation of phenomena occurring within different regions of the A-V conduction system in man.

Thus, concealed conduction of atrial, junctional, and ventricular impulses can result in delay or block in the conduction of a subsequent impulse, delay in the expected discharge of a junctional pacemaker or, occasionally, facilitation or acceleration in conduction of a subsequent impulse. Concealed conduction is also involved in producing the irregular ventricular response during atrial fibrillation.

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Clinical Significance of Exit Block*

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The confinement of an ectopic discharge to its focus, and its consequent inability to invade the adjacent myocardium when falling outside of the refractory period of the heart, is a well established phenomenon called "exit block." This cardiac arrhythmia was originally described by Kaufmann and Rothberger (8) to explain the failure of a parasystolic focus to activate the heart. All pacemakers are subject to exit block (9, 13, 15, 14, 11, 16, 12, 3, 10, 7, 1), however, by convention, conduction disturbances involving the sinus node (S-A block) are usually excluded from this concept, and the term is reserved for ectopic pacemakers. Recent electrophysiological and clinical studies have shown that exit block may complicate reentrant arrhythmias and may be of either Wenckebach type I or II (2, 5). Several examples of exit block will be discussed in an attempt to show some different clinical aspects of this mechanism.

Sinoatrial Block. In figure 1, precordial leads, V1-3 demonstrate a sinus rhythm at a rate of approximately 65 per minute. The P-R interval measures 0.13 seconds, and the QRS complexes are of normal contour and duration. The first P-P interval in V3 measures 0.84 seconds, the second, 1.76 seconds, the third P-P, 0.96 seconds, the fourth, 0.86 seconds, and the fifth P-P interval, 1.84 seconds.

This is an instance of sinoatrial block. The second and fifth P-P intervals are longer than twice the shorter P-P intervals. Such variation of P-P intervals could be explained by Wenckebach conduction from the sinus node to the atria. Sinoatrial block is a true form of exit block, but the term is ordinarily

reserved for ectopic pacemakers, rather than the sinus node.

High Grade Atrioventricular Block. In virtually all instances, exit block occurs in the presence of higher degrees of A-V block. Failure of the impulse to propagate from the subsidiary ectopic focus to either the ventricles, atria, or both is characteristic of this form of exit block. Several examples are illustrated. In figure 2, there is high grade A-V block causing A-V dissociation. The atria are under the control of the sinus node at a rate of 71 per minute, and the ventricles are controlled by a subsidiary ectopic pacemaker, probably originating in the right bundle branch at a rate of approximately 40 per minute. In AVL the two first R-R intervals measure 1.46 seconds after the third QRS complex; a long pause of 2.74 seconds occurs, probably due to exit block from the Purkinje pacemaker, and only atrial activation is seen. In another instance of high-grade A-V block (fig. 3), sinus tachycardia is present at a rate of 105 per minute. There is complete A-V dissociation, and the ventricles are under the control of a sub-junctional pacemaker, probably located in the right bundle branch system, at a rate approximately of 25 per minute. In aVF and V1, the R-R intervals are almost the same with a duration of 2.40 seconds. However, the first R-R interval in V2 is 2.64 seconds and suggests concealed conduction to the level of the subsidiary pacemaker. The second R-R interval in V2 measures 5.72 seconds and is longer than twice the R-R intervals in aVF and V1, probably due to a combination of both exit block and concealed conduction as is shown by the diagram. In figure 4, three records are taken from a patient with an inferior myocardial infarction. A high degree of A-V block is present. The

* Presented by Dr. Dreifus at the Symposium on Cardiac Arrhythmias, June 8, 1972, at Virginia Beach, Virginia.

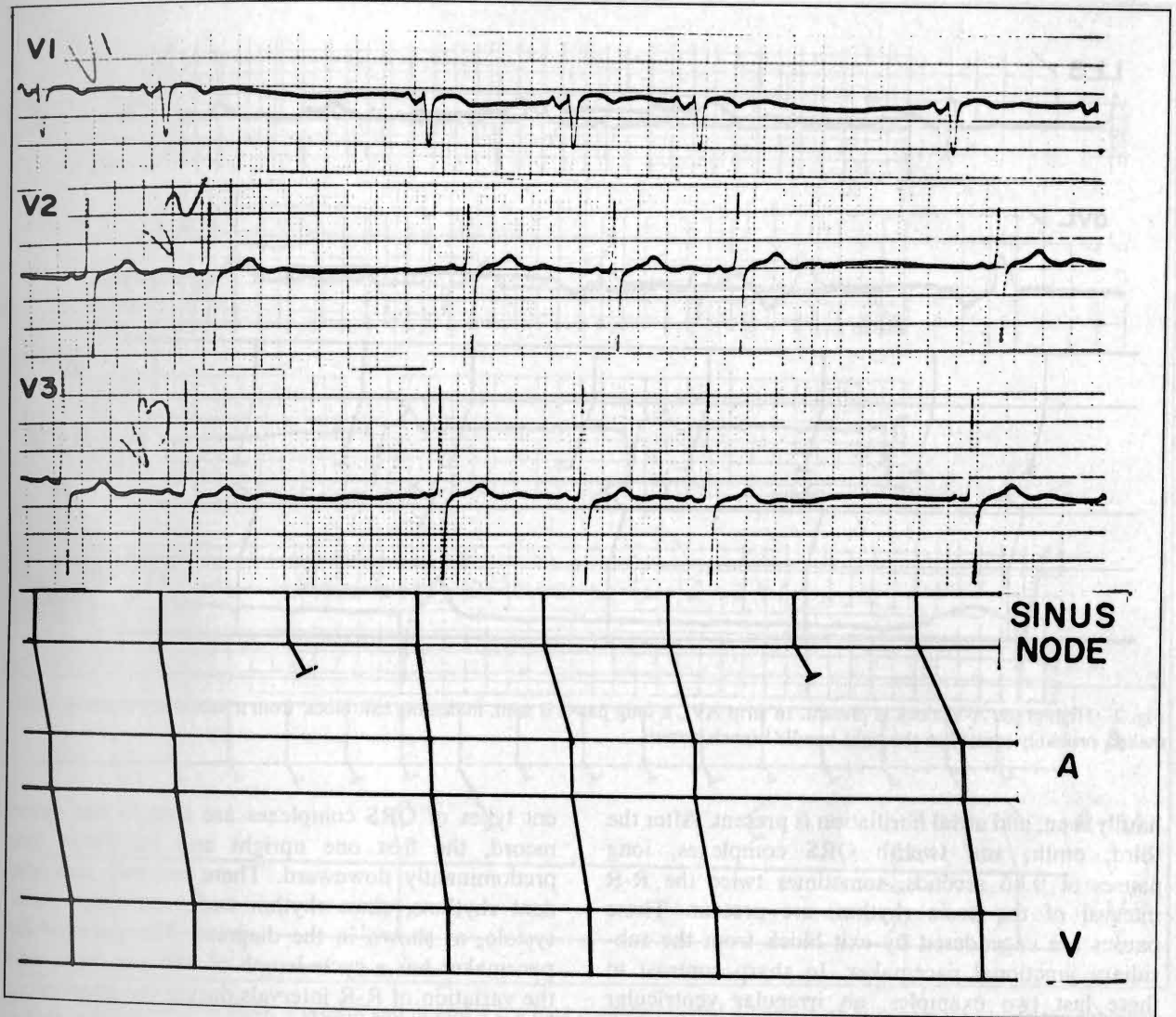


Fig. 1—Sinoatrial block. Three sinus beats are seen followed by a pause. The fourth P wave is not visible as 4:3 block occurs between the sinus node and atria as seen in diagram.

atria are under the control of the sinus node at a rate of 91 per minute, and the ventricles are under a control of a junctional pacemaker at a rate of 66 per minute. In B, longer pauses are observed, but the atrial rate is decreased to 83 per minute, and the ventricular rate is 63 per minute. In C, the atrial rate is 97 per minute, and the ventricular rate is 32 per minute. The R-R intervals measure 1.87 seconds, twice the R-R interval seen in B, probably due to exit block of the junctional pacemaker.

In many instances, high-grade A-V block may be associated with atrial fibrillation. Exit block from

the subsidiary pacemaker can be easily identified if the block occurs with a precise conduction ratio as seen in figure 5. In this example, there is atrial fibrillation, and the ventricles are under the control of a junctional pacemaker at a rate of 64 per minute. In V2, the R-R intervals become more prolonged and measure 1.83 seconds, almost twice that seen in I and II, and are probably due to exit block from the subsidiary junctional pacemaker. Another example of this problem is illustrated in figure 6. Junctional tachycardia is present at a rate of approximately 125 per minute. The atrial activity is

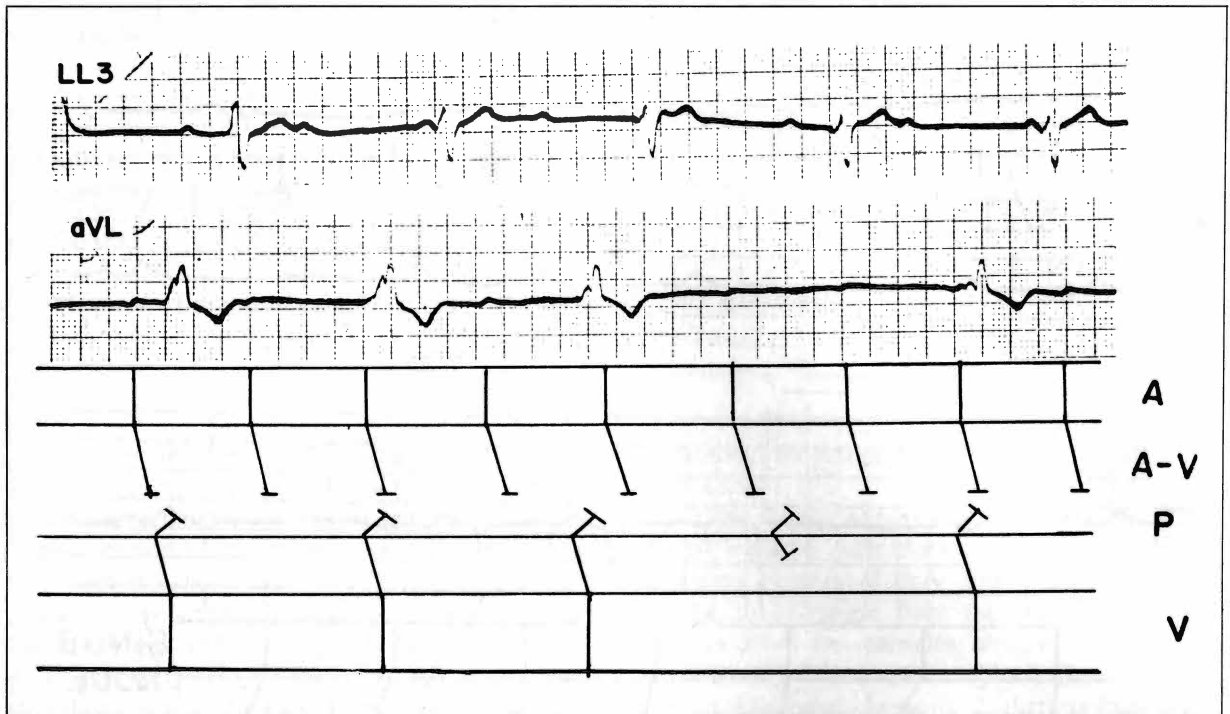


Fig. 2—High-grade A-V block is present. In strip AVL a long pause is seen, indicating exit block from a subsidiary Purkinje pacemaker, probably located in the right bundle branch system.

hardly seen, and atrial fibrillation is present. After the third, ninth, and twelfth QRS complexes, long pauses of 0.86 seconds, sometimes twice the R-R interval of the basic rhythm, are present. These pauses are engendered by exit block from the subsidiary junctional pacemaker. In sharp contrast to these last two examples, an irregular ventricular response in the presence of atrial fibrillation can cause some diagnostic confusion unless Wenckebach conduction from the subsidiary pacemaker is considered. In figure 7, atrial fibrillation is present. The ventricles are under the control of a junctional pacemaker at a rate of approximately 136 per minute. The R-R intervals as seen by the diagram vary slightly. After the seventh QRS complex, right carotid sinus pressure was applied, and the R-R intervals became prolonged from 0.44–0.46 to 0.88 seconds, twice the R-R intervals seen previously. This is due to exit block from a subsidiary junctional pacemaker. At the end of record B, 2:1, 3:2, and 4:3 ratios are seen. This variation of R-R intervals in B is caused by Wenckebach conduction from the subsidiary junctional pacemaker.

Ventricular Parasystole. In figure 8, two differ-

ent types of QRS complexes are seen in the upper record, the first one upright and the other one predominantly downward. There are two independent rhythms, sinus rhythm and ventricular parasystole, as shown in the diagram. The parasystolic pacemaker has a cycle length of 580 per msec, and the variation of R-R intervals during the parasystole is due to Wenckebach phenomenon in the transmission of the impulse from the ectopic parasystolic pacemaker to the ventricles. When exit block of the parasystolic pacemaker occurs with a ratio of 4:3, sinus impulses are transmitted to the ventricles. The coupling intervals show slight variation beats in 2, 6, 10, 14, 18.

Among the clinical examples, figure 1 was presented to demonstrate a similar mechanism between sinoatrial block and exit block. Hence, only the failure of an ectopic pacemaker to activate adjacent myocardium is considered exit block. However, other authors admit that exit block can occur in all excitable tissues of the heart with pacemaker or latent pacemaker properties (2, 6). Thus, if the latter assumption is accepted, it would be very hard to differentiate sinoatrial block from exit block of

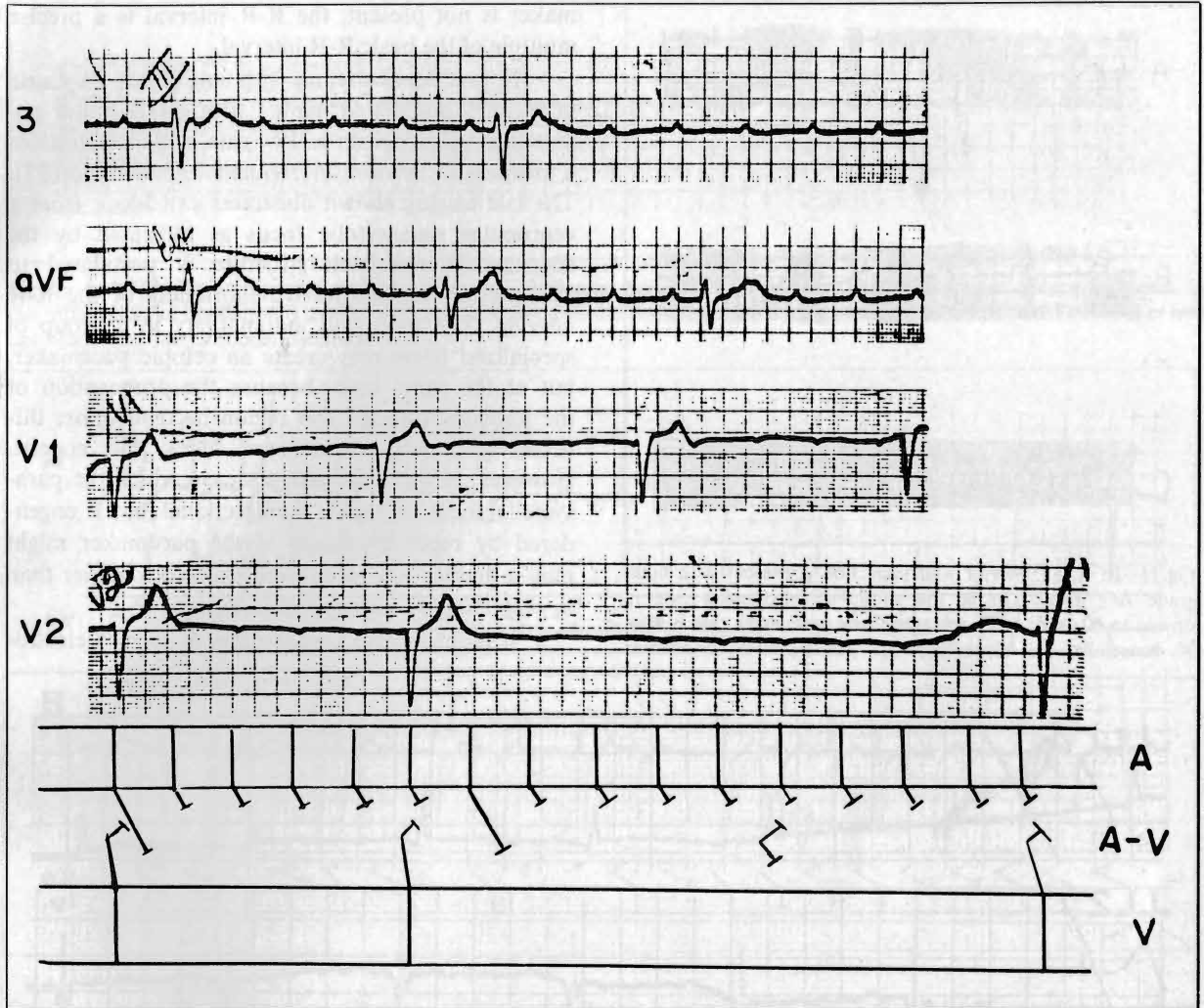


Fig. 3—High-grade A-V block is present and in lead V2, a long diastolic interval is seen which is greater than twice the subsidiary junctional pacemaker rate. Two possibilities may be considered: (1) exit block from the subsidiary pacemaker and (2) concealed penetration into the subsidiary pacemaker by one of the sinus beats, delaying the rhythmicity of the subsidiary pacemaker.

sinus impulse origin. It is true that fibers possessing high degrees of automaticity such as those in the sinoatrial node generally show a lower level of resting membrane potential, a smaller action potential amplitude, and a markedly slower rate of depolarization than other cardiac fibers. These factors engender a slower conduction velocity and may even cause decremental conduction and precipitate exit block (4, 6). In fact, loss of resting membrane potential due to phase 4 depolarization in fibers surrounding the actual pacemaker may produce slow conduction, fractionation of the wave front, decrement, and finally, exit block.

Exit block at a level of the junctional pacer,

the Purkinje tissue, and the ventricular parasystolic pacemaker focus were shown above. However, exit block is most commonly observed in junctional rhythms with accelerated impulse formation due to digitalis excess (13, 17).

In figure 3, a combination of concealed conduction and exit block is shown in the ladder diagram. The differentiation between these two rhythm disturbances by electrocardiographic techniques is made by the identification of concealed conduction. Note that the R-R interval is shorter than two basic R-R intervals in the presence of exit block. Since Wenckebach conduction from the junctional pacer,

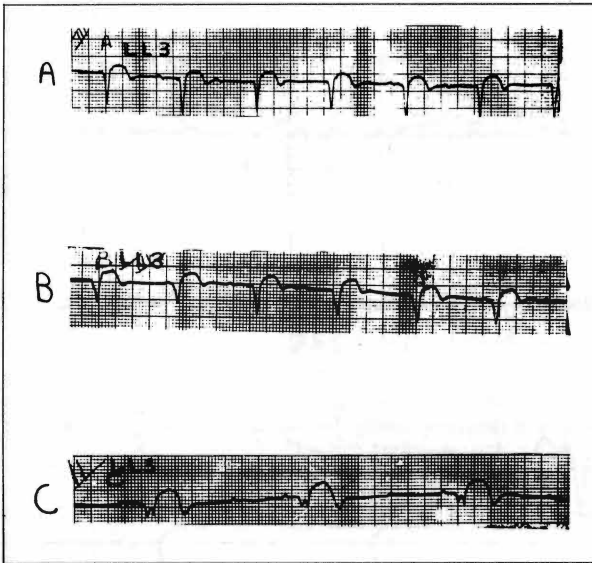


Fig. 4—In A, an inferior wall infarction is present with high-grade A-V block; In B, the subsidiary pacemaker rate is slowed to 60/min; In C, the subsidiary pacemaker rate is now 30, hence, 2:1 exit block from this pacemaker is considered.

maker is not present, the R-R interval is a precise multiple of the basic R-R interval.

In junctional rhythm with exit block, the cause of block is attributed mainly to a small action potential amplitude with a slow rate of depolarization, a mechanism favoring decremental conduction (17). The last tracing shown illustrates exit block from a ventricular parasystolic focus as indicated by the diagram. Wenckebach structure is postulated to account for the progressive shortening of the R-R interval. The increased automaticity in a group of specialized fibers may create an ectopic pacemaker, but at the same time, because the propagation of the impulses through this region becomes more difficult, both entrance and exit block may coexist. However, in this particular case, in which the parasystolic focus is rapid, unidirectional block engendered by rapid discharge of the pacemaker might play a greater role in causing exit block rather than in protecting the parasystolic focus.

It is impossible on the basis of surface electro-

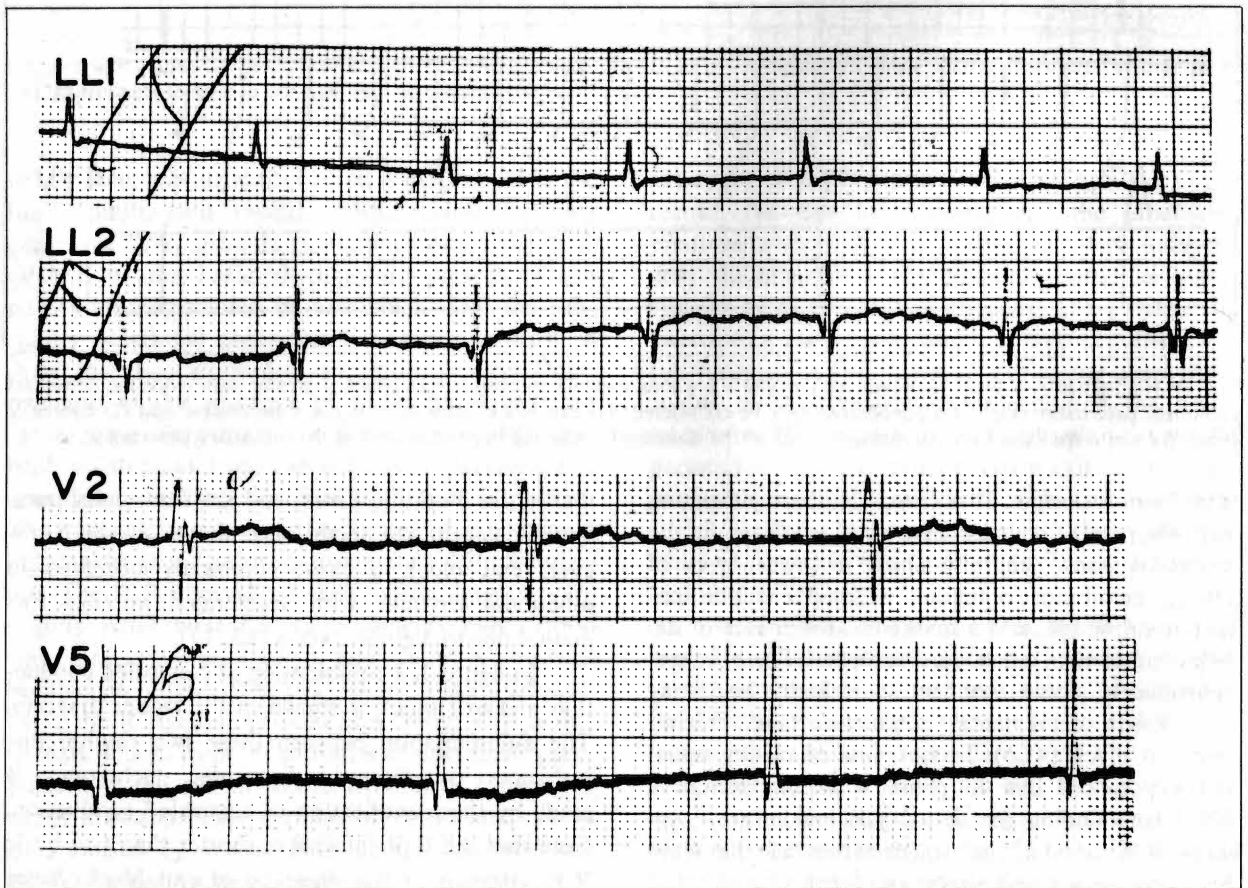


Fig. 5—In the upper two strips, atrial fibrillation is present, although the ventricular rate is quite regular at 60/min. In the lower two strips, the rate is 30/min, hence, exit block from the subsidiary pacemaker is present in the face of atrial fibrillation.

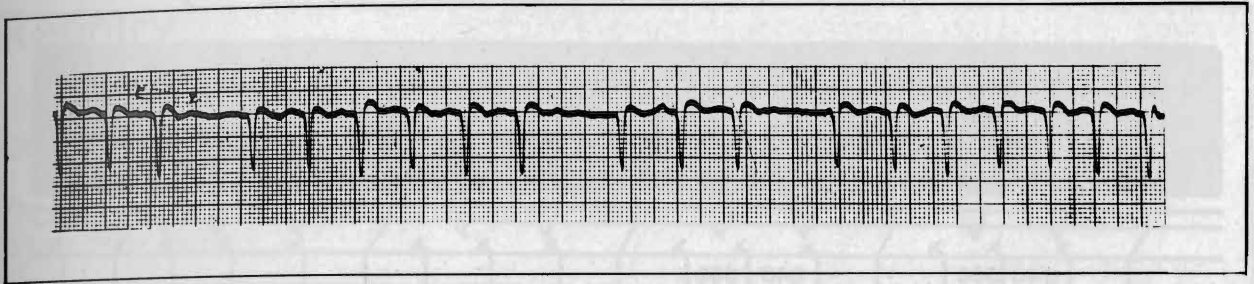


Fig. 6—Atrial fibrillation is present with group beating. The longer diastolic pauses are equal to two of the basic junctional beats. In this instance, atrial fibrillation is present with complete A-V dissociation due to A-V block, with escape of junctional pacemaker and exit block from the junctional pacemaker.

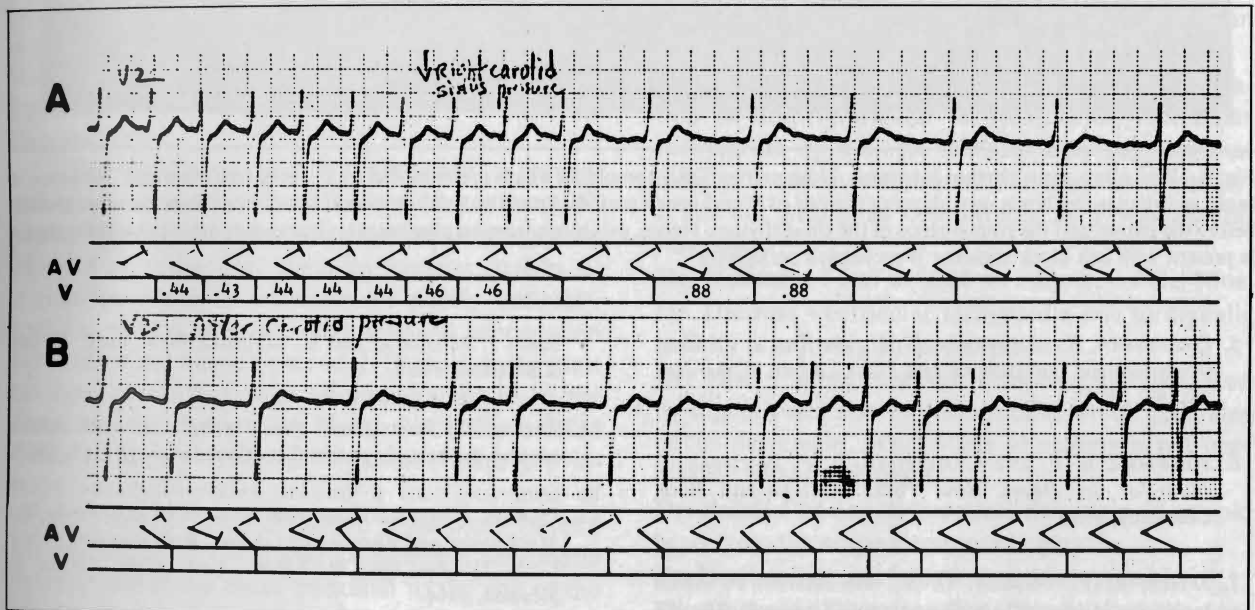


Fig. 7—A. At the left-hand portion of the strip, a rapid regular rhythm is present at 140/min. Following right carotid sinus pressure, the rate in the right portion of the strip is slowed to 75/min, and 2:1 exit block from the subsidiary junctional pacemaker is present. B. Here the rhythm is irregular although group beating is seen, particularly bigeminy. Wenckebach conduction from the subsidiary pacemaker is present.

cardiograms to be certain if the exit block is due to alteration in phase 4 of the pacemaker action potential or to failure of conduction once the impulse leaves the pacemaker cell (5). However, electrophysiological studies and *in vivo* experiments have shown that exit block is a result of conduction depression surrounding the site of impulse formation and can be a feature of both an automatic and reentrant rhythm (2, 4, 17).

Summary. Clinical features of exit block were shown and its probable electrophysiological mechanisms discussed. Based on recent electrophysiological studies, it is emphasized that exit block is a result of depressed conduction surrounding the ectopic pacemaker.

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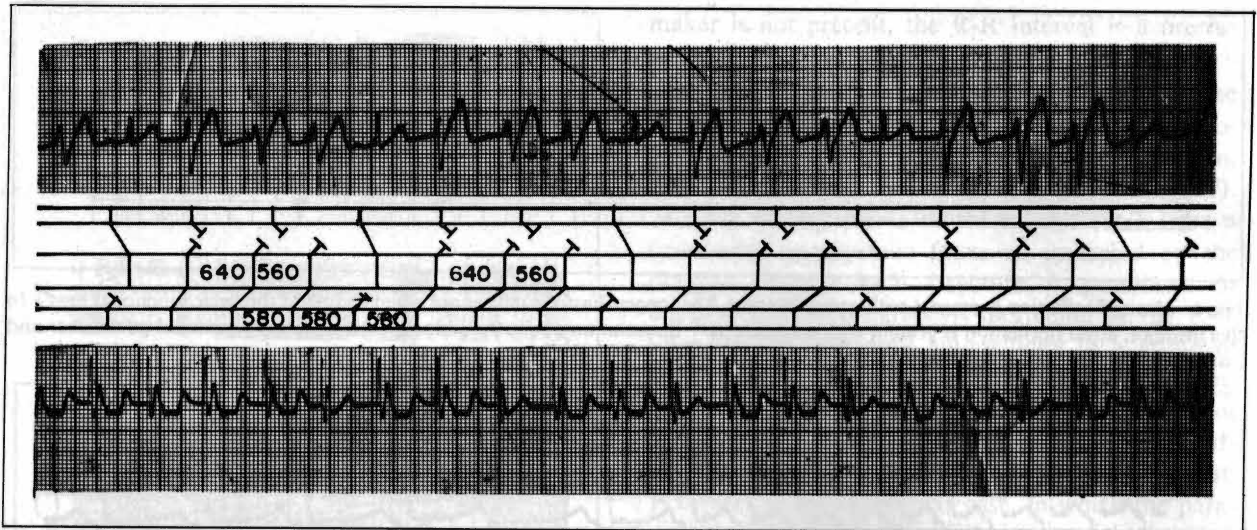


Fig. 8—Basically a sinus rhythm is present. Note narrow QRS complexes which are preceded by P waves (see diagram). However, a rapid ventricular rhythm is seen showing periods of Wenckebach periodicity as the R-R interval of the ectopic beats becomes shorter before the pauses and the reemergence of the sinus rhythm. Hence, exit block from an accelerated, ventricular parasystolic tachycardia is present with exit block showing Wenckebach periodicity.

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Reentry*

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There are two ways in which impulses can be generated: one is by the spontaneous discharge of a pacemaker cell in either the normal site or a subsidiary site, and the other is by reentry. The concept of reentry is a very old one postulated by clinical cardiologists many years before its demonstration.

The conditions that are necessary to permit this to happen have been known for at least 75 years. First of all, the conduction pathway must be blocked at some site; thus, an impulse arrives at a junction which is refractory or poorly excitable, and the margin of safety for continued propagation falls below the magic figure of 1. Second, there must be slow conduction over an alternate route to the tissue beyond the site of block. Since the cardiac tissue is largely syncytial in nature, there are always alternate routes around a localized area of block. Third, delayed excitation must occur beyond the site of the block. If that excitation is sufficiently delayed and if the tissue proximal to the site of the block is by that time recovered, it can then be excited from the opposite direction, and this would complete the circuit. Reentry can and probably does commonly happen. Reentry may be concealed; in other words, there may be localized reentrant activity which never escapes from that site because of refractoriness in the conduction pathway.

Therefore, it does not appear on the surface electrocardiogram, and it may not even appear in records from localized electrodes. So I repeat: of the four conditions necessary, the *sine qua non* is block. There has to be block for reentry to occur. Second, there is slow conduction over an alternate route to the tissue beyond the block; and third, there is delayed activation of that tissue beyond the block, and finally, reentry occurs.

* This is a transcription, edited by Dr. Charles L. Baird, Jr., of a lecture presented by Dr. Moe at the Symposium on Cardiac Arrhythmias, June 8, 1972, at Virginia Beach, Virginia.

PANEL DISCUSSION

Dr. Baird: Is it possible to differentiate from the scalar electrocardiogram whether the mechanism of ectopic beats is due to reentry or automaticity?

Dr. Moe: I do not think it is possible. The termination of supraventricular tachycardia or ventricular tachycardia by a single stimulus only suggests that reentry is the mechanism rather than automaticity. I am not nearly as comfortable as I was several years ago.

Dr. Hoffman: I feel at least as insecure as Dr. Moe.

Dr. Dreifus: Ventricular tachycardia due to digitalis toxicity is probably on an ectopic basis.

Dr. Moe: I agree, however, ectopic activity initiated by digitalis can also be the stimulus which generates circus movement. What starts something is not necessarily what continues it.

Dr. Baird: Can one differentiate the origin of ectopic beats from the scalar electrocardiogram?

Dr. Dreifus: I do not believe that this is possible.

Dr. Hoffman: Digitalis affects the cells of the specialized conduction system, and ectopic rhythms arise because of the depression of these specialized fibers which are more sensitive to the digitalis effects than ventricular muscle. Evidence is also accumulating that the internodal tracts of the atrium are more sensitive to the effects of digitalis than the atrial muscle fibers.

Dr. Moore: We have produced unifocal ventricular tachycardia experimentally in dogs, and mapping studies demonstrated that the left ventricle was the origin of the ectopic rhythm. Isolated studies of the Purkinje fibers from both the right and left ventricles also demonstrated that the left side was more sensitive.

Dr. Dreifus: Clinically, the ectopic beats occur at the site of the preexisting conduction block. However, it is very difficult to determine from where ventricle ectopic beats are arising, since the scalar electrocardiogram only provides the axis deviation.

The Gouaux-Ashman Phenomenon: His Bundle Recordings*

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The differentiation of ventricular premature beats from supraventricular beats with aberrant ventricular conduction is often difficult on the basis of the surface electrocardiogram. The diagnosis of aberrant conduction has been based largely on the presence of a right bundle branch block pattern appearing in a short cycle subsequent to a longer cycle (2). Several other criteria for diagnosing aberrant conduction of a supraventricular beat such as variable coupling time have been used to differentiate these abnormal ventricular complexes from ventricular premature beats which are most commonly followed by a full compensatory pause. This differentiation is often inexact and under some critical clinical circumstances cannot be accomplished with any degree of reliability. In 1947, Gouaux and Ashman wrote a report entitled: "Auricular Fibrillation with Aberration Simulating Ventricular Paroxysmal Tachycardia" (2). It is thus in the clinical context of atrial fibrillation that the diagnosis of aberrant conduction of supraventricular beats as opposed to ventricular tachycardia becomes particularly difficult. Recent reports in the literature have emphasized the use of the His bundle-electrocardiographic technique as a means of differentiating between aberrant conduction and ventricular ectopic complexes (3, 4, and 6). In order to evaluate this method of differentiation, it is important to note the physio-

logical behavior of A-V nodal and His bundle conduction under these two circumstances.

Figure 1, taken from a study by Damato *et al.* (1), shows the response of the His-Purkinje system to atrial premature beats delivered at varying intervals after the previous cardiac cycle. A slight degree of aberration can be seen even with no prolongation of the H-V or H-Q time. However, more marked aberration occurs with the prolongation of His-Purkinje conduction time from 45 to 65 msec. Finally, block is shown distal to the recorded His bundle deflection, and these properties of the His-Purkinje system during premature activation have been confirmed in other clinical laboratories. Therefore, the normal response to atrial premature or His premature beats which result in aberrant ventricular conduction is either an unchanged or prolonged H-V time.

In contrast to the constancy or prolongation of the H-V interval during supraventricular beats conducted with aberration, ventricular ectopic beats or fusion beats show either no His potential preceding the aberrant QRS complex or a shortened H-V time. In figure 2, the His bundle-ECG tracings reveal an H-V time of 50 msec with a wide QRS complex. Note that the P-R interval is 190 msec during sinus rhythm. In the second beat in panel A, a shortening of the P-R interval from 190 to 175 msec with a narrowing of the QRS complex is observed. Also, a shortening of the H-V time to 35 msec occurred. That this beat represents in fact a fusion of a normally conducted atrial impulse and a ventricular ectopic beat is indicated in panels B and C. Here the P-R shortens to 135 msec in the sec-

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ond beat of each panel with a negative H-V time, that is, ventricular activity precedes His bundle activity by 5 msec and 20 msec, respectively. It can be seen that the change in H-V time from normal is appropriately matched by the change in the P-R interval.

Unfortunately, these quantitative aspects of the His bundle recording in regard to ventricular ectopic beats and supraventricular beats conducted with aberration have been essentially ignored in several recent publications. In a report by Lau *et al.* (3), the authors were the first to note that the recording of His bundle activity represents a valid method for diagnosing aberrant conduction, particularly in differentiating supraventricular beats and ventricular premature contractions of ventricular tachycardia. However, in illustrating this point, a case of atrial fibrillation was examined with simultaneous recordings of His bundle electrogram and a standard ECG lead (fig. 3). The authors state that the second complex in this figure is a supraventricular beat conducted from above with aberrant ventricular activation. However, the H-V time is clearly shorter in this beat than in the normally conducted beats, 1, 4, and 6. Note that the H-V time is measured from the H deflection to the earliest ventricular activation which in this case is the standard ECG lead. In the normally conducted beats, the earliest ventricular activation occurs in the His bundle electrogram.

In another recent report by Massumi, a case was presented (fig. 4) in which the first two beats shown are sinus beats showing atrial, His bundle, and ventricular activity. The third beat shows a QRS complex which the author describes as a pattern of "incomplete right bundle branch block and left axis deviation suggesting impaired conduction through the right bundle branch and superior division of the left bundle branch." Massumi localizes the extrasystolic focus as occurring within the His bundle and bases this conclusion on the observation that this extrasystole is preceded by a His bundle potential. However, it should be noted that the H-V time of this third beat is markedly shortened compared to the H-V time seen during sinus beats. Both of the previous records can be interpreted as ventricular beats arising in the proximal portion of the right or left bundle branch which are simultaneously conducted antegrade to the ventricular myocardium and retrograde to the His bundle. Under these circumstances the QRS would be aberrant and if one were only recording His bundle activity, this poten-

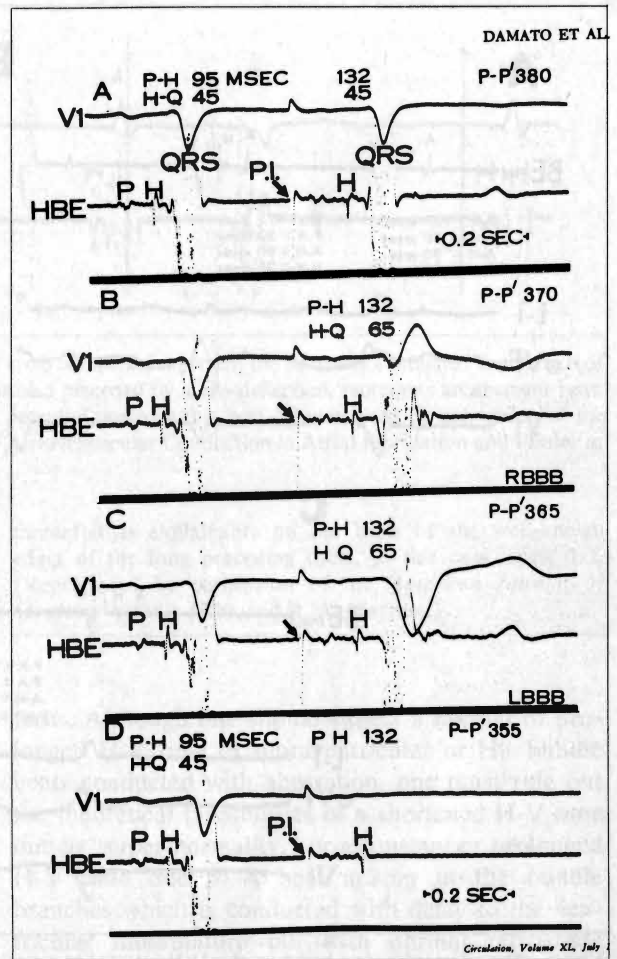


Fig. 1—In panels A through D, the top tracing is a lead V_1 and the bottom tracing a His bundle electrogram (HBE). When the atrium was prematurely stimulated at a coupling interval of 380 msec (panel A), a delay in A-V conduction occurred as manifested by an increase in the P-H interval to 132 msec. The H-Q interval remained constant, and ventricular depolarization was only slightly altered. Shortening the coupling interval to 370 msec (panel B) and 365 msec (panel C) resulted in aberrant ventricular depolarization (RBBB and LBBB) with an associated prolongation of the H-Q interval. At a coupling interval of 355 msec (panel D), complete block below the His bundle resulted. (Reproduced by permission of the American Heart Association, Inc. from Damato, A. N. *et al.* "A Study of Atrioventricular Conduction in Man Using Premature Atrial Stimulation and His Bundle Recordings." *Circulation* 40:64, 1969).

tial would appear before the QRS with a shortened H-V time.

Just such recordings have been made in our clinical laboratory by Narula *et al.* (5). Figure 5 shows a simultaneous recording of His bundle and left bundle activity during sinus rhythm in a patient

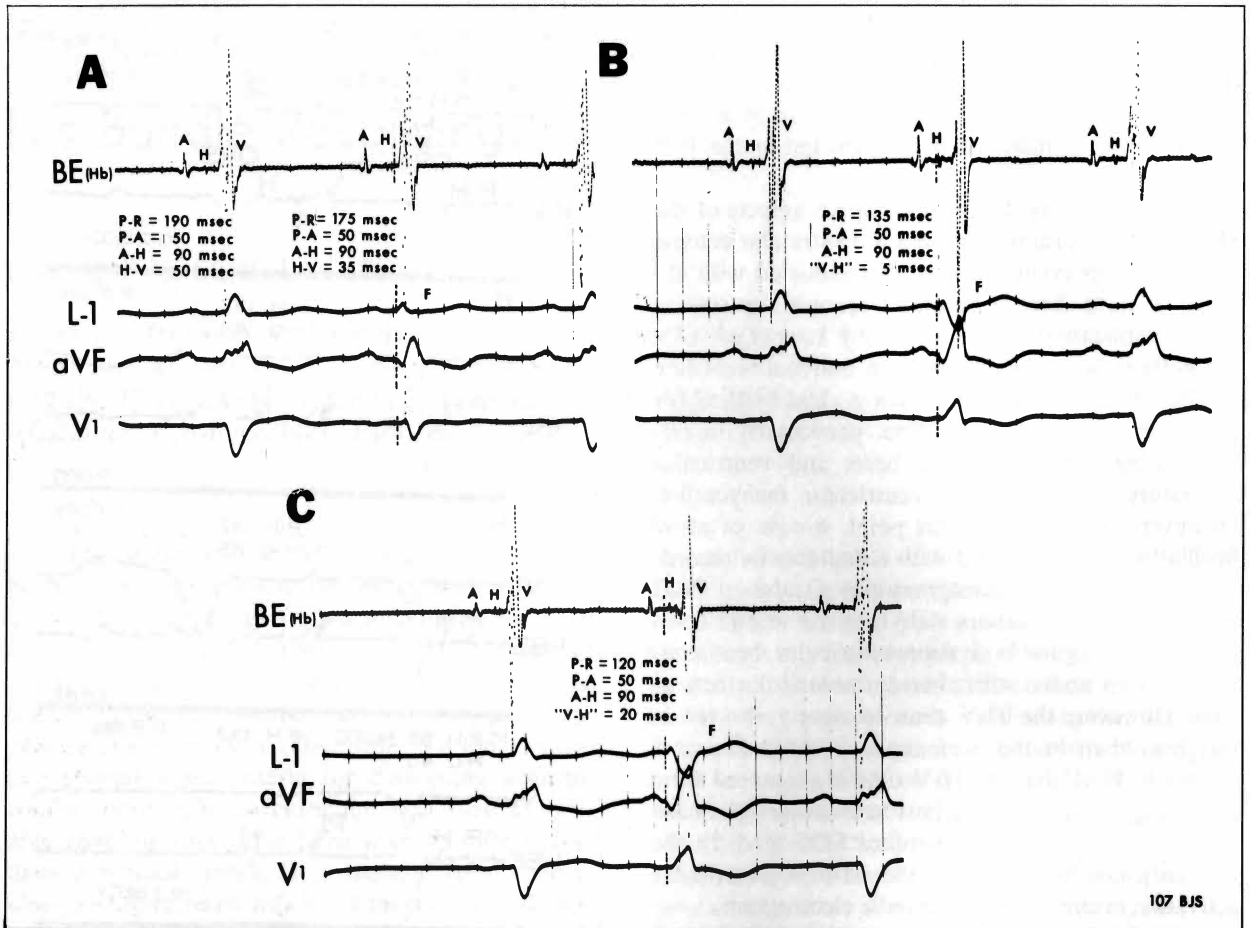


Fig. 2—The effect of fusion beats on the H-V interval in a patient with intermittent ventricular ectopic beats. Traces from above: Bipolar His bundle electrogram (BE, Hb) and 3 simultaneously recorded ECG leads I, AVF, and V₁. A. During sinus beats, the P-R of 190 msec was composed of intra-atrial conduction time (P-A = 50 msec), A-V nodal conduction (A-H) = 90 msec and His-Purkinje conduction (H-V) = 50 msec. A fusion beat (F) caused a shortening of the "P-R" to 175 msec entirely due to H-V diminution of 15 msec (50-35 msec). The vertical dotted line indicates the earliest ventricular activation in all leads. B. Another fusion beat (2nd complex marked F) causes a further shortening of the P-R to 135 msec and a reversal of the H-V with the onset of ventricular activation preceding His bundle activation by 5 msec. C. Another fusion beat (F) produced "normalization" of the QRS complex as compared to other beats. Note that the shortening of the P-R in each case is matched exactly by the alteration in H-V or V-H time; the P-A and A-H interval remain constant throughout. The interval between time lines equals 100 msec.

with a normal QRS complex. The second beat in panel A shows left bundle activity preceding His bundle activity during ventricular premature contractions which probably arose in the area of the proximal left bundle. In panel B, a series of beats arising in the same region of left bundle activity preceding His bundle activity is seen. Without the left bundle recording, one could interpret the aberrant beats with a shortened H-V time as arising in the His bundle and conducting through the ventricles aberrantly.

In conclusion, it is important to state that the use of His bundle-electrocardiography in differentiating supraventricular beats with aberration from ventricular beats requires a critical approach to the interpretations of deflections appearing in the P-R segment. The use of quantitative rather than qualitative tests is essential when only the His bundle recording is used as opposed to the simultaneously recorded activity from the proximal bundle branches. In some cases, His bundle pacing may be helpful in reproducing spontaneously occurring aberrant pat-

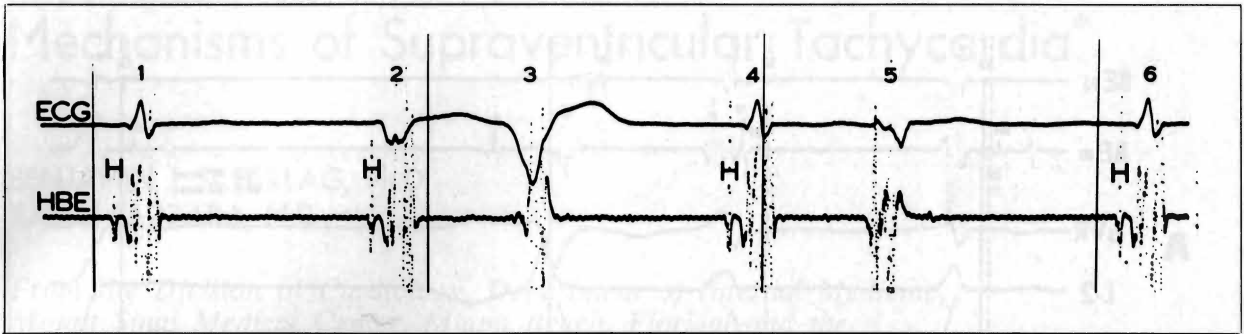


Fig. 3—In this clinical case of atrial fibrillation, the first, fourth, and sixth complexes represent the normally conducted beats, each of which is preceded by a His deflection. The second complex, which is also preceded by a His deflection, represents an aberrant beat. The third complex is a premature ventricular contraction. No His potential precedes this beat. (Reproduced by permission of the American Heart Association, Inc. from Lau, S. H. *et al.* "A Study of Atrioventricular Conduction in Atrial Fibrillation and Flutter in Man Using His Bundle Recordings." *Circulation* 40:73, 1969).

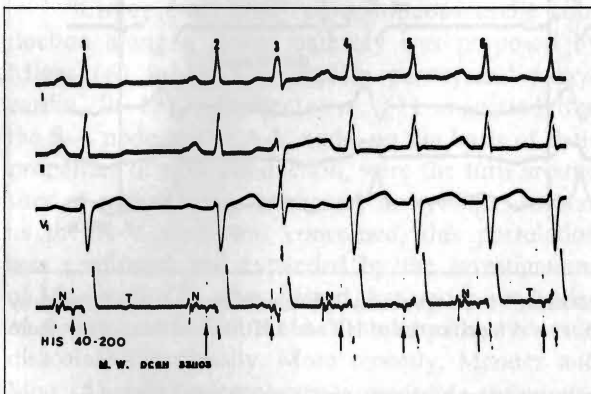


Fig. 4—Simultaneous recording of leads I, II, and V_1 together with His bundle potentials recorded from the main His bundle. The sinus P waves before beats 1, 2, 4, 6, are clearly visible in leads I and II and also in the His bundle recording just before the atrioventricular node potentials marked N. Note that the His bundle potentials, marked by arrows, precede not only the QRS of the sinus beats 1, 2, 4, 6, but also the interpolated extrasystoles 3, 5, and 7. The aberrant intraventricular conduction of the first interpolated extrasystole No. 3, is of the incomplete right bundle branch block and left axis deviation type, suggesting impaired conduction through the right bundle branch and the superior division of the left bundle branch. Our localization of the extrasystolic focus within the His bundle is based on the observation that the extrasystoles 3, 5, and 7 are preceded by His bundle potentials but not by atrioventricular node potentials like the sinus beats. Had they arisen from the atrioventricular node, the atrioventricular node potentials would have also been recorded just before the His potentials of the extrasystoles. This indicates that the extrasystoles originate below the atrioventricular node. The low frequency, low amplitude distortion of the baseline seen before the His potential of the extrasystoles represents the T wave of the preceding beat, two of which are marked with T. Finally, the reason for aberration of the first beat of the run of tachycardia with normal conduction

thereafter is explainable on the basis of the well-known effect of the long preceding cycle, in this case, cycle 1-2. (Reproduced by permission of the *American Journal of Medicine* 49:267, 1970, and R. A. Massumi).

terns. Although one should expect a normal or prolonged H-V time in supraventricular or His bundle beats conducted with aberration, one must rule out the theoretical possibilities of a shortened H-V time due to "super-normality," or a constant or prolonged H-V time due to a beat arising in the bundle branches which is conducted with delay to the ventricular musculature but with normal retrograde conduction to the His bundle.

Author's note: We thank Mrs. Marie Ellis for her dedicated assistance in the preparation of this manuscript.

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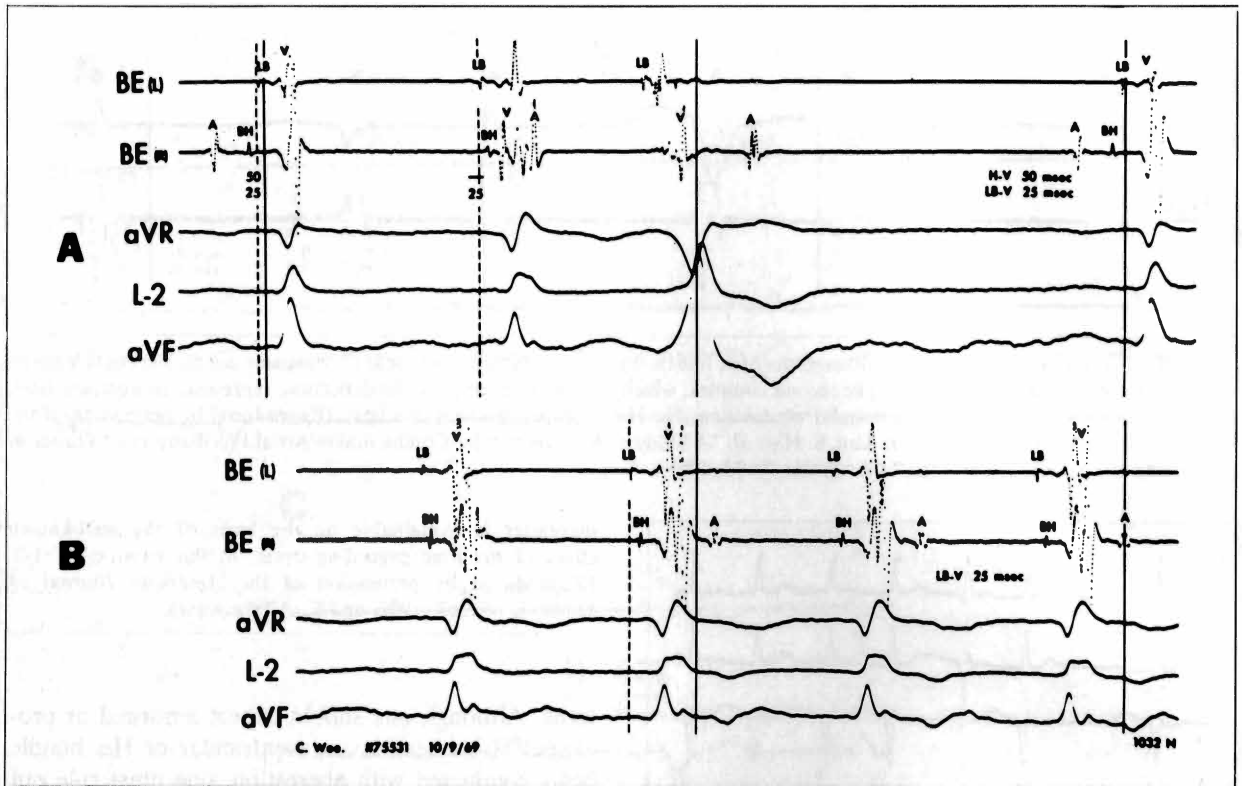


Fig. 5—Case 5: Retrograde activation of the BH by premature “ventricular” beats (probably left bundle beats). (Reproduced by permission of the American Heart Association, Inc. from Narula, O. S. *et al.* “Significance of His and Left Bundle Recordings from the Left Heart in Man.” *Circulation* 42:395, 1970).

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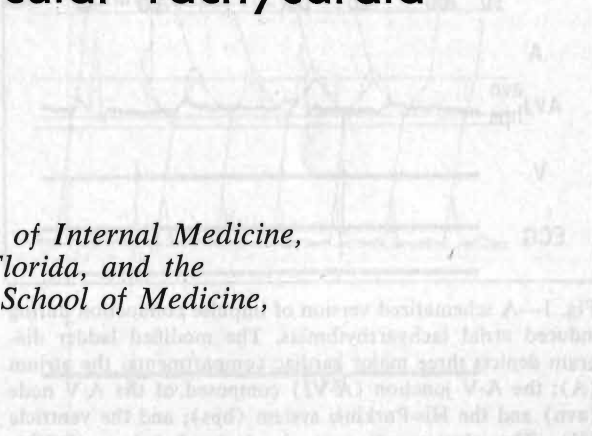
Mechanisms of Supraventricular Tachycardia*

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"Circus movement" or continuous cyclic conduction along a closed pathway was proposed by Mines (6) in 1913 to explain paroxysmal tachycardia. In 1943, Barker *et al.* (1) suggested that the S-A node or the A-V node, on the basis of their properties of slow conduction, were the turn around sites of such a circus or reentry arrhythmia. Insofar as the A-V node was concerned, this postulation was confirmed and expanded by the investigations of Moe *et al.* (7) who showed that under conditions of slowed conduction the A-V nodal pathways could dissociate functionally. More recently, Mendez and Moe (5) using microelectrode recording techniques have found that areas within the A-V node can be identified as the sites of rebound or echo beats which returned to the atrium. Wit *et al.* (13) were able to induce paroxysmal tachycardias in isolated portions of rabbit atria containing the A-V node. Clinically, Goldreyer and Bigger (2), induced and terminated, in patients with a predisposition to paroxysmal supraventricular tachycardia, periods of supraventricular tachycardia with appropriately placed atrial premature beats. Their evidence from His bundle recordings pointed to the A-V node as a site of reentry for these paroxysmal supraventricular tachycardias in man.

In figure 1, a schematic representation is shown of the series of events that might occur in the course of an induced period of supraventricular tachycardia. After a normally conducted sinus beat (SB), an



atrial premature beat (APB) occurring spontaneously or electrically induced is conducted slowly through the A-V node. If the A-V nodal delay is great enough to produce functional longitudinal dissociation, a reentrant pathway can be set up either giving rise to one rebounding beat into the atrium, an echo beat (EB), or a continuous circuit may ensue within the A-V node with atrial and ventricular responses being thrown out of the node with each intra-nodal circuit. The interruption of the circuit can occur due to another atrial premature beat thus terminating the paroxysm and reinstating sinus activity. There is both clinical and experimental evidence supporting the intra-A-V nodal circuit as the prime mechanism involved in reentry arrhythmias such as paroxysmal atrial tachycardias or in reciprocal beating. On the other hand, there are studies which clearly indicate that the atrium participates in the reentry pathway. For example, in the study of Wit *et al.* (13), these authors found that excision of a large portion of atrial muscle prevented the induction of paroxysmal tachycardia in the isolated rabbit preparation, and Goldreyer and Bigger (3) also indicated on the basis of A-V nodal conduction times during paroxysmal supraventricular tachycardia in patients that the atrium was involved in the reentry path. Thus, in our schematic representation, we have indicated by the dotted lines the possibility that activity echoing back from the A-V node, the first site of reentry, can enter the atrium, which serves as the second site of reentry, to continue the paroxysmal tachycardia. It is at this point, where intra-atrial reentry is implicated that one encounters a controversy that has occupied a great deal of journal space

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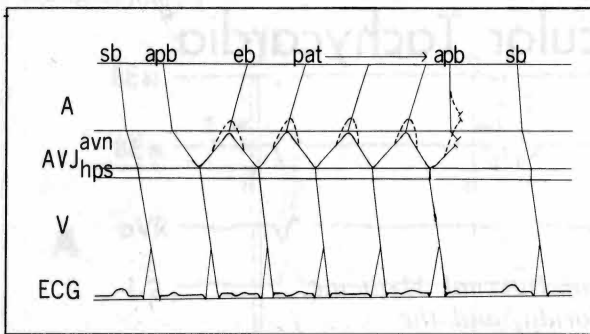


Fig. 1—A schematized version of impulse conduction during induced atrial tachyarrhythmias. The modified ladder diagram depicts three major cardiac compartments: the atrium (A); the A-V junction (A-VJ) composed of the A-V node (avn) and the His-Purkinje system (hps); and the ventricle (V). The electrocardiogram is depicted below (ECG). Other abbreviations are: sb = sinus beats; apb = atrial premature beats; eb = echo beats; pat = paroxysmal atria tachycardia. See text for discussion.

recently. In looking at the schematic, particularly the atrial bridge, one notices that at the point at which atrial activation must reverse itself atrial refractoriness must be infinitely rapid or another area of slow conduction must be postulated to account for the atrial bridge. In a recent issue of *Chest*, Surawicz (11) has concisely addressed himself to this point and indicates that the electrophysiologist must return to the drawing board, so to speak, in order to elucidate mechanisms by which the atrial bridge hypothesis can be substantiated. Below, we would like to present evidence for perhaps one mechanism by which an intra-atrial bridge or a second reentry site may be involved in paroxysmal supraventricular tachycardias.

Our investigations were based on an interesting observation and clever postulation made by Vassalle, Greenspan, and Hoffman in 1963 (12). They observed that a ventricular escape beat which terminated a vagal arrest of the heart often initiated atrial fibrillation. They postulated that in some way the retrograde impulse entering the atrium proceeded in a heterogeneous fashion so that the dissociated atrial wave front could establish a return pathway(s) within the atrium thereby initiating atrial flutter or fibrillation.

We were able to reproduce this phenomenon and analyze atrial activation patterns (fig. 2). In panel A, close bipolar electrograms were recorded in various parts of the dog atria in order to find the earliest and latest epicardial areas of activation.

These corresponded to the high right atrium in the area of the sinus node and the inferior-posterior left atrium, respectively. The total antegrade atrial activation time, that is the time from the beginning of the earliest activation to the end of the latest activation or total atrial activation time (AA), was 100 msec. In contrast, during ventricular pacing with retrograde atrial activation, AA was only 65 msec. Note that the sequence of activation during retrograde conduction showed low atrial activity occurring first and sinus activity as well as posterior left atrial activation occurring last.

In panel C, an asystolic interval with a ventricular escape time equal to 12 seconds due to vagal stimulation was terminated by a ventricular escape beat which produced a normal retrograde atrial activation pattern. Note that the sequence of activation as well as the total atrial activation is the same during this retrograde atrial activation as that seen with ventricular pacing in panel B. No arrhythmia occurred subsequent to this ventricular and atrial beat. In the same animal, panel D, with a 13-second asystolic period, a ventricular escape beat was associated with activation of the atria which differs markedly from the normal retrograde atrial activation pattern. Although the first area to be activated in the low right atrium is in the area of the coronary sinus ostium, the other low right atrial region approximately 3–5 mm away is activated later. Note that in panel C, both areas were activated almost simultaneously. Total duration of retrograde atrial activation now occupies 100 msec instead of the normal 65 msec. Subsequent to this initial aberrant atrial activation pattern atrial fibrillation ensued. In those animals in which ventricular escape beats often produced runs of atrial fibrillation, this phenomenon of dispersion of atrial activation was regularly seen and was clearly related to the occurrence of atrial arrhythmias.

We found that the dispersion of atrial activation was not limited to ventricular escape beats with retrograde atrial activation. It also occurred commonly with retrograde Wenckebach cycles (fig. 3). During ventricular pacing at 120 beats per minute there was regular 1:1 retrograde atrial activation. The total atrial activation time was 55 msec. When the ventricular rate was increased to 145 per minute, the Wenckebach phenomenon was seen with a reciprocal beat. The retrograde atrial activation interposed between the ventricular and normal sinus beat shows a total activation time of 65 msec com-

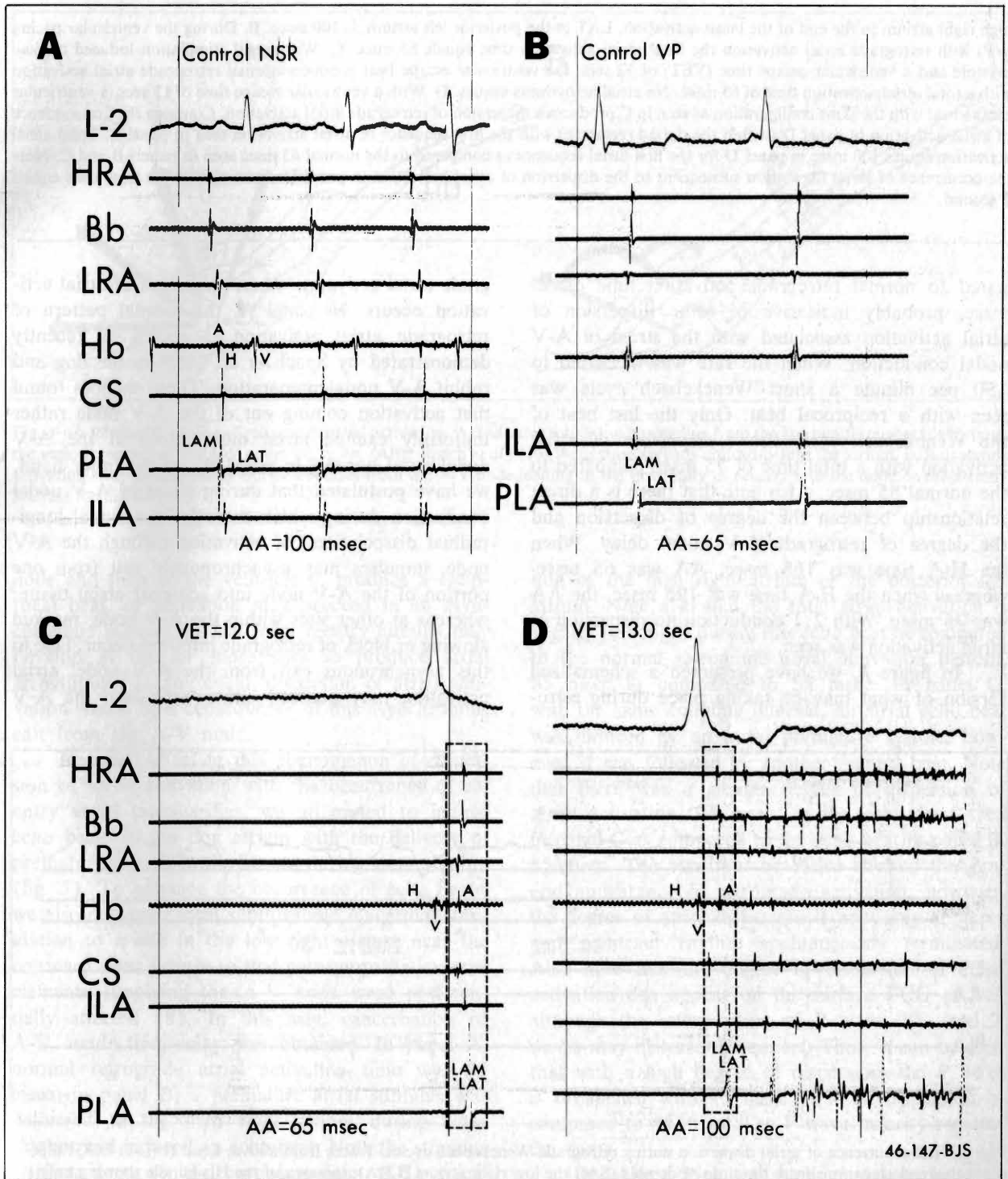


Fig. 2—The phenomenon of atrial fibrillation associated with a ventricular escape beat during vagal induced cardiac arrest. Traces from top down: Lead II (L-2) ECG; bipolar plunge wire electrograms from the high right atrium (HRA); Bachmann's bundle (Bb); low right atrium (LRA); His bundle region (Hb) showing atrial (A), His bundle (H), and ventricular (V) activation; coronary sinus ostium (CS); posterior left atrium (PLA) showing left atrium muscle (LAM), and left atrial tract (LAT) potentials (13); and from the inferior left atrium (ILA). A. Total atrial activation time (AA) measured from the beginning of the earliest activation in the

high right atrium to the end of the latest activation, LAT in the posterior left atrium, is 100 msec. B. During the ventricular pacing (VP) with retrograde atrial activation the total atrial activation time equals 65 msec. C. With vagal stimulation induced cardiac asystole and a ventricular escape time (VET) of 12 secs, the ventricular escape beat produces normal retrograde atrial activation with a total atrial activation time of 65 msec. No atrial arrhythmia ensues. D. With a ventricular escape time of 13 secs, a ventricular escape beat with the same configuration as seen in C produces a dispersion of retrograde atrial activation. Compare the first sequence of atrial activation in panel D (within the dotted rectangle) with the first sequence of atrial activation seen in panel C. Total atrial activation equals 100 msec in panel D for the first atrial sequence as compared to the normal 65 msec seen in panels B and C. Note the occurrence of atrial fibrillation subsequent to the dispersion of atrial activation in panel D. Interval between time lines equals 1 second.

pared to normal retrograde activation time of 55 msec, probably indicative of some dispersion of atrial activation associated with the stress of A-V nodal conduction. When the rate was increased to 150 per minute a short Wenckebach cycle was seen with a reciprocal beat. Only the last beat of the Wenckebach cycle shows dispersion of atrial activation with a total time of 75 msec compared to the normal 55 msec. Also note that there is a direct relationship between the degree of dispersion and the degree of retrograde A-V nodal delay. When the H-A time was 165 msec, AA was 65 msec, whereas when the H-A time was 195 msec, the AA was 75 msec. With 2:1 conduction no dispersion of atrial activation was seen.

In figure 4, we have presented a schematized version of what may be taking place during retro-

grade atrial activation when dispersion of atrial activation occurs. In panel A, the normal pattern of retrograde atrial activation is shown as recently demonstrated by Spach *et al.* (10) in the dog and rabbit A-V nodal preparation. These authors found that activation coming out of the A-V node rather uniformly excited atrial musculature at the A-V nodal-atrial border. In panel B, on the other hand, we have postulated that during stress of A-V nodal conduction during which there is "functional longitudinal dissociation" of activation through the A-V node, impulses may asynchronously exit from one portion of the A-V node into adjacent atrial tissue; whereas at other sites within the A-V node, marked slowing or block of retrograde impulses occur. Due to this asynchronous exit from the A-V node, atrial activation may proceed either back into the A-V

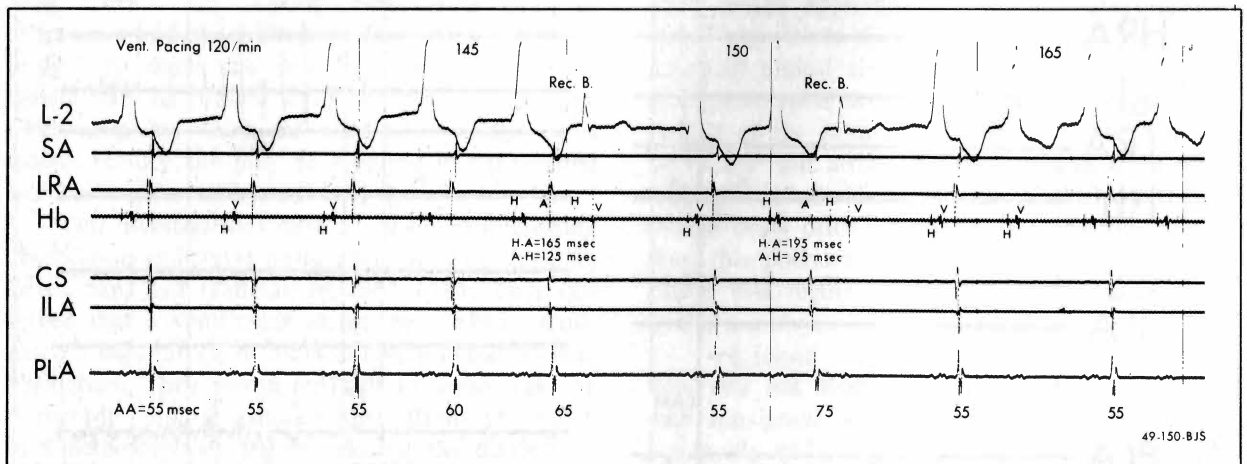


Fig. 3—The occurrence of atrial dispersion during retrograde Wenckebach cycles. Traces from above: Lead II (L-2) ECG; bipolar plunge wire electrograms from the sinus node area (SA); the low right atrium (LRA); the area of the His bundle showing only His bundle activity (H) and ventricular activation (V); coronary sinus ostium (CS); the inferior left atrium (ILA); and the posterior left atrium (PLA). During ventricular pacing at 120 per minute with 1:1 retrograde conduction, atrial activation time (AA) equals 55 msec. As the rate is increased to 145 per minute, a Wenckebach cycle occurs ending in a reciprocal beat (Rec. B). Note that the total atrial activation time increases from 60 to 65 msec just prior to the reciprocal beat and coincident with the retrograde Wenckebach cycle. With a ventricular pacing rate of 150 per minute, another Wenckebach cycle occurs and now the beat prior to the reciprocal beat shows dispersion of atrial activation, 75 msec. With ventricular pacing at 165 per minute there is 2:1 retrograde conduction with no change in the atrial activation pattern or total atrial activation time from the normal.

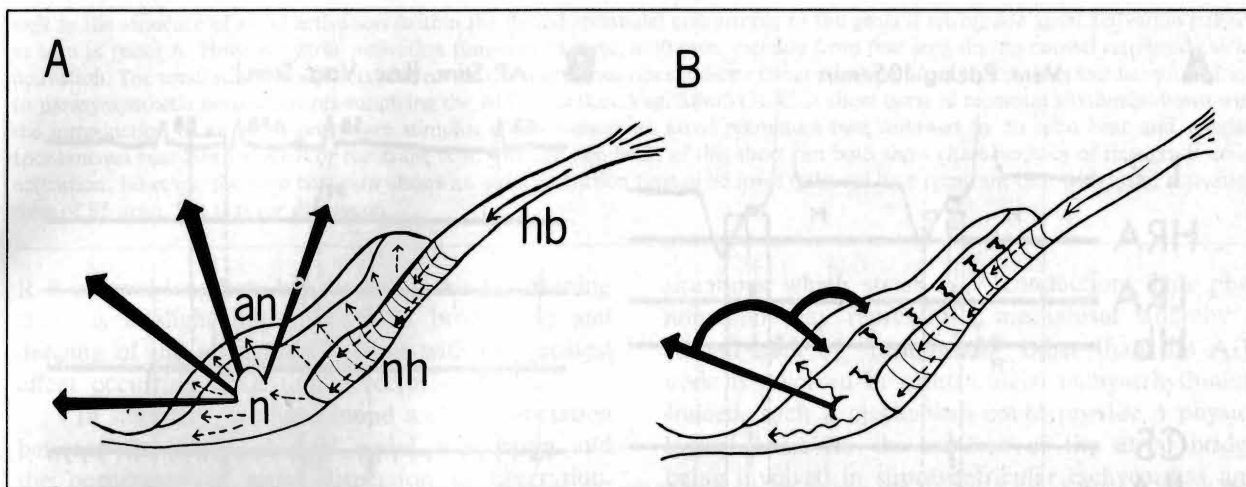


Fig. 4—A schematic version of retrograde atrial activation. A. Indicates activation proceeding from the His bundle retrograde through the various regions of the A-V node: nh, n, an. (After Spach *et al.*) (10). Activation spreads uniformly into the atrium. B. Retrograde activation with asynchronous exit of impulses from the A-V node leading to the possibility of reentry into the node or the atrium. See text for discussion.

node and then to the ventricle to produce a reciprocal beat, or activation may proceed in an asynchronous manner so that local reentry circuits may develop at one or more sites to produce atrial arrhythmias. In any event, dispersion of atrial activation would be a consequence of this asynchronous exit from the A-V node.

In order to relate this phenomenon of dispersion of atrial activation with the occurrence of reentry atrial tachycardias, we attempted to induce echo beats in the dog atrium with the delivery of premature stimuli to the atrium during sinus rhythm (fig. 5). To enhance the occurrence of echo beats, we also delivered local subthreshold epicardial stimulation to a site in the low right atrium near the coronary sinus ostium so that parasympathetic nerve elements supplying the A-V node were preferentially affected (8). In this way, exacerbation of A-V conduction delay was obtained. In panel A, normal retrograde atrial activation time was 55 msec; in panel B, a premature atrial stimulus was delivered to the high right atrium during sinus rhythm and induced an echo beat. Note the stimulus artifacts seen on the coronary sinus (CS) trace. These are due to the subthreshold stimuli applied to epicardial parasympathetic nerve elements (local vagal stimulation). The echo beat has a general appearance of retrograde atrial activation with activation in the low right atrium occurring before activa-

tion of the high right atrium or the posterior left atrium. Note also that the total atrial activation is slightly prolonged during this echo beat as compared to the normal retrograde atrial activation pattern, 85 msec as compared to 55 msec. In panel C, with the same coupling interval, an atrial echo beat was induced by an atrial premature systole, however, it was followed by another reentry beat. Note that there was a greater degree of dispersion of atrial activation, 95 msec, in the echo beat seen in panel C as compared to the echo beat in panel B, 85 msec. The reentrant beat also showed the general appearance of retrograde activation; however, the degree of atrial dispersion is now only 85 msec and reentrant rhythm spontaneously terminated. Also note that the degree of dispersion of atrial activation can appear on the surface ECG as well although the interposition of P wave, ST, and T waves may obscure this aspect. Thus, it can be seen that with a high degree of dispersion, the P wave is broadened with 95 msec of atrial dispersion as compared to 85 msec. The P wave polarity remains the same.

Dr. Alfred Pick was kind enough to bring to our attention some suggestive evidence that atrial dispersion does occur in patients under conditions of compromised A-V conduction. In figure 6, taken from Katz and Pick (4), it can be seen that during retrograde Wenckebach cycles not only does the

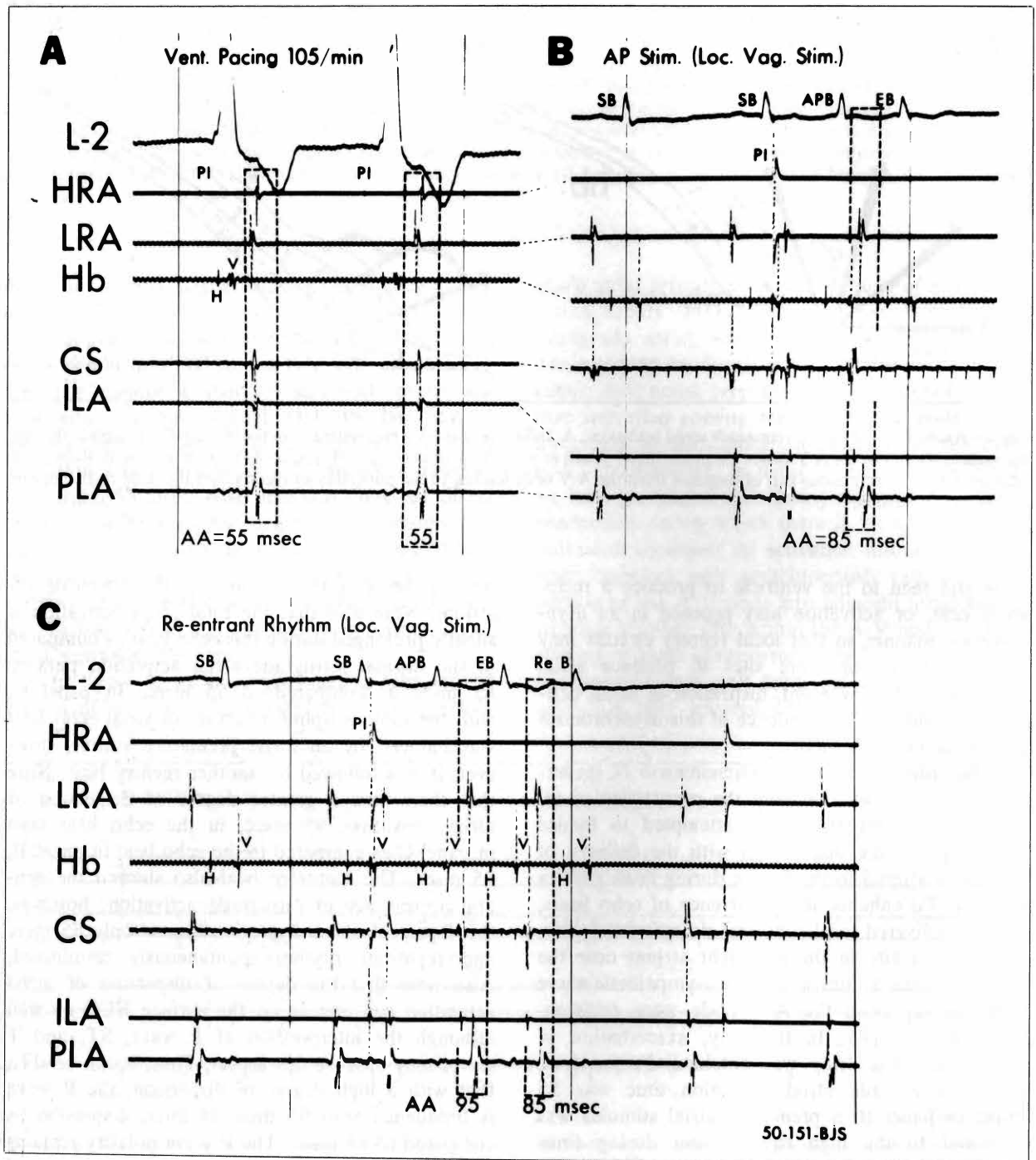


Fig. 5—Comparison between normal retrograde activation in the atrium and dispersion of atrial activation. Traces from above: Lead II (L-2) of the ECG; bipolar plunge wire electrograms from the high right atrium (HRA); the low right atrium (LRA); the His bundle region (Hb); the coronary sinus ostium (CS); the inferior left atrium (ILA); and the posterior left atrium (PLA). A. During ventricular pacing at 105 beats per minute retrograde conduction to the atrium indicates early activation of the low right atrium and coronary sinus regions with activity proceeding to the high right atrium and posterior left atrium. The total atrial activation time (AA) in each beat is 55 msec. PI = pacer impulse. B. Atrial premature stimuli (AP Stim.) was applied to the heart after two simultaneous sinus beats (SB). The atrial premature beat (APB) is followed by an echo beat (EB). Note the inverted P wave in lead II as

well as the sequence of atrial activation (within the dotted rectangle) conforming to the general retrograde atrial activation pattern as seen in panel A. However, atrial activation time was 85 msec, a 30 msec increase from that seen during normal retrograde atrial activation. The small stimulus artifacts seen on the coronary sinus trace indicate the application of subthreshold epicardial stimulation to parasympathetic nerve elements supplying the A-V node (Loc.Vag. Stim.) (5). C. A short burst of reentrant rhythm is shown with the introduction of an atrial premature stimulus which induces an atrial premature beat followed by an echo beat and another spontaneous beat labelled REB or reentrant beat. The last two beats of this short run both show characteristics of retrograde atrial activation; however, the echo beat now shows an atrial activation time of 95 msec followed by a reentrant beat with atrial activation time of 85 msec. See text for discussion.

R-P interval lengthen, but also with this lengthening there is a slight but appreciable broadening and deepening of the retrograde P wave with the greatest effect occurring prior to the reciprocal beat.

In summary, we have found a close association between the stress of A-V nodal conduction and the occurrence of atrial dispersion or aberration. We could not explain atrial dispersion on the basis of incomplete recovery of atrial activity, slowing of atrial conduction, or the occurrence of atrial fusion. We postulate that the phenomenon of dispersion of atrial activation is related to the functional dissociation within the A-V node seen during

situations which stress A-V conduction. This phenomenon may represent a mechanism whereby a second area of "turnaround" other than the A-V node is involved in reentry atrial tachyarrhythmias. Indeed, such a mechanism could provide a physiological basis for the concept of the atrial bridge being involved in supraventricular tachycardias and reciprocal beating.

Authors' note: We thank Mrs. Marie Ellis for her dedicated assistance in the preparation of this manuscript.

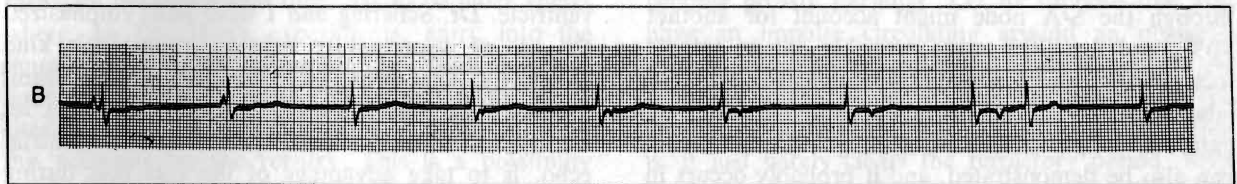


Fig. 6—An electrocardiograph tracing taken from a patient showing a retrograde Wenckebach cycle ending in a reciprocal beat. Note that with the progressive lengthening of the R-P interval, there is a broadening and deepening of the P wave (Reproduced with permission from Katz, L. N. and Pick, A. *Clinical Electrocardiography*, Part I. "The Arrhythmias." Lea and Febiger, Philadelphia, 1958, Chapt. 9, fig. 67).

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Some Mechanisms of Supraventricular Tachycardia*

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Reciprocal rhythm was proposed about 30 years ago by Barker, Wilson, and Johnston as a probable mechanism for the explanation of supraventricular tachycardia. They proposed, on the basis of approximately 100 clinical records at the University of Michigan Hospital, that reentry through the A-V node, better known as reciprocal tachycardia, would account for approximately 40% of their cases. They also postulated that reentry through the S-A node might account for another 40%, and that 20% were probably due to ectopic foci. Ectopic focal activity is demonstrable in the laboratory, and it probably happens in man. Reentry or reciprocal activity through the A-V node can also be demonstrated, and it probably occurs in man.

Wilson and collaborators based their conclusions upon the termination of supraventricular tachycardia by brief periods of vagal stimulation induced by carotid sinus pressure. The postulate was that the effect of the vagus was to depress transmission or even block it within one part of the reentrant pathway. In those cases of reciprocal tachycardia in which the P waves were inverted, the postulate was that this was through the A-V node, and, therefore, the effect of the vagus terminating the episode was due to depressed conductivity or block within the A-V node. In another 40% in which the P waves were upright, the postulate was that the sinus node was the site of reentry and that the effect of vagal stimulation was to depress the conductivity in the sinus node. In others who had bizarre P waves and were unresponsive

to vagal stimulation, it was postulated that these were in fact ectopic rhythms.

We have performed experiments through the years and arrived at the conclusion (much later than the clinical cardiologists) that dissociation can occur in the node. Reciprocation could conceivably be induced by premature stimulation of the atrium, which Dr. Scherlag has already shown you, or it could be induced by premature activity within the ventricle. Dr. Scherlag and I have both emphasized the use of a premature beat to initiate this kind of activity. That is not as artificial as it might seem; the only reason for introducing a premature beat, let us say to induce atrial reciprocation or an atrial echo, is to take advantage of the fact that during the relatively refractory period potentially dissociable pathways will be dissociated.

It is also conceivable, as Dr. Moore told you, to have concealed conduction. It is perfectly possible to have block below the site of the junction of two dissociated pathways, so that an impulse initiated in the atrium and returning to it fails to reach the ventricle because of the depressed conductivity below that junction. A premature atrial response which activates one pathway within the node returns to the atrium over an alternate route, reengages the first path within the node, and only then reaches the ventricle. Thus, we can have an impulse initiated within the atrium which takes, let us say, the alpha pathway down to the junction of the final common pathway which is still refractory and therefore fails to conduct to the ventricle. It nevertheless returns over the beta pathway of this y-shaped structure, activates the atrium, and reactivates the alpha pathway. By that time, the lower nodal pathway has recovered, and it is perfectly possible to have a 2:1 A-V block on the basis of circus movement within the node. Thus,

* This is a transcription, edited by Dr. Charles L. Baird, Jr., of a lecture presented by Dr. Moe at the Symposium on Cardiac Arrhythmias, June 9, 1972, at Virginia Beach, Virginia.

paroxysmal atrial tachycardia with block does not exclude the possibility of circus activity.

I mentioned that Barker, Wilson, and Johnston proposed that some of these paroxysmal atrial tachycardias may be due to reentry within the sinus node. Dr. Han, in our laboratory, tackled this rather difficult problem seeking to demonstrate whether or not this was indeed possible. He explored the sinus node, rather laboriously, since this is a relatively difficult area to study over an extended period of time. It is easy to get responses from pacemaker cells within the sinus node, but it is difficult to hold them for a long enough period to get satisfactory evidence. At any rate, the technique here was to record an electrogram from atrial tissue within an excised scrap of muscle and to drive it for a time at a regular frequency, followed by a premature stimulus. Obviously, if this premature impulse is going to enter the sinus node and return, it had to fail to activate some elements of the sinus node; in other words, the one prime requisite for reentrant activity is that there has to be block somewhere. In Dr. Han's experiments, entry into the sinus node from the atrium and exit from the sinus node to the atrium were clearly not at the same sites. In other words, a loop was inscribed, and this accounts for the reentry. This is a possibility which was suggested by Dr. Hoffman about 15 years ago.

Atrial flutter has also been thought to be on the basis of a self-sustained reentrant circuit. The experimental technique for inducing flutter in dogs is first to crush an area of atrium in order to provide a circuit of suitable dimensions. The most convenient area lies between the superior vena cava and inferior vena cava. Thus, an obstacle is created which includes the crushed, nonconducting atrial tissue, plus the openings of the vena cava. Flutter can then be induced by stimulating the atrium at a rate more rapid than it can follow; in other words, to induce by electrical stimulation a brief period of atrial fibrillation. Upon terminating the stimulation, one of two things can happen—either the atria will stop momentarily until the sinus node resumes

control of the activity or the atrial fibrillation will be replaced by flutter movement.

One of the characteristics of flutter is that sometimes it appears to drift into a state of fibrillation and back out. This has been taken as evidence that the same fundamental mechanism is involved both in flutter and in fibrillation, with the only difference being the rate of discharge of an ectopic focus. I think that one can understand that if the rate of discharge of an ectopic focus is sufficiently slow so that adequate time for recovery (and adequate does not need to be more than a few milliseconds) from the refractory state occurs between events, then the activation pattern of the atrium would be relatively uniform, abnormal but uniform. If, however, that pacemaker were to accelerate to a point where it impinged upon the refractory period of some elements within the atrium and not on others (and we call upon biological nonhomogeneity of the tissue to say that some elements may recover before others), then the activation pattern would become grossly irregular. Let us suppose that you have an impulse circulating around an obstacle, and that the dimensions of the obstacle and the refractory period of the tissue are such that the impulse is struggling to make it each time; that is, it just barely clears the refractory period. Now let us suppose we stimulate the vagus by carotid sinus massage. We will abbreviate the refractory period of atrial tissue which ought to make it easier for the circulating impulse to continue; it ought to accelerate. But when the vagus is stimulated there is not a uniform abbreviation of refractory period. The response is a spotty one because some fibers are closer to vagal endings than others; the effect of the vagus would be to abbreviate the refractory period and facilitate conduction in some areas of the circus loop, and to fail to affect it in others. Transmission will accelerate in those parts of the loop in which conduction is facilitated but will infringe upon fibers that are still totally refractory and cannot participate. This will fractionate the wave front and will generate fibrillation. This is the textbook picture of conversion of atrial flutter to fibrillation by digitalis.

Ventricular Tachyarrhythmias*

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The mechanisms of ventricular tachyarrhythmias fall into two broad categories of increased automaticity and reentry. It is usually difficult to differentiate clinically between the two mechanisms; however, I plan to discuss certain approaches that may be helpful in this regard.

Experimental evidence of increased automaticity in the isolated Purkinje fibers can be obtained by placing cardiac tissue in a bath and adding epinephrine, isoproterenol, digitalis, or lowering the potassium concentration in the bath. This suggests that ventricular tachycardias precipitated by infusion of isoproterenol, excessive doses of digitalis, or hypokalemia may be ascribed to increased automaticity. On the other hand, quinidine or hyperkalemia suppresses automaticity in isolated preparations, and therefore ventricular arrhythmias occurring in patients treated with excessive doses of quinidine or potassium are probably due to reentry rather than to increased automaticity. This type of extrapolation from an experimental setup to a clinical situation does not prove the mechanism but the data may be used in support of a reasonably sound working hypothesis.

The experimental evidence for reentry presented by Drs. Hoffman, Cranefield, Moe and others in the isolated preparation appears soundly documented. Similar conclusions can be drawn from experimental studies in the entire heart following production of myocardial infarction in dogs (fig. 1). Figure 1 shows the result of an experiment in which electrograms are recorded from right atrium (AD), right ventricle (VD), and left ventricle (VS) after experimental occlusion of the left coronary artery in a dog. In the infarcted area (VS) the conduction is slow as evidenced by delayed onset and long

duration of the QRS complex. This QRS complex is inscribed at the time when the recovery of the noninfarcted area (QT interval in the right ventricle) is completed. Therefore, the extrasystole (Ex) can be ascribed with reasonable certainty to the reentry of the slowly propagating impulse from the infarcted into the noninfarcted area.

Since most of our patients have closed chests, we have no access to local electrograms, and we must limit our analysis to the surface electrocardiogram. This may occasionally provide information concerning the mechanism of ectopic beats which initiate ventricular tachycardias. There are two types of ectopic beats—dependent and independent. The dependent requires the presence of a preceding dominant pacemaker. Features that support a dependent mechanism are: 1) fixed coupling; that is, the beats are coupled in a fixed way to the preceding sinus beat, and 2) predictable response to change in the rate of the sinus pacemaker. For instance, when the cardiac rate slows, the ectopic beats become less frequent in response to carotid sinus stimulation (fig. 2), but when the sinus rhythm accelerates, the number of ectopic beats increases. Figure 3 illustrates some of the possible explanations for the dependent mechanism. The propagated impulse disturbs a quiescent Purkinje fiber and induces diastolic depolarization (3B). Such a fiber would acquire pacemaker properties, and by firing before the next sinus impulse, would produce a ventricular extrasystole with a fixed coupling interval due to repetitive firing. Another possibility of a repetitive firing is shown in figure 3C. In this case the fiber has a short refractory period as evidenced by short duration of action potential. This fiber can be depolarized again by a current generated during repolarization. In this case reentry preceding a closely coupled extrasystole is ascribed to non-

* Presented by Dr. Surawicz at the Symposium on Cardiac Arrhythmias, June 9, 1972, Virginia Beach, Virginia.

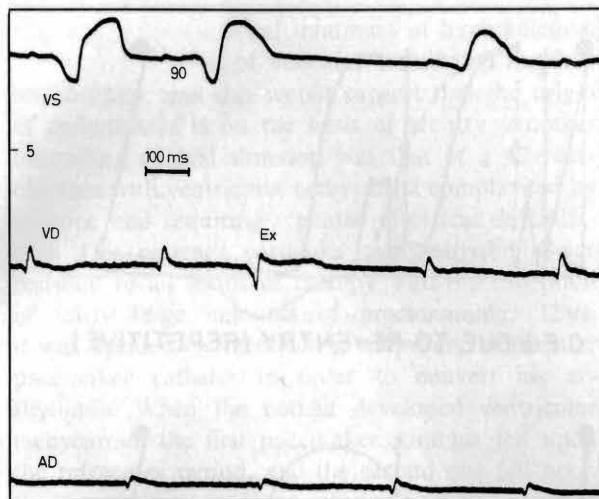


Fig. 1—Electrograms of a dog with experimental occlusion of left coronary artery. (Reproduced by permission of L. Baschieri, L. Palagi, and M. Puletti. "Experimental Study of the Pathogenesis of Ventricular Extrasystolia." *Cardiologia*, 50:371, 1967. Explanation in text.)

homogeneous refractoriness. The third mechanism which supports the dependent type, and which is most commonly illustrated in textbooks, is the mechanism whereby a particular fiber is bypassed on the way to the ventricle (3D). In such a case of a so-called unidirectional block, the bypassed fiber does not fire during normal propagation of an impulse but becomes depolarized when the impulse returns from another side and causes an ex-

trasystole. These are the three possibilities whose occurrence may produce a ventricular extrasystole of a dependent type.

An example of an independent mechanism is a parasystole. How does one diagnose parasystole? Obviously, we look for evidence of variable coupling, fusion beats, and a common denominator indicating the assumed rate of firing of the independent, or "protected" pacemaker. When the parasystolic impulses do not appear at the expected time, we postulate an exit block, or intermittence due to temporary loss of protection. When application of carotid sinus stimulation suppresses the dominant pacemaker, the so-called parasystolic focus will emerge undisturbed and fire at the same rate as prior to the carotid sinus stimulation (fig. 4).

In clinical practice, automaticity and reentry can be occasionally distinguished on the basis of response to treatment. For instance, treatment of digitalis induced ectopic atrial tachycardia with potassium demonstrates that the rate of the ectopic pacemaker gradually decreases. This would suggest that the rate of diastolic depolarization is slowed and that this type of arrhythmia is based upon automaticity rather than reentry. We believe that reentry would be more likely to cease rather abruptly and not by gradual slowing of the rate. This is shown in figure 5. In this patient severe hyperkalemia produced ventricular flutter which did not

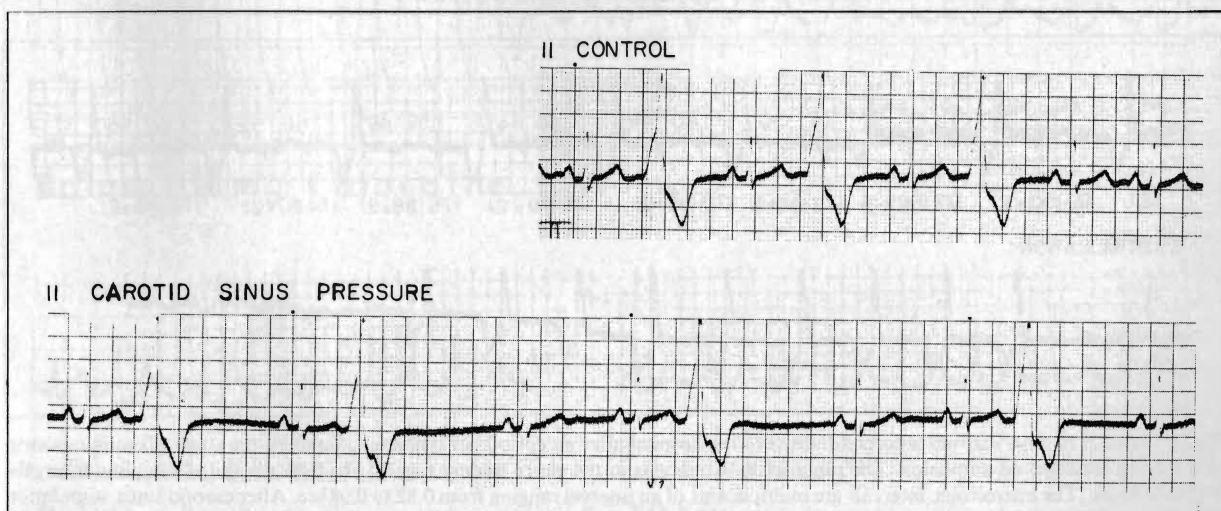


Fig. 2—Continuous tracing of lead II of a 48-year-old man with rheumatic heart disease. Ventricular ectopic beats with fixed coupling interval. After carotid sinus stimulation (lower tracing), the sinus rate is slower but the coupling interval remains unchanged and no ventricular ectopic beats appear during long P-P intervals. (Reproduced by permission of B. Surawicz and M. G. MacDonald and the *American Journal of Cardiology*, 13:199, 1964.)

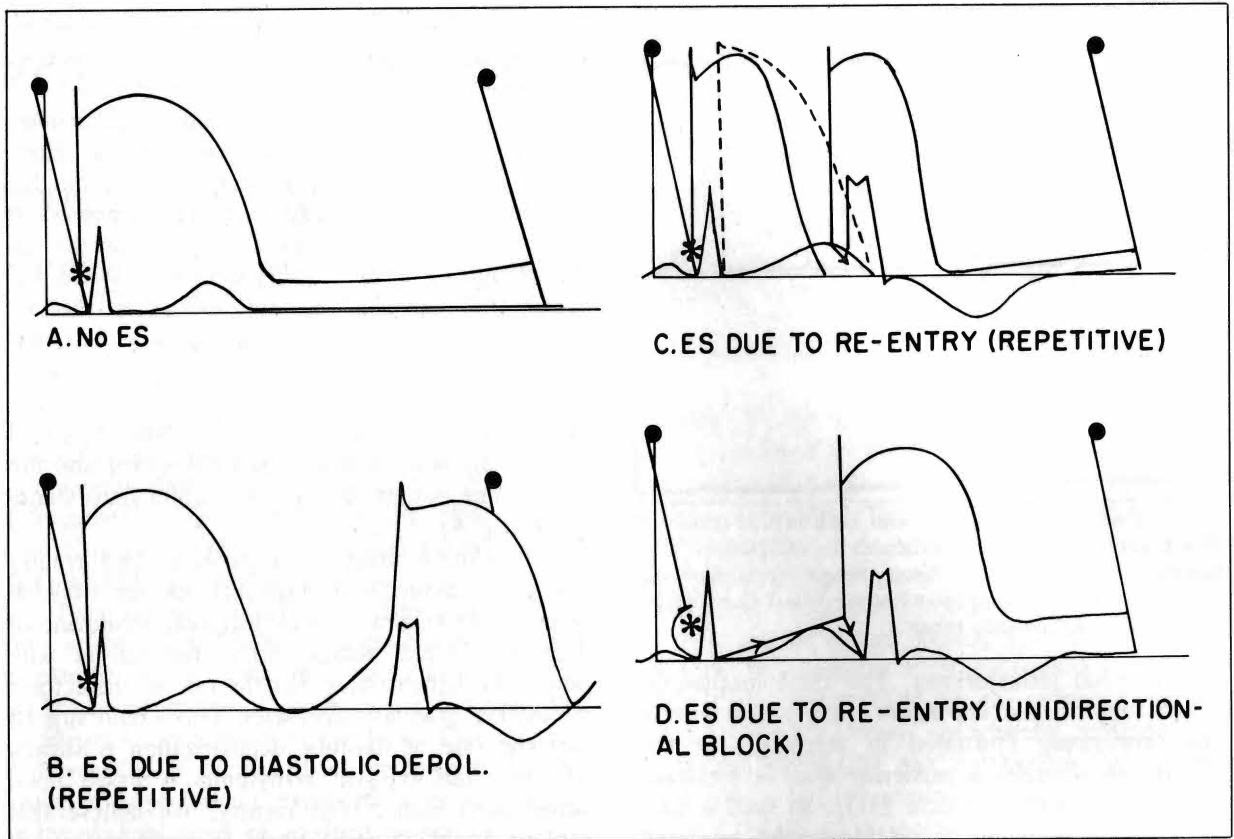


Fig. 3—Diagram representing 3 different mechanisms of dependent ventricular extrasystole originating in a Purkinje fiber marked by asterisk. In A, the fiber is depolarized by the impulse spreading from the sinus node (black dot) and no extrasystole ensues. In B, the sinus impulse enhances diastolic depolarization which causes repetitive firing. In C, the refractory period of the depolarized Purkinje fibers is short, and the repolarization is completed during ventricular repolarization (dashed action potential). In this case, reentry may be due to potential difference between the ventricular fiber and the prematurely repolarized Purkinje fiber if these two fibers are in close proximity to each other. In D, reentry is due to unidirectional block (see text).

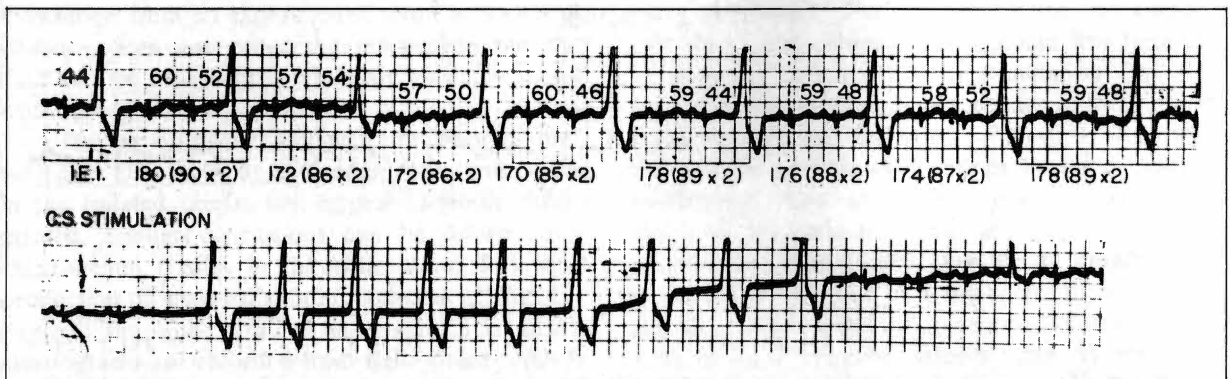


Fig. 4—Lead II of a 64-year-old laborer admitted to the hospital after an episode of syncope suffered on the street. Continuous strip of a tracing recorded on admission. The range of R-R intervals in the entire tracing was 0.52 to 0.68 sec and of coupling intervals, 0.42 to 0.56 sec. The interectopic intervals are multiplicants of an interval ranging from 0.82 to 0.98 sec. After carotid sinus stimulation (lower tracing), the sinus pacemaker is inhibited and the first and second ventricular ectopic beats appear before the first atrial deflection is recorded. The intervals between ventricular ectopic beats measure 0.98 sec and are constant. The P waves are apparent on the descending limb of the T wave from the 2nd to the 8th ventricular ectopic beats but the corresponding atrial impulses are not conducted to the ventricles. Note a fusion beat at the end of the lower strip. (Reproduced by permission of B. Surawicz and M. G. MacDonald and the *American Journal of Cardiology*, 13:199, 1964.)

respond to conventional treatment of hyperkalemia. The administration of lidocaine terminated the flutter abruptly, and this would suggest that the origin of arrhythmias is on the basis of reentry. Another interesting clinical situation was that of a 42-year-old man with ventricular tachycardia complicated by syncope and requiring repeated electrical defibrillation. This patient's particular tachyarrhythmia was resistant to all forms of therapy with the exception of fairly large amounts of procainamide. Thus, it was decided to introduce a temporary ventricular pacemaker catheter in order to convert his arrhythmia. When the patient developed ventricular tachycardia, the first pacemaker stimulus fell upon the refractory period, and the second one fell upon the T wave and produced a fusion beat that resulted in prompt reversion to sinus rhythm (fig. 6). It is interesting to observe that the pacemaker rate was slower than the rate of the ventricular tachycardia. This type of response suggests a reentry mechanism rather than one based upon automaticity.

There have been other methods for managing refractory ventricular tachycardia, such as aorto-coronary bypass and resection of a ventricular aneurysm. It is reasonable to conclude that the removal of dead myocardium with resultant disappearance of the arrhythmia suggests a reentry mechanism rather than increased automaticity. Finally, it is conceivable that certain tachyarrhythmias may be due to combinations of increased automaticity and reentry, for example, repetitive reentry into a partially, or intermittently protected parasystolic focus.

In summary, there is well documented experimental evidence of both increased automaticity and reentry in the experimental preparations. However, in the clinical setup, the distinction between these two mechanisms of ventricular tachyarrhythmia is usually very difficult to determine. Certain diagnostic clues can be obtained from the observations of the dependence of the ectopic beats upon the preceding dominant impulses and from the responses to therapeutic interventions.

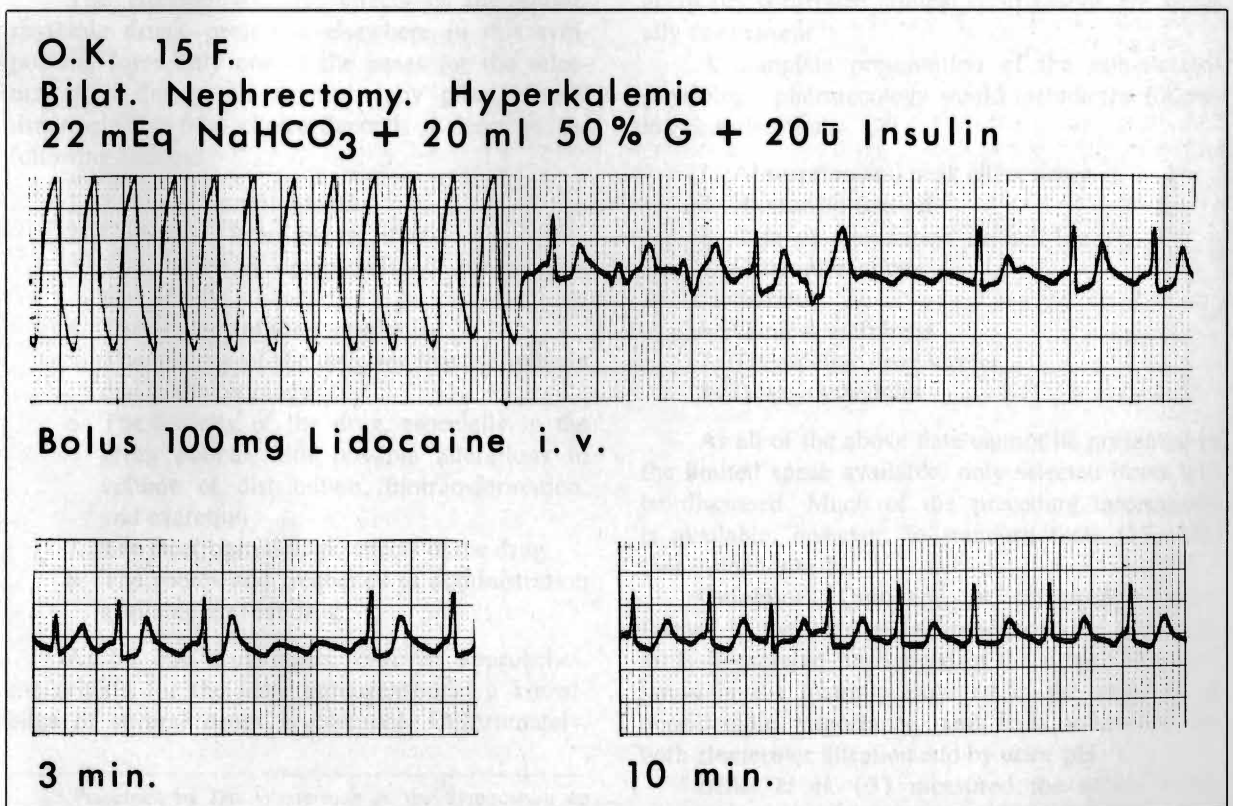


Fig. 5—Abrupt termination of ventricular flutter after administration of lidocaine in a 15-year-old patient with hyperkalemia and atrial flutter. Note the characteristic peaked T wave after termination of ventricular tachyarrhythmia. Lidocaine was administered after the failure of conventional therapy with sodium bicarbonate, glucose and insulin.

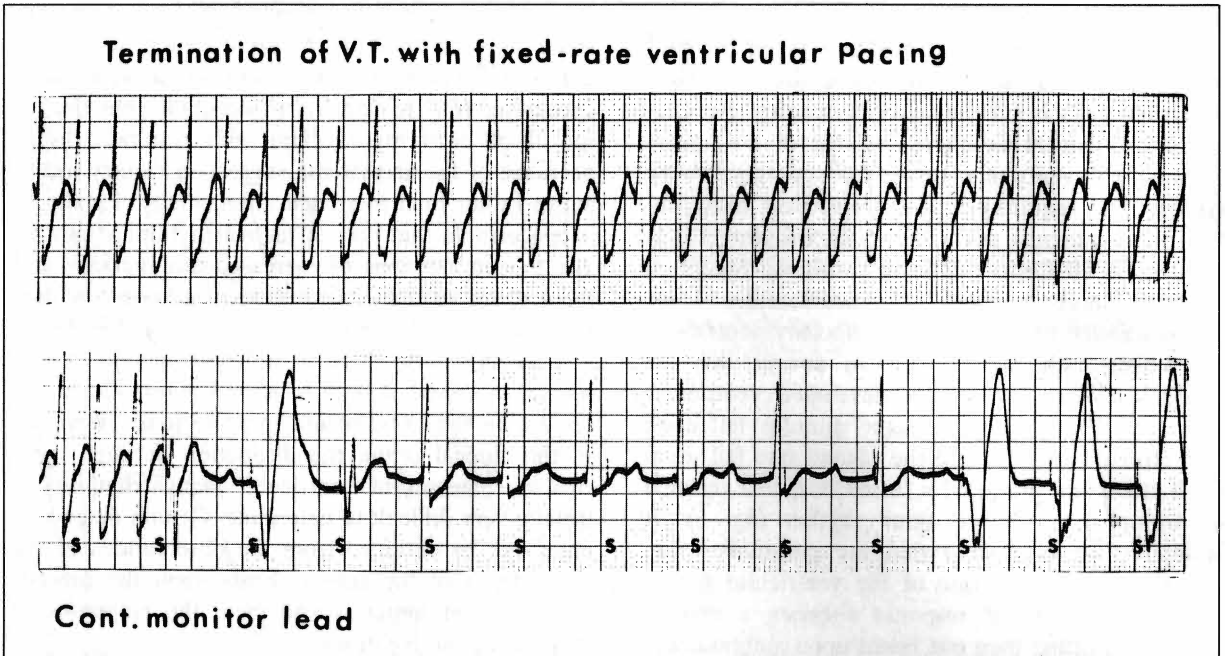


Fig. 6—Monitor lead of a 42-year-old man with ventricular tachycardia terminated by transvenous right ventricular pacing (see text).

Pharmacology of Antiarrhythmics: Quinidine, Beta-Blockers, Diphenylhydantoin, Bretylium*

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The electrophysiologic effects of the antiarrhythmic drugs, presented elsewhere in this symposium, form only one of the bases for the selection of a therapeutic agent in any given clinical situation. The final choice depends at least on the following factors:

1. The specific arrhythmia
2. Underlying heart disease, if any
3. The degree of compromise of the circulation, if any
4. The etiology of the arrhythmia
5. The efficacy of the drug for that arrhythmia due to that etiology
6. The toxicity of the drug, especially in the given patient with possible alterations in volume of distribution, biotransformation, and excretion
7. The electrophysiologic effects of the drug
8. The routes and frequency of administration available for that drug

As no one drug meets, or even approaches, the criteria for the ideal antiarrhythmic, a knowledge of several drugs is essential. Unfortunately,

adequate, controlled clinical comparisons are virtually nonexistent.

A complete presentation of the non-electrophysiologic pharmacology would include the following considerations:

1. Absorption and peak effect times
2. Biotransformation
3. Rate of elimination or half-life ($t_{1/2}$)
4. Drug interactions
5. Toxicity
6. Clinical usefulness
7. Therapeutic drug levels
8. Dosage schedules

As all of the above data cannot be presented in the limited space available, only selected items will be discussed. Much of the preceding information is available, however, in standard texts (17, 10). (See Addendum 1)

Quinidine. Quinidine is principally transformed in the liver by hydroxylation, but some 10-50% is excreted unchanged in the urine. This variation in the quantity excreted in the urine is of considerable importance, and it is influenced by both glomerular filtration and by urine pH.

Bellet *et al.* (3) measured the serum levels of quinidine in three groups of ten subjects after 600 mg of oral quinidine. Normal subjects had, af-

* Presented by Dr. Wasserman at the Symposium on Cardiac Arrhythmias, June 9, 1972, at Virginia Beach, Virginia.

ter two hours, significantly lower serum quinidine levels than the subjects with congestive heart failure (creatinine clearances of 35-80 ml per minute), or the subjects with renal disease and azotemia. While this study does not consider alterations in the volume of distribution, liver function, and so forth, the correlation between the peak level of quinidine and the rate of fall of the serum levels with glomerular filtration is evident. Thus, we must consider renal function much in the same way as when we use digoxin.

In addition to renal function, the pH of the urine is important in the excretion of quinidine. As urine pH rises, more of the urinary tubular quinidine is nonionized and, hence, more readily passes across the tubular epithelium, thus decreasing the quantity of filtered quinidine excreted in the urine.

Figure 1 is taken from the study of Gerhardt *et al.* (9). In normal subjects, urine pH was raised by administering acetazolamide and sodium bicarbonate. As shown, serum quinidine levels rise as urine pH increases and, furthermore, the pharmacologic significance of the higher serum quinidine levels is indicated by progressive increase in the Q-T interval.

Molar sodium lactate has been recommended as

a means of treating the arrhythmic abnormalities associated with quinidine toxicity. While such alkalinizing therapy may improve the arrhythmias, it surely will also delay the excretion of quinidine and might prolong the duration of the toxicity. Also a large segment of the population has been consuming a very effective urinary acidifier, ascorbic acid, in a huge dose. The doses of quinidine needed to establish an antiarrhythmic effect might be titrated in such an individual, who then discontinues the ascorbic acid. A considerable increase in serum quinidine could occur with a significant chance of serious toxicity.

Thus the physician must consider glomerular filtration rate and urine pH when prescribing quinidine. Alterations in liver function and the apparent volume of distribution are probably also important but less quantifiable.

The serum half-life ($t_{1/2}$) is known for all of the available antiarrhythmic drugs, and this simplified concept is useful in understanding the necessity for loading doses, the frequency of dosing, the duration of toxicity, and the timing of clinical observations of the patient.

The serum half-life is defined as the time required to reduce the serum level of a drug to one-

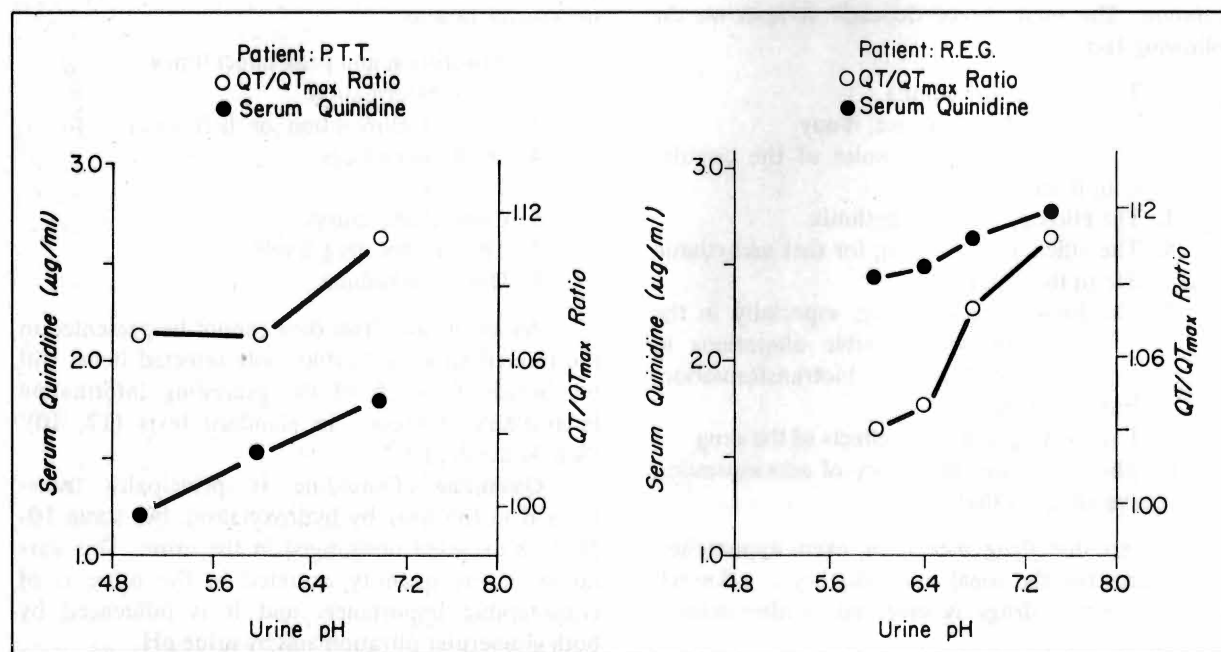


Fig. 1—Change of serum quinidine and change of ratio of measured Q-T interval to the maximum normal Q-T interval at measured heart rate (expression of quinidine effect), plotted relative to urine pH, for two subjects. (Reproduced by permission of *Annals of Internal Medicine*, 71:929, 1969, and R. E. Gerhardt).

half its initial level. As the great majority of drugs follow first-order kinetics (the amount eliminated is proportional to the quantity present), the following "rules" of half-life are widely applicable:

1. The serum half-life is independent of the quantity of drug present. In figure 2, the disappearance curve declines 50% each half-life, decreasing from 100% to 50% the first half-life, from 50% to 25% the second half-life, and so forth.
2. The half-life concept is independent of the mechanism of elimination; urinary or intestinal excretion, hepatic transformation, and so forth.
3. The dosing interval must be shorter than the half-life to avoid wide fluctuations in serum levels and body stores of a drug.
4. Essentially complete elimination of a drug is achieved after five half-lives and conversely, with regular dosing, at frequencies of the half-life, or more often, equilibrium levels are achieved after five half-lives (see accumulation curve). After 3.3 half-lives, 90% of equilibrium levels are achieved. This would then be an appropriate time to make clinical observations on the pharmacologic effects of the drug.

For quinidine, the half-life is about 4-6 hours. Doctors Richardson, Zee, and Wyso (21) from our institution reported on studies in which quinidine was given at 9 A.M., 1, 5, and 9 P.M. While the serum levels before the next day's dose were still adequate, they were achieved at the expense of excessive levels one and one-half hours after the 9 P.M. dose. A six-hour schedule would have avoided the potentially toxic levels at bedtime.

In a study to be described further below, Bloomfield *et al.* (7) gave patients quinidine 300 mg at 0, 3, and 6 hours, as a loading attempt and then gave 300 mg every 6 hours thereafter. Fig-

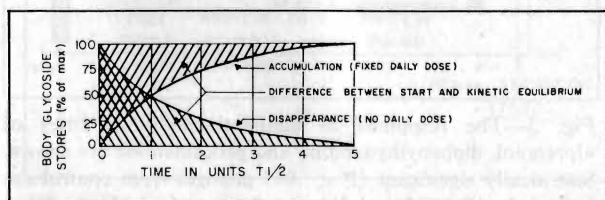


Fig. 2—The accumulation and disappearance of a drug is depicted in terms of its half-life.

ure 3 shows that the serum concentrations did not reach equilibrium levels until after 24 hours, in keeping with the principles noted above.

In summary, application of the rules of $t_{1/2}$ to quinidine suggests that where prompt action is needed, a loading dose should be given and that quinidine should be given every six hours to avoid peaks and troughs of serum levels and associated toxicity and subtherapeutic concentrations.

"Quinidine Syncope" is the name employed by Selzer and Wray (23) to describe recurrent ventricular fibrillation, usually self-terminating, seen in patients treated with quinidine. It usually occurs after the first few doses, and it may be noted in patients with normal or even low serum quinidine levels. While tachyarrhythmias and ventricular fibrillation are well-known toxic effects of quinidine, these individuals seem to be unusually susceptible to this serious adverse effect. While most patients receiving quinidine have underlying heart disease, quinidine syncope can occur in patients with no detectable organic heart disorder.

Some clinicians are attempting close monitoring of patients during the initiation of quinidine therapy. The effectiveness of such monitoring will be difficult to assess because of the infrequency of this syndrome. Selzer and Wray estimated that 3-5% of patients treated with quinidine may develop this idiosyncratic toxicity, but Bjerkelund (6) reported only 1+% and Lown (16) reported only 0.5% sudden deaths in his series of 650 patients.

Finally, in regard to quinidine, some note of its efficacy need be made. Bloomfield *et al.* (7) studied 53 patients with acute myocardial infarction in a placebo controlled, randomly allocated prospective

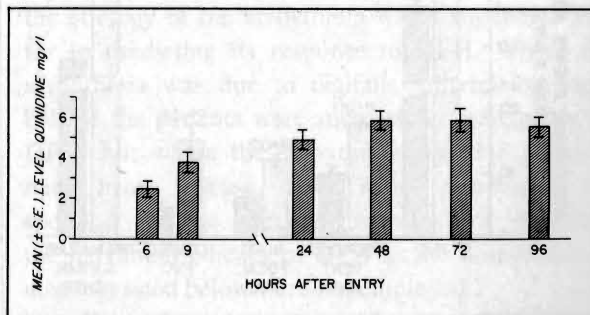


Fig. 3—Blood quinidine concentrations at various intervals during five days of prophylactic quinidine therapy in 27 patients with acute myocardial infarction. (Reproduced by permission of the *New England Journal of Medicine*, 285: 981, 1971, and S. S. Bloomfield).

trial of oral quinidine (*vide supra*). Because of the lag in achieving therapeutic serum quinidine levels, there was no difference between the treated and placebo groups in the first six hours, but thereafter (see fig. 4), there was a statistically significant reduction in premature ventricular and supraventricular contractions and in "serious ventricular arrhythmias." As has also been true of the studies of other antiarrhythmics in acute myocardial infarction, there was no difference in mortality between the treated and control groups.

Beta Adrenergic Receptor Blockers. The serum half-life of oral propranolol (Inderal®) is 3-4 hours. Successful management with less frequent dosing intervals is likely due to the fact that the large doses used result in blood levels which remain above the therapeutic level for a longer period of time.

The major concern in beta-blocker therapy is the marked cardiovascular depression which these agents induce. In three separate series of dogs, we (19) determined the mean doses of three antiarrhythmic drugs required to convert ouabain (a cardiac glycoside)-induced ventricular tachycardia to normal sinus rhythm. Alprenolol is an effective beta-blocker, the dose of which (intravenously) does not differ from propranolol. These doses of the three antiarrhythmics were then studied in a new

series of paced, open chest dogs, and the electrocardiographic and hemodynamic effects of these drugs given in "equi-antiarrhythmic" doses are depicted in figure 5. The beta-blocker significantly prolonged the P-R and Q-T intervals and depressed blood pressure, cardiac output (aortic flow via an electromagnetic flow transducer), and left ventricular contractility (dp/dt, peak left ventricular rate of pressure rise). Directionally similar but less marked alterations occurred with procainamide, while diphenylhydantoin did not affect these or any of the other measured cardiovascular functions. Beta-blockers are, therefore, the most likely of the antiarrhythmics to induce cardiac depression, and even in low doses, a worsening of heart failure or the precipitation of pulmonary edema may result. While it is true that the correction of an arrhythmia by the beta-blocker may so improve the heart's overall function as to counteract any direct myocardial depression, such therapy is fraught with the danger that should the beta-blocker not affect the arrhythmia, its negative inotropic action will still be manifest.

Except where an arrhythmia is caused by adrenergic mechanisms, beta-blockers are best avoided in patients with myocardial disease unless other therapy has failed and the situation is desperate.

Diphenylhydantoin. Diphenylhydantoin (DPH) is

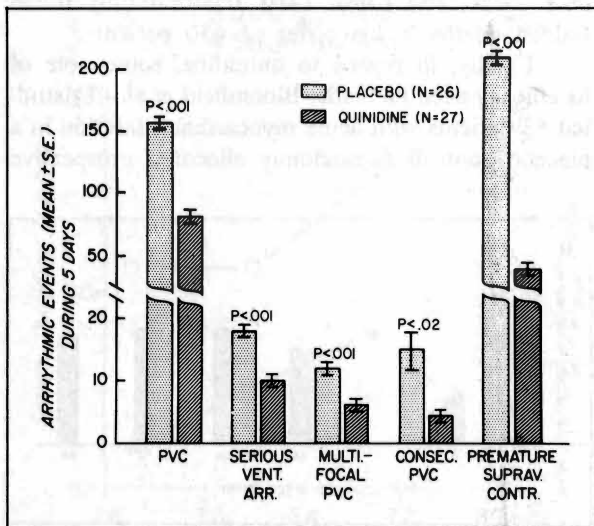


Fig. 4—Occurrence of arrhythmias during five days of prophylactic quinidine or placebo therapy in 53 patients with acute myocardial infarction. (Reproduced by permission of the *New England Journal of Medicine*, 285:984, 1971, and S. S. Bloomfield).

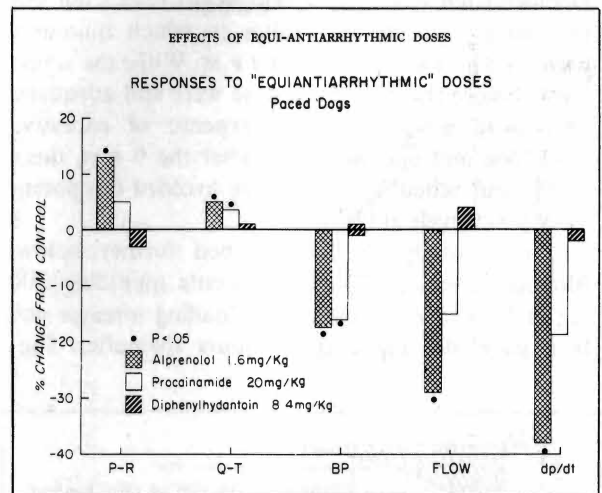


Fig. 5—The responses to equi-antiarrhythmic doses of alprenolol, diphenylhydantoin, and procainamide are shown. Statistically significant ($P < .05$) changes from control are indicated. (Reproduced by permission of *Archives Internationales de Pharmacodynamie et de Therapie*, 190:354, 1971, and J. D. Proctor).

of particular interest. The differences in its electrophysiologic effects have already been noted elsewhere. Also, any consideration of DPH must include information about its pharmacokinetics and biotransformation.

Diphenylhydantoin is slowly absorbed by mouth, peak levels not being achieved for hours. This drug should not be given intramuscularly since its absorption is erratic. Even intravenously, DPH effect requires 1-5 minutes, and rapid (bolus) injections must be avoided.

The biotransformation of DPH is shown in figure 6. Diphenylhydantoin is parahydroxylated by oxidizing enzymes in the liver microsomes, converting DPH to HPPH (hydroxyphenyl, phenylhydantoin or 5 phenyl 5'parahydroxyphenylhydantoin). It is this enzyme which is so susceptible to both enzyme inhibition and enzyme induction, accounting for the large number of reported DPH drug interactions (see addendum 2). Hydroxyphenyl, phenylhydantoin, the inactive metabolite, is conjugated with glucuronide, and its excretion in the urine normally accounts for about 75% of the elimination of DPH. Letteri *et al.* (15) have found that patients with uremia have lower serum levels of DPH than do normal subjects receiving the same dose, and that furthermore, the $t_{1/2}$ in uremia is shorter (more rapid DPH disappearance). This, of course, is quite the opposite from most drugs where renal failure results in higher serum levels and longer $t_{1/2}$. The mechanism whereby lower DPH levels are seen in uremia has not been completely elucidated, but several possible mechanisms have been suggested. It is known that HPPH levels are higher in uremic patients. It might be that something in the uremic state induces the parahydroxylating enzyme, hence more rapidly converting DPH to HPPH, or it may be

that the renal failure blocks the excretion of HPPH which competes with DPH for serum protein binding sites (see fig. 6). The unbound, free DPH would be more accessible to enzymatic conversion to HPPH and also more accessible to its receptor site. Thus, while total DPH would be reduced, the free (active) portion might be normal. Finally, it is known that serum protein binding is altered in uremia and this, too, could account for the lower total DPH and its more rapid conversion to HPPH due to more of the serum DPH existing in the free, unbound form.

The clinical role of DPH is receiving more attention. Lown and Wolf (16) report studies in which ventricular fibrillation was induced in dogs by occluding, and if necessary, later releasing the occlusion, of the anterior descending coronary artery. About 75% of untreated dogs developed ventricular fibrillation, and pretreatment with DPH had no effect. On the other hand, pretreatment with procainamide reduced the incidence of ventricular fibrillation to about 20%; quinidine, lidocaine, practolol (a beta-blocker), and bretylium tosylate reduced it to about 35%; and dextro-propranolol and ajmaline reduced ventricular fibrillation to about 50%.

Last year an Australian cooperative group reported a clinical trial of DPH prophylaxis in patients discharged from the hospital after their first acute myocardial infarction (8). Diphenylhydantoin, 300-400 mg per day, was given to 283 patients while the control group received 3-4 mg per day. Although the high dose DPH group had less palpitations and less documented arrhythmias than the control group, survival was unaffected.

Mercer and Osborne (18) in 1967, noted that the etiology of the arrhythmia was a significant factor in predicting its response to DPH. Where the arrhythmia was due to digitalis intoxication, one-half of the patients were successfully managed with DPH, but where the arrhythmia was due to coronary heart disease, only about one-fourth responded. (These percentages may not represent the maximum efficacy of DPH as the dosage schedules suggested below were not employed.)

From these data, it would appear that digitalis intoxication is the prime indication for DPH and that its usefulness in coronary heart disease is likely to be limited.

The effective serum concentration of DPH was

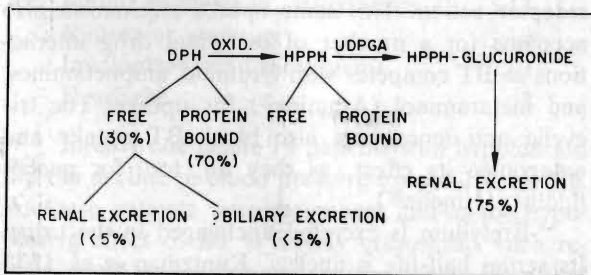


Fig. 6—Major route of metabolism of DPH. (Reproduced by permission of the *New England Journal of Medicine*, 285:651, and Joseph M. Letteri).

established by the elegant studies of Bigger and his colleagues (5) (fig. 7). These data indicate an effective level of about 6-18 μg per ml, the same range as that established for anti-convulsant efficacy (10-20 μg per ml).

Diphenylhydantoin does not follow first-order kinetics as even usual doses approach saturation of the parahydroxylating enzyme system. Thus, the "rules" of half-life do not, strictly speaking, apply to DPH. In the effective serum level range, however, DPH serum levels decline by one-half over 18-24 hours. It is evident then, that without a loading dose, several days will be needed to achieve equilibrium levels. Kutt and McDowell (14) and Bigger *et al.* (5) have recommended the following dose schedule for prompt DPH effect:

Day	Dose (mg)
1	1,000
2	500-600
3	500-600
Thereafter	400-500

Where urgent indications exist, DPH may be given intravenously, 50-100 mg at 5 minute intervals until a therapeutic effect, a toxic effect, or 1,000 mg is given (5). If less than 1,000 mg is given IV, the

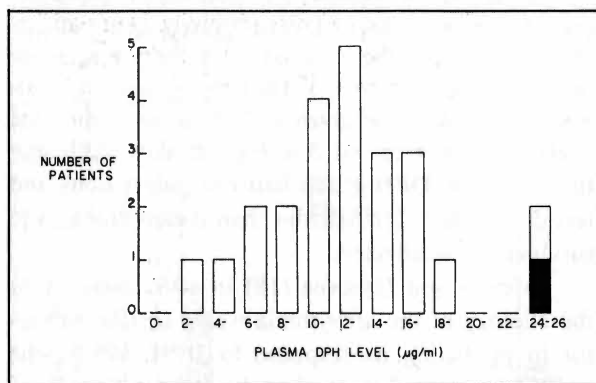


Fig. 7—Plasma levels at which ventricular arrhythmias were abolished. Plasma DPH concentrations are plotted on the abscissa. The number of patients whose arrhythmia was abolished in each range of plasma level is represented on the ordinate as unfilled bars. The one patient whose arrhythmia was unaffected by DPH is represented by the filled bar; this unresponsive arrhythmia was a typical ventricular parasystole. Seventy percent of the conversions occurred at plasma concentrations between 10 and 18 $\mu\text{g/ml}$. Only one patient required a plasma concentration above 18 $\mu\text{g/ml}$ before conversion occurred. (Reproduced by permission of the American Heart Association from *Circulation*, 38:367, 1968, and J. T. Bigger, Jr.).

rest of the loading dose may be given slowly IV or orally over the next 6-18 hours. Where less urgency exists, the 1,000 mg should be given orally over 6-18 hours.

One last point needs to be made in regard to DPH. This is one of the very few currently available drugs for which generic non-equivalence exists. (Digoxin is the other important example.) Generic brands of DPH have been shown to result in *higher* serum levels than the first marketed product, Dilantin®. An "epidemic" of DPH toxicity occurred when the source of supply of DPH was changed to a generic product and its greater bioavailability resulted in toxic effects in previously stable patients with convulsive disorders (25). Patients on DPH should receive a single manufacturer's product.

Bretylum Tosylate. Bretylum tosylate, BT, is a drug of considerable current interest. It is available only on an investigational basis, *viz.*, it is not approved for marketing in this country.

Much of the action of bretylum can be understood in light of its effects on the sympathetic neuron. Norepinephrine is present in the terminal sympathetic neurons in two pools, a larger storage pool and a smaller labile pool. Bretylum tosylate does not affect the former, but its acute administration causes a sudden release of norepinephrine from the latter. This release of norepinephrine accounts for a number of the early effects of parenterally administered BT, such as the early transient hypertension, enhanced automaticity, and increased conduction velocity. The initial positive inotropic effect (increased myocardial contractility) is largely, if not totally due to this norepinephrine release. Chronic bretylum therapy does, however, cause a supersensitivity to circulating and infused epinephrine and norepinephrine since BT blocks the sympathetic neuronal uptake of these catecholamines, the major route of modulating the catecholamine-receptor action. This same uptake mechanism also accounts for a number of bretylum drug interactions as BT competes with tyramine, amphetamines, and metaraminol (Aramine®) for uptake. The tricyclic anti-depressants also block BT uptake and antagonize its effect, as they do, too, for guanethidine (Ismelin®).

Bretylum is excreted unchanged in the urine. Its serum half-life is unclear. Kuntzman *et al.* (13) studied four normal subjects and found a nonexponential decline of serum levels with the rate of

disappearance quite rapid early ($t_{1/2} = \pm 1$ hour) and somewhat slower later ($t_{1/2} = \pm 5$ hours). Romhilt and associates (22), using the serum method established by Kuntzman, studied eight patients. They found an exponential decline of serum levels with a $t_{1/2} = 10$ hours (fig. 8). There was no apparent relationship between the $t_{1/2}$ and the levels of BUN in this latter study, and personal communication failed to resolve this discrepancy. The $t_{1/2}$ value for bretylium tosylate may not be critical, however, since, as shown in figure 8, there is a temporal disparity between the serum levels and the antiarrhythmic efficacy. Bretylium tosylate may, therefore, be one of the so-called "hit-and-run" drugs (12). On the other hand, there appears to be an excellent correlation between the hypotensive effects and the serum levels of this "peripheral sympathetic blocker." This temporal dispersion of hypotensive and antiarrhythmic action prompted these authors (22) to suggest that BT's antiarrhythmic effect may not be related to its action on the sympathetic neuron.

There are both animal and human data to suggest that other antiarrhythmic drugs antagonize the effects of bretylium. Bernstein and Koch-Weser (4) found that patients concurrently receiving other antiarrhythmic drugs were less likely to respond to BT, confirming the observations of Bacaner (2) in experimental animals. Therefore, it would appear wise to discontinue all other antiarrhythmics when initiating bretylium therapy.

Bernstein and Koch-Weser (4) noted the following incidence of adverse effects:

Side Effects of Short-Term Bretylium Therapy in 30 Patients

	%
Hypotension	63
Hypertension	17
Initial increase in arrhythmias	13
Nausea or vomiting	10
Involuntary head movements	3
Headache	3

In only one of the 19 patients with hypotension did the decline in blood pressure exceed 20 mm Hg. As these patients were recumbent and as the hypotensive effect of BT is largely orthostatic, such results could be anticipated (*vide infra*). Transient hypertension and transient enhanced automaticity (increase in arrhythmias) were surely related to

the initial release of norepinephrine. Nausea and vomiting are rare with intramuscular administration, but common if bretylium is given intravenously.

Chronic oral administration commonly produces severe, persistent parotid pain during mastication. This pain is of sufficient magnitude to be the major cause for discontinuing chronic oral therapy. Postural hypotension is a problem early, but tolerance to this action develops fairly promptly.

The clinical role of bretylium is still unclear, but the drug may find a place in the management of recurrent severe ventricular tachyarrhythmias, *viz.*, ventricular tachycardia, and ventricular fibrillation. Bacaner reviewed 250 reported cases of ventricular tachyarrhythmias (1). Eighty-five percent re-

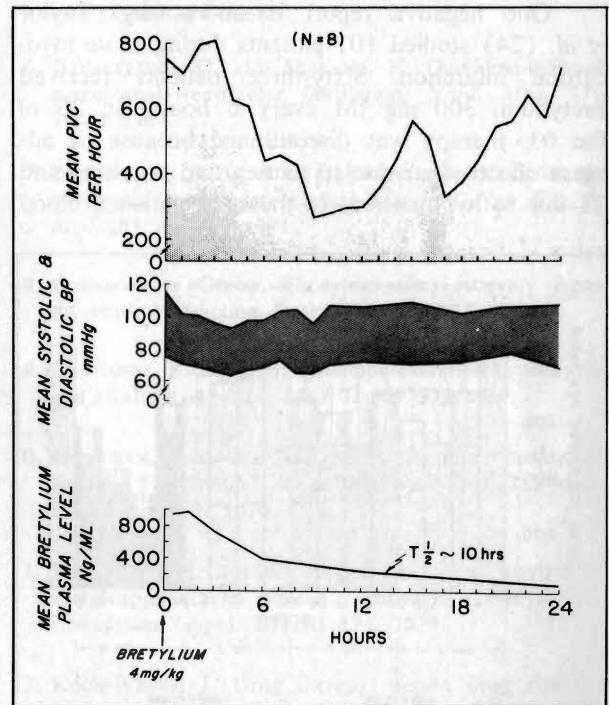


Fig. 8—Comparison of the onset and duration of action of bretylium, 4 mg/kg, on PVC frequency and arterial pressure in relation to blood levels. On the average, hypotensive effect was present in the first hour, when mean plasma concentration of bretylium was at its peak, and continued until the ninth hour after administration. By contrast 50% suppression of mean PVC frequency began at the sixth hour and continued until the 18th hour. The mean elimination half-life of bretylium was about 10 hours. N refers to number of patients. (Reproduced by permission of the American Heart Association from *Circulation*, 45:804, 1972, and D. W. Romhilt).

sponded favorably. Romhilt *et al.* (22) continuously monitored eight patients with frequent premature ventricular contractions (fig. 9). The effectiveness of bretylium tosylate, 4 mg per kg intramuscularly, is evident after a six-hour lag. Bernstein and Koch-Weser (4) found an excellent response in 18 of 30 patients with ventricular tachycardia unresponsive to other drugs. Five patients had a partial response and in seven, no response was evident. Those failing to respond were more often receiving other antiarrhythmic drugs concurrently and were more likely to have had the arrhythmia for a longer period of time. These authors rightly caution against an over zealous interpretation of these data, noting that had these patients been first treated with bretylium, the failures could well have responded to whatever the second drug might have been.

One negative report is noteworthy. Taylor *et al.* (24) studied 101 patients during acute myocardial infarction. Sixty-three patients received bretylium, 300 mg IM every 6 hours. In 25 of the 63, therapy was discontinued because of adverse effects, four due to nausea and vomiting and 21 due to hypotension. In these 21 patients, blood

pressure averaged 65/40 mm Hg, a marked degree of hypotension for patients with acute infarction. It is likely that the unstable state of the circulation in such patients and their use of bedside commodes, thus enhancing orthostasis, accounts for the strikingly higher incidence of significant degrees of hypotension than those noted in the table above. Furthermore, among those who continued BT therapy, there was no decrease in ventricular arrhythmias. Supraventricular arrhythmias, however, were less in the treated group. Again, one patient died in each of the treated and control groups.

Finally, the role of bretylium tosylate in the management of digitalis-induced ventricular tachyarrhythmias should be considered. Our group (20) infused ouabain in a group of ten dogs. In half, the ouabain was continued until stable ventricular tachycardia was established. Bretylium was then given in incremental doses, beginning with 5 mg per kg and increasing to 40 mg per kg total dose. In every dog, the ventricular tachycardia not only persisted, but indeed, the ventricular rate accelerated. Furthermore, when the ouabain infusion was stopped at the time frequent ventricular premature contractions had occurred, bretylium, in each of the five dogs, promptly induced ventricular tachycardia (fig. 10). This augmentation of automaticity by BT was also noted by Kleiger and Shander (11). They produced ventricular tachycardia in dogs with acetyl-strophanthidin (another cardiac glycoside). When the tachycardia had subsided spontaneously after cessation of the glycoside, they administered bretylium and a recurrence of the ventricular tachycardia ensued. Both of these animal studies were completed before the time of maximal antiarrhythmic efficacy of BT, but they indicate the potential danger during the period of initiation of such therapy.

In conclusion, time and space have not allowed a classical pharmacological discussion of these four important antiarrhythmic drugs. In order to use a drug rationally so as to obtain a maximum efficacy:toxicity ratio, one must understand the drug's absorption, its route and mechanism of biotransformation, and its effective half-life. Such data are available for the antiarrhythmic drugs.

Where the achievement of one's therapeutic goal is so readily measurable, as it is with antiarrhythmic drugs, we must demand of ourselves a more knowledgeable and rational therapeutic approach.

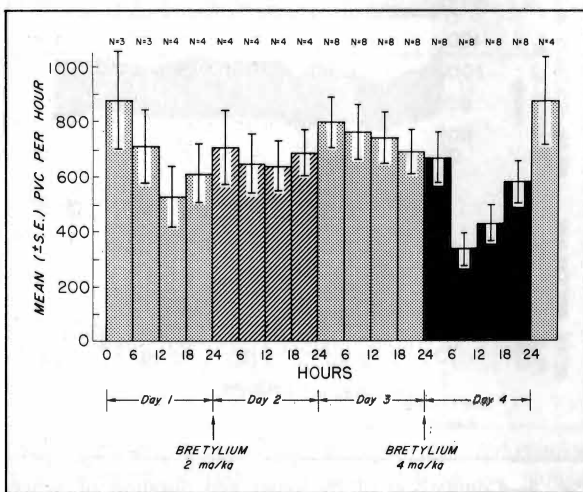


Fig. 9—Mean PVC frequency during treatment days compared with control days. There was 50% suppression of mean PVC frequency in the second and third 6-hour intervals following bretylium 4 mg/kg (solid bars), while no suppression was seen after 2 mg/kg (shaded bars). Control days are shown in stippled bars. N refers to number of patients. On day 1, data were not obtained in one patient during the first 12 hours due to recording-equipment failure. (Reproduced by permission of the American Heart Association from *Circulation*, 45:805, 1972, and D. W. Romhilt).

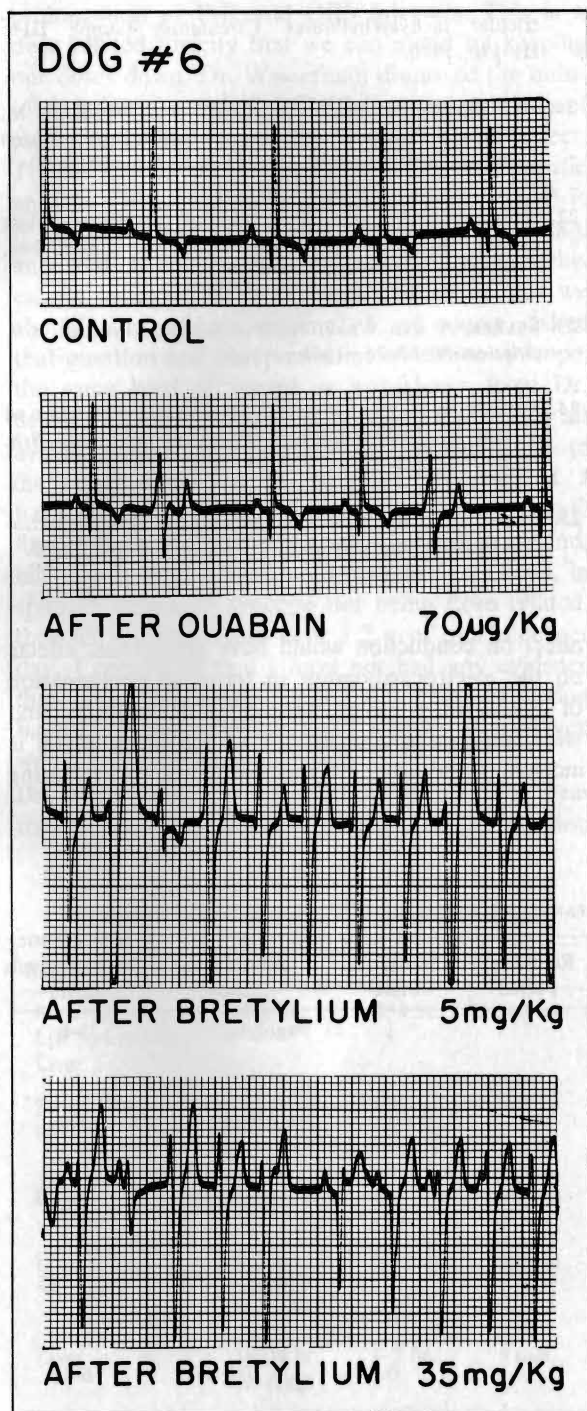


Fig. 10—Ouabain was given to this dog until frequent premature ventricular contractions developed. Treatment, then, with bretylium induced ventricular tachycardia.

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PANEL DISCUSSION

Dr. Surawicz: I use quinidine less, and some people have stopped using it. This is actually the only true antiarrhythmic drug because it is the only drug that will reasonably consistently convert atrial fibrillation to sinus rhythm. As Dr. Hoffman pointed out, its

effect on conduction would have predictable effects on the electrocardiogram in terms of prolongation of the QRS complex and the P-R interval, and with increasing concentration of the drug, which is increasing the dose, we have evidence of increasing

Addendum 1

ANTIARRHYTHMIC DRUGS

Name of Drug	EFFECT OF DRUG ON HEART						Therapeutic Plasma Levels μg/ml
	Automaticity Atrium	Automaticity Ventricle	Conduction Velocity	Refractory Period	Inotropic State	Autonomic Effects	
Quinidine	↓	↓	↓	↑	↓	Vagolytic	3-6
Procainamide (Pronestyl®)	↓	↓	↓	↑	↓	Vagolytic	4-8
Lidocaine (Xylocaine®)	0	↓	0	↓	0	0	2-5
Propranolol (Inderal®)	↓	↓	↓	↓	↓↓	Beta-adrenergic Blocking	.05-.15
Diphenylhydantoin (Dilantin®)	↓	↓	↑	↓	0	0	6-18
Bretylium (Darenthin®)	Initial↑	Initial↑ then↓(?)	Initial↑ then 0	Initial↓ then↑	Initial↑	NE Release Followed by Sympath Block	—

prolongation of P-R and QRS intervals. This is a dose related toxicity that we can avoid by keeping our doses down. Dr. Wasserman discussed the quinidine induced ventricular fibrillation and pointed out that this is not necessarily a dose related effect. This occurs when the concentrations are therapeutic and the QRS interval is not widened and the P-R is not prolonged. Therefore, we have no warning, and that is much more frightening because this cannot be avoided. Now, does that mean that we should stop using quinidine? I, of course, asked that question and observed some quinidine syncope, the same kind of record as was shown from Dr. Selzer's and Dr. Wray's paper. Then I reviewed all available data on quinidine toxicity and came to the conclusion that all published reports that I have been able to review showed three things: first, all people had severe heart disease; second, all people were treated with digitalis; and third, in spite of quinidine syncope not being dose related, they all received more than 1.2 g of quinidine per day. I concluded that I have not had any evidence that lower doses will induce fibrillation. On that basis I still use quinidine, and I wonder whether you would like to comment on that.

Dr. Wasserman: Yes. In some of the cases it is clear that preceding the fibrillation there was prolongation

of the Q-T interval; thus, whether or not this is predictable in the majority of cases, I do not know. It certainly would be in some, and it is for this reason that we are monitoring. I can tell you about a case in which a young lady who had no heart disease whatsoever was erroneously treated for VPC's which I am sure in retrospect were due to alcoholism. In the absence of digitalis and with standard doses she developed this syndrome. She was shocked 20 or 30 times with typical findings. We did not have a quinidine level in her, but her renal function was normal, her heart was normal, and we simply stopped the drug. Within the usual six hour period, actually four hours, she stopped having ectopic activity and stopped her recurrent bouts of ventricular fibrillation. Subsequently, we have found normal and even low levels of serum quinidine in patients exhibiting quinidine syncope, including cases where syncope followed a single usual initial dose of quinidine.

Questioner: Did your alcoholic patient have hypokalemia?

Dr. Wasserman: No, she did not. As a matter of fact, she came in with pelvic inflammatory disease but unfortunately was seen by a medical intern who was certain that he knew how to take care of her

Biotransformation	Plasma Half-Life $t_{1/2}$	Peak Effect Time		Dosage		Adverse Effects (See Heart Effects)
		p.o.	i.v.	p.o. (gm)	i.v. (mg)	
Renal 10-50% (↓if ↑urine pH) Liver	4-6 hr.	2-4 hr.	5 min.	0.4 × 1; 0.2-0.4q 6 hr.	25/min. to 1000	"Syncope"; Shock; Hemolysis; Thrombocytopenia; G-I Sx; Paralysis; Cinchonism
Renal 60% (↓if ↑urine pH)	3-4 hr.	1 hr.	Stat	1.0 × 1; 0.5q 3 hr.	50/min. to 1-2,000	Lupus; Shock; ? Syncope; Agranulocytosis; G-I Sx; Psychosis; Paralysis
Liver	2 hr.	—	Stat	—	50-100 Stat 1-4/min.	Twitching, Seizures; CNS Depression; Shock
Liver	±3 hr.	few hrs.	10 min.	.04 × 1; .01-.03q 6 hr. ?	0.1/min. to 10	Heart failure; Bronchospasm; Hypoglycemic Unresponsiveness; Rash; G-I Sx
Liver	18-24 hr. average	1-2 hr.	5 min.	1.0 first day 0.5 next day then 0.4/day	50-100mg 5/min. to 1,000	Ataxia; Sedation; Gums; Lymphoma; Lupus; Rash; Folate Def; Hepatitis; Osteomalacia; Thyroiditis Nystagmus
Renal	±10 hr.	hrs.	15 min.	.3-.6q 8-12 hr.	4-5 mg/Kg	Initial Tachycardia; Postural Hypotension; Parotid pain; Vomiting I.V.

Addendum 2

DIPHENYLHYDANTOIN DRUG INTERACTIONS

I. DRUGS LEADING TO INCREASED DPH EFFECT AND TOXICITY		
DRUGS		MECHANISM
A. Bishydroxycoumarin (Dicumarol®)		Inhibition of liver metabolism
B. Disulfiram (Antabuse®)		Inhibition of liver metabolism
C. Isoniazid		Not definite—probably inhibition of liver metabolism
D. PAS	slow-inactivators	Unknown—Possibly due to its increased blood levels of concomitant INH
E. Phenylbutazone (Butazolidin®)		Binding displacement of DPH
F. Phenylramidol (Analexin®)		Inhibition of liver metabolism
G. Sulfaphenazole (Sulfabid®) and Sulthiame (Ospolot®)		Unknown
H. Salicylates		Binding displacement of DPH
I. Chloramphenicol		Inhibition of liver metabolism
J. Benzodiazepines		Unknown
K. Methylphenidate (Ritalin®)		Not definite—probably inhibition of liver metabolism
II. DRUGS LEADING TO DECREASED DPH EFFECT AND TOXICITY		
A. Phenobarbital		Increased hepatic microsomal metabolism
B. Amphetamines		Decreased absorption of DPH
C. Alcohol		Increased liver metabolism of DPH
III. DPH'S EFFECT ON OTHER DRUGS		
DRUGS	EFFECT	MECHANISM
A. Coumarin Anticoagulants	Enhancement	Not definite—probably binding displacement
B. Corticosteroids	Inhibition	Increased microsomal metabolism
C. Methotrexate	Enhancement	Binding displacement
D. Vitamin D	Inhibition	Increased liver metabolism of Vit. D

VPC's. Of course when she developed the first episode of ventricular fibrillation, he concluded that he simply had not given her enough. She received two doses of quinidine, but that was all.

Dr. Dreifus: I too use quinidine. I just want to mention two things. The first point Dr. Surawicz already inferred was low potassium, and this seems to be one of the settings in which I have seen this repetitive ventricular tachycardia with quinidine and with other antiarrhythmic drugs that prolong Q-T intervals. The second point, which is much more serious, is acute coronary insufficiency with very long Q-T intervals. It is usually seen on the basis of sinus bradycardia. These patients do worse with quinidine or procainamide because you may move the premature systole into the long Q-T interval. The VPC will bisect the T wave, and then ventricular fibrillation or runs of ventricular tachycardia occur. Actually, the only way to deal with such patients is to pace them. The reason I wanted to mention this is, if patients at high risk were on a prophylactic agent and quinidine or a congener of quinidine was one on these agents, the patients

who were tending to develop long Q-T intervals with their bouts of coronary insufficiency might be more vulnerable to sudden death. This is a very serious problem, and I think when you use quinidine you have to take all these facts into consideration if you want to avoid mistakes.

Dr. Dreifus: I would like to ask Dr. Wasserman if he feels that bretylium has any membrane effects as an antiarrhythmic agent.

Dr. Wasserman: Yes. The problem of course has been to forget the initial articles, all of which were merely reflecting the release norepinephrine. I think it is quite clear that it does have direct myocardial effects. It certainly does so in the absence of norepinephrine depleted by pretreatment reserpine or guanethidine, and it has effects which differ from guanethidine in terms of the ventricular fibrillation threshold which suggests that it is not simply the depletion of catecholamines. Thus, I think it clearly must have some effect. I think its role is not yet clear, and I think we need to know more about it before we can use it wisely.

The Pharmacology and Clinical Use of Lidocaine and Procainamide*

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Both procainamide and lidocaine are useful for acutely treating cardiac arrhythmias, and procainamide can be useful in chronic antiarrhythmic regimens. Successful management of cardiac arrhythmias requires knowledge of: 1) the mechanism and natural history of the arrhythmia, 2) the physiologic state of the patient, and 3) the cardiac effects, pharmacodynamics, and general pharmacology of the antiarrhythmic drugs.

Although often done, it is foolhardy to undertake treatment of a cardiac arrhythmia without a precise diagnosis. The rationalization for such an undertaking frequently is that, no matter which of several possible arrhythmias is at hand, the treatment to be initiated would be beneficial or at least not harmful for any. This rationalization is often invoked to avoid

the considerable effort which may be required in order to precisely diagnose the nature of the arrhythmia. There are many specific cases where one not only treats a harmless arrhythmia, or, by not making a diagnosis, fails to use the correct therapy, but also employs a therapy which is actually harmful. Figure 1 shows an example of unnecessary therapy on the basis of an error in diagnosis. This patient had occasional ventricular premature depolarizations (VPD's). The VPD's were often followed by an aberrantly conducted beat of supraventricular origin. These couplets of wide QRS's were incorrectly considered to be salvos of VPD's and were treated with lidocaine. In fact, the patient had no indication for antiarrhythmic drug therapy at all. As luck would have it, lidocaine caused undesirable central nervous system effects in this patient. As mentioned above, therapy may be not only inappropriate but also damaging. For example, patients with atrial flutter with variable A-V conduction not infrequently show wide aberrant beats. In intensive care units, these are often mistakenly called VPD's. The fact that a non-standard bipolar chest lead is used for monitoring may obscure the fact that the beat has a RBBB configuration, a finding which might lead the physician to suspect aberrant conduction. Also, treatment may be initiated on the basis of observation of the rhythm on the oscilloscope screen. Thus, the physician may overlook the typical group beating of the Gouaux-

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‡ Fellow of the New York Heart Association; part of this work was done during her tenure as Special Fellow, NIH, USPHS, 1-F03-HL-50709-01; and initiated while she was a National Heart and Lung Institute Trainee, Grant 5-T12-HL-05864.

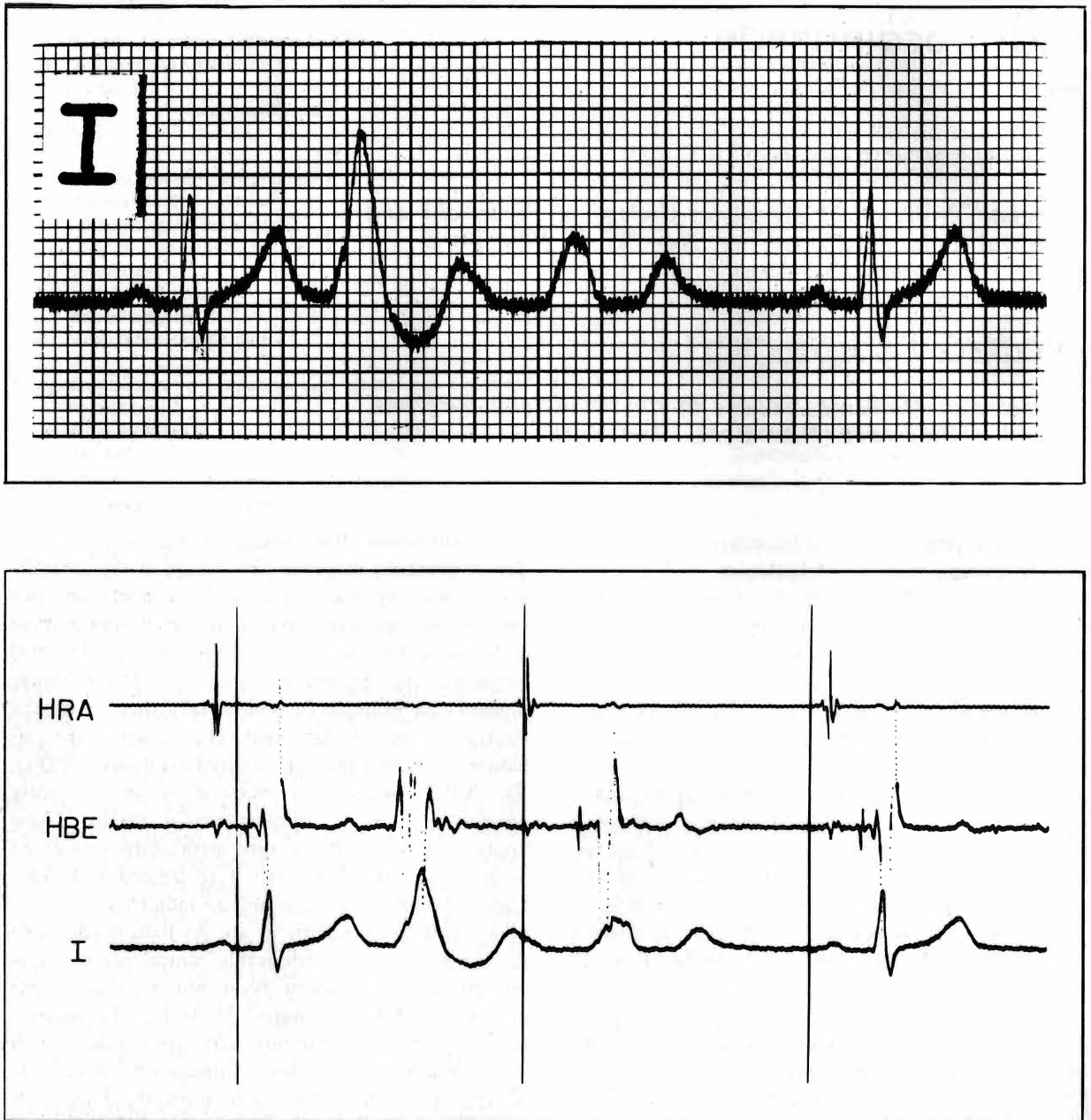


Fig. 1—Incorrect interpretation of rhythm leading to unnecessary therapy. The *upper* panel shows lead I of the ECG which was incorrectly interpreted as salvos of VPD's, and on this basis lidocaine was begun.

The *lower* panel shows recordings from high right atrium (HRA), the bundle of His (HBE), and lead I of the ECG. Actually, the rhythm was occasional VPD's with concealed retrograde conduction resulting in aberrant conduction of the subsequent beat (LBBB configuration).

Ashman phenomenon which would have been more obvious in analyzing a paper recording. This combination of errors in the intensive care unit can cause aberrant beats to be treated with lidocaine. Lidocaine can slow the atrial rate and enhance A-V conductivity, leading to a striking increase in ventricular rate. Lidocaine in these circumstances has caused atrial flutter to conduct with a 1:1 A-V ratio and has produced ventricular rates of nearly 300 per minute. If the heart is hemodynamically impaired, rapid heart rates caused in this way can be catastrophic. Other examples could be given, but these two suffice to underscore the importance of obtaining a correct diagnosis of the arrhythmia before embarking on a therapeutic course.

Even after precise identification, obviously, not all arrhythmias deserve treatment with suppressant antiarrhythmic drugs. Many arrhythmias do not deserve any therapy whatsoever. The past decade of coronary care unit experience has taught us a great deal about the natural history and indications for treating arrhythmias which arise between 4 and 72 hours after onset of symptoms in acute myocardial infarction. A great error which has become a national epidemic has been the unjustifiable extrapolation of the CCU experience to the first two hours of infarction or of the late postinfarction period. At both of these times the pattern arrhythmias, their meaning, or their response to therapy seem to be very different from arrhythmias encountered in the CCU and, at present, less well characterized. Even worse, there is a widespread tendency in recent years to use the same criteria for treating arrhythmias in other etiologic forms of heart disease as those used in acute myocardial infarction. In most forms of heart disease, our knowledge of the meaning and natural history of arrhythmias is even more rudimentary than our knowledge of arrhythmias in various stages of coronary heart disease. However, in many diseases, it is abundantly clear that arrhythmias do not need treatment even though the same ECG pattern would dictate therapy in acute myocardial infarction.

Once an arrhythmia is identified and the need for treatment established, the regimen of therapy may or may not require a specific antiarrhythmic drug. Arrhythmias encountered outside the coronary care unit very often are caused or seriously aggravated by non-cardiac factors such as electrolyte, acid-base, or blood gas derangements or drug toxicity. When initially evaluating any cardiac arrhythmia, the physician should consider the many possible non-

cardiac causes and institute the appropriate clinical and laboratory investigations to identify these, even though temporary emergency therapy is required immediately. Not only will correction of non-cardiac causes usually control the arrhythmia but also arrhythmias generated by electrolyte imbalance or blood gas derangement may be highly resistant to "specific" antiarrhythmic drugs like procainamide or lidocaine.

When a drug is finally selected to treat an arrhythmia, the goal is to maintain the plasma concentration above the minimum effective concentration without inadvertently producing toxic concentrations. To successfully achieve this goal requires a considerable knowledge about the pharmacokinetics, metabolism, and excretion of the drugs utilized.

It is our purpose to discuss briefly the clinically relevant electrophysiologic properties, clinical usage, pharmacodynamics, and toxicity of procainamide and lidocaine.

Electrophysiologic Properties. The following are a few clinically relevant electrophysiologic effects of procainamide and lidocaine.

Lidocaine. Lidocaine is a Group II antiarrhythmic drug. It suppresses automaticity in cardiac Purkinje fibers by increasing the potassium conductance of the sarcolemma but does not significantly alter threshold voltage. It shortens action potential duration and refractoriness in Purkinje fibers and ventricular muscle but has practically no effect on atrial tissues. It does not alter conduction velocity or responsiveness very much in either normal atrial or normal ventricular tissues. Under certain circumstances, lidocaine can improve conduction or reverse conduction block in ventricular tissues. Lidocaine depresses sinus node function less than procainamide. Rarely, it has been reported to suppress sinus function, usually in older patients, particularly with inferior myocardial infarction and/or preexisting signs of sinus node dysfunction. Lidocaine has little effect on atrial arrhythmias as might be predicted from its lack of effect on atrial tissues from normal animals. The drug can, but does not always, cause slight slowing of atrial rate in atrial flutter. Also, lidocaine causes no change or decrease in A-V conduction time and A-V refractoriness. Since the drug does not prolong conduction in the ventricular tissues, it does not prolong the QRS, and since it does not prolong action potential duration in the ventricles, it does not prolong the QT. It is still not clear how lidocaine abolishes reentrant ventricular arrhythmias in man.

Our studies to date suggest that it may do so either by improving conduction throughout the reentrant circuit or by blocking conduction in abnormal components of the circuit without affecting normal components.

Procainamide. Procainamide (like quinidine) is a typical Group I antiarrhythmic drug. It suppresses automaticity and moves the threshold voltage of heart muscle toward zero. Also, it lengthens action potential duration and lengthens the refractory period of atrial and ventricular cell types. It slows conduction in the atrium, A-V node, and ventricle and decreases membrane responsiveness of atrial and ventricular fibers. Many of these actions are reflected in the ECG. Procainamide does not usually affect the sinoatrial rate in intact man, but it can cause dramatic slowing of sinus rhythm in patients with derangements of sinus node function. This drug often causes minimal flattening and widening of the P wave. The atrial rate is slowed by procainamide in atrial fibrillation and flutter, and high concentrations will convert these rhythms to sinus rhythm. A direct action of procainamide is to slow A-V conduction and increase the refractoriness of the A-V conducting system; the magnitude of this effect is quite variable from patient to patient under similar conditions and

is modified by many other variable factors. Administration of procainamide to treat VPD's caused by digitalis toxicity may unpredictably produce severe A-V conduction disturbances. Slowing of conduction in the His-Purkinje system and in ordinary ventricular muscle caused by this drug is reflected in a widening of the QRS interval. In a given patient, QRS width changes usually increase linearly as a function of plasma drug concentration. The changes in repolarization produced by procainamide usually cause prolongation of the QT interval and alteration in T wave contour. The rather reliable change in QRS and QT intervals has proved quite useful in estimating therapeutic and toxic cardiac effects during therapy. The profound changes procainamide causes in conduction, responsiveness, and refractoriness of ventricular tissues no doubt underly its impressive ability to suppress VPD's or ventricular tachycardia. Our recent experiments in man suggest that as the plasma concentration of this drug rises, it causes a steadily increasing depression of conduction in a ventricular reentrant circuit until conduction fails altogether and the arrhythmia is abolished.

Clinical Use. Lidocaine. Lidocaine is not effective against a wide variety of cardiac arrhythmias, being most useful in combatting ventricular arrhythmias.

TABLE 1.
Effectiveness of Lidocaine and Procainamide Against Cardiac Arrhythmias*

ARRHYTHMIA	LIDOCAINE		PROCAINAMIDE	
	# of Success/# of Cases		# of Success/# of Cases	
SUPRAVENTRICULAR:				
Atrial premature depolarizations	15/ 31	(48%)	8/ 13	(62%)
Paroxysmal supraventricular tachycardia	5/ 11	(46%)	28/ 40	(70%)
Supraventricular tachycardia with A-V block	0/ 4	—	—	—
Atrial flutter	0/ 11	(0%)	14/ 53	(26%)
Atrial fibrillation	3/ 41	(7%)	73/215	(34%)
A-V junctional premature contractions	4/ 8	(50%)	9/ 13	(69%)
Non-paroxysmal A-V junctional tachycardia	0/ 7	(0%)	26/ 33	(79%)
Unspecified supraventricular tachycardia	3/ 9	(33%)	14/ 23	(61%)
Total:	30/122	(25%)	172/390	(44%)
VENTRICULAR:				
Ventricular premature contractions	389/495	(79%)	210/244	(86%)
Ventricular tachycardia	48/ 69	(70%)	98/122	(80%)
Total:	437/564	(77%)	308/366	(84%)

* A comparison of clinical effectiveness of lidocaine and procainamide against supraventricular and ventricular arrhythmias. Calculations are based on a review of the literature up to 1972 and include arrhythmias that were completely suppressed or at least 90% improved after drug therapy. The percentage was not determined where total cases were less than five.

mias. It is practically worthless against atrial flutter or fibrillation (Table 1); the rare instances in which it appears to abolish one of these rhythms may only be due to coincidence, or to indirect effects. Lidocaine is also, as a rule, ineffective against atrial or A-V junctional tachycardias unless they are caused by digitalis excess. Of course, lidocaine is highly effective against ventricular arrhythmias arising in many circumstances, but it is limited to relatively short-term use because it must be administered parenterally.

It should be emphasized that there is considerable difference in electrophysiologic action between procainamide and lidocaine, and it is common to see an arrhythmia that is resistant to one, submit to the other.

Procainamide. Procainamide is an antiarrhythmic drug of broad spectrum, effective against a wide variety of atrial, A-V junctional, and ventricular arrhythmias (Table 1). In general, higher plasma concentrations are required to convert or prevent atrial fibrillation than those needed to control ventricular arrhythmias. Early in its use, this fact led to the mistaken impression that the drug was ineffective against atrial arrhythmias. However, as will be discussed later, procainamide has a short half-life which means to continuously maintain plasma concentrations effective against atrial arrhythmias requires large doses every six hours. Large doses may produce toxic peak concentrations and necessitate more frequent dosing, a change which is usually inconvenient for the patient. This drug is a poor choice against ventricular arrhythmias in patients with severe A-V conduction disturbances because it may worsen conduction. Although it can be effective against many digitalis-toxic arrhythmias, its actions in this circumstance are too unpredictable to warrant its use.

Prophylaxis. In very recent years, studies have evaluated prophylactic use of procainamide or lidocaine, as well as other antiarrhythmic drugs, in the CCU. These studies, conducted in first-rate university hospitals, fail to show a decrease in mortality in the treated versus the control group. This might be expected since patients with heart failure, shock, sinus bradycardia, A-V block, or arrhythmias requiring immediate treatment were not admitted to the studies. Furthermore, these CCU's were all well-staffed so that sophisticated hospital-based physicians were almost instantly available to analyze and treat arrhythmias which developed in either the placebo or drug-treated group. It would seem that a pa-

tient in a university hospital CCU has little to gain from prophylactic therapy. On the other hand, a patient residing in any one of the many community hospital CCU's in this country where the staff may be less plentiful or well-trained and the patient's physician is based in his office practice, might have a great deal to gain from routine prophylaxis. Prophylaxis might prevent harmful results where premonitory arrhythmias were overlooked. However, routine prophylaxis in every case of myocardial infarction might increase the morbidity and mortality in patients with cardiac failure or shock, or those with bradyarrhythmias or conduction defects. Thus, even in community hospitals, the case for routine prophylaxis in acute myocardial infarction is not entirely clear.

Prophylaxis for arrhythmias in ambulatory, apparently well patients with coronary heart disease is even less well-grounded than prophylaxis in acute myocardial infarction. Several pertinent facts are emerging. First, VPD's are extremely common in asymptomatic coronary heart disease patients. Second, middle-aged men who have frequent VPD's (>10 VPD's per 1,000 beats) or sustained relative bradycardia have a much higher incidence of sudden death in follow-up periods than their peers without one of these two rhythm disturbances, even though neither group has clinically evident coronary heart disease. What is not clear is whether any available drug can significantly and persistently reduce the incidence of these arrhythmias for long periods of time without undue undesirable effects. Neither is it clear that, if one could alter these arrhythmias that are correlated with sudden death, the incidence of sudden death would be reduced. Thus, at present, prophylaxis in such a population is highly experimental and should be controlled since we do not even know that prophylaxis would do more good than harm.

Another related area of current interest arises from the fact that patients who die from arrhythmias during early stages of acute myocardial infarction or ischemia probably suffer from either ventricular fibrillation or bradyarrhythmias. It has been suggested that patients who are known to be at risk to myocardial ischemia, that is, patients with known coronary heart disease, carry syringes containing lidocaine and/or atropine. These patients would be advised, on experiencing symptoms of myocardial ischemia, to inject their drug intramuscularly and come to the hospital. Again, with the evidence avail-

able at present, we are not certain that such a course of action would not be more harmful than helpful, and such therapy cannot be recommended for more than controlled trials. However, it is reasonable to urge immediate contact between the patient with coronary heart disease who has a change in symptoms and the health care system. Analysis of the ECG either transmitted by telephone or obtained by a medical team invading the community would allow early specific treatment on the basis of the arrhythmias encountered in the individual patient. Some variant of this method would seem greatly preferable to self-injection of drug or drugs initiated on the basis of symptoms alone without regard for the presence or type of rhythm disturbance.

Pharmacodynamic Considerations. Particularly in treatment of acute arrhythmias, one of the most important aspects of antiarrhythmic drug therapy is pharmacodynamics. It is necessary to maintain the plasma drug level above the minimum effective concentration (MEC) because life-threatening arrhythmias may emerge when plasma concentrations dip below this level. Also, the rate at which MEC is achieved may be quite important. Knowledge of drug kinetics is even necessary in order to assess the effectiveness of the drug being used. Lack of a consummate knowledge of pharmacodynamics often leads physicians to conclude that a particular drug is ineffective in combatting a particular arrhythmia. In actuality, this conclusion is often incorrect because the physician is unaware of the expected time course of drug action and thus evaluates drug effectiveness at an inappropriate time. Since many of the arrhythmias treated in emergency situations, for example, acute myocardial infarction, are short-lived, the need for antiarrhythmic drug therapy is brief. Usually, a few days of such therapy is sufficient. When discontinuing or interrupting the antiarrhythmic drug therapy under such circumstances, knowledge of the expected course of elimination is vital. This knowledge allows maximum intensity of observation at appropriate times without wasting effort on unnecessarily intense vigilance at inappropriate times.

Lidocaine. Lidocaine is only used parenterally. This drug is very popular in treating acute ventricular arrhythmias where it is usually given as a sudden intravenous injection. If the arrhythmia requires treatment for a few days, constant-rate IV infusion is employed. Intramuscular injections of a special 10% formulation of lidocaine is being studied

by our group and others for possible use against arrhythmias.

Brief IV injection. Empirical trial has determined that IV lidocaine doses of 0.5 to 1.5 mg per kg body weight can be repeated every three to five minutes until a 200 to 300 mg dose is reached. This method is usually safe. The time course of plasma lidocaine after an IV injection is shown in figure 2. Several features of interest can be noted. First, the lidocaine concentration rapidly drops below the MEC (15–40 minutes), and the arrhythmia being treated may return. The early rapid drop ($t_{1/2} = 9$ minutes) in concentration is due to distribution of the drug into its large apparent volume of distribution ($V_D = 120$ liters). After distribution, the rate of elimination slows and is accomplished by a combination of renal excretion and hepatic metabolism. The hepatic metabolism of lidocaine is so rapid that under ordinary circumstances, less than 5 to 10% of lidocaine is excreted unchanged by the kidney. A note of caution about repeated IV injections or injections during infusions: the volume of distribution is partially filled with drug under these circumstances, and an unexpectedly large increase in plasma concentration may occur.

Intravenous constant-rate infusion. This mode of therapy is commonly used. Figure 2 shows the time course of the rise in plasma lidocaine when infusion is begun without prior doses. Because the MEC for lidocaine is usually so low (1 to 2 μg per ml) and the elimination $t_{1/2}$ so short (1.5 to 2 hours), the plasma concentration usually rises to MEC within an hour. If elimination of lidocaine is normal, a simple, empirical rule can be applied to estimate the plasma lidocaine concentration at steady state—the infusion rate of lidocaine in μg per minute per kg body weight divided by 10 equals the plasma concentration of lidocaine in μg per ml, for example, an infusion of 30 μg per minute per kg body weight should produce a plasma concentration of 3.0 μg per ml at steady state. Like any drug with first order kinetics, 90% of the steady state value is achieved in 3.3 times the $t_{1/2}$. Most commonly, lidocaine infusions are given following one or more IV injections as shown in figure 3. Since the elimination $t_{1/2}$ of lidocaine is fairly brief, plasma lidocaine changes fairly rapidly to a new steady state when IV infusion rate is increased or decreased and falls rapidly when an infusion is discontinued. Low cardiac output is associated with reduced hepatic blood flow and a

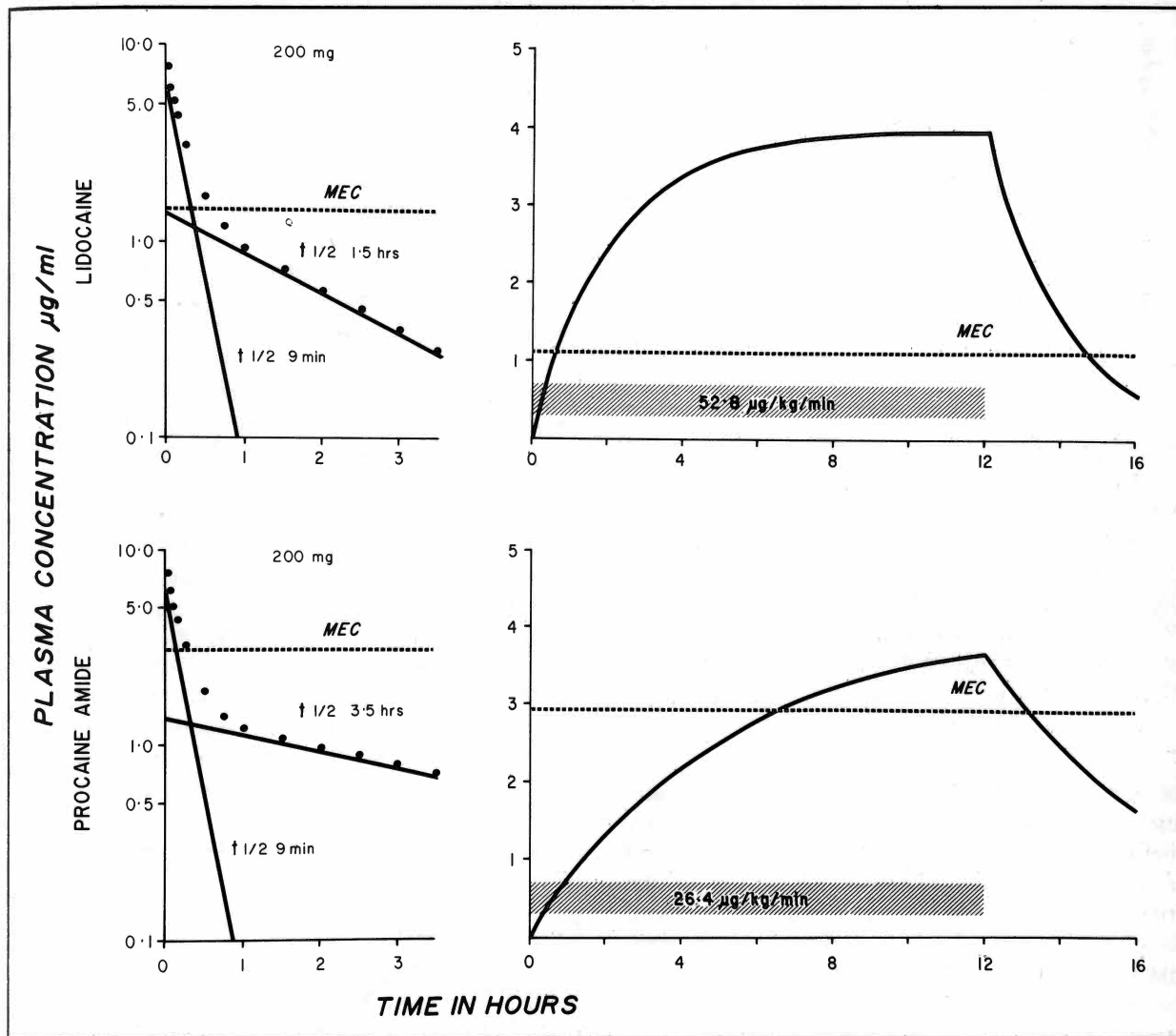


Fig. 2—Time-plasma concentration course of lidocaine and procainamide produced by sudden 200 mg intravenous injection (*left*) and constant-rate intravenous infusion (*right*).

After IV injection of either drug (*left*), the early, rapid fall in plasma drug concentration is due to distribution of drug into its large apparent volume of distribution (V_D). A slower late phase of disappearance is seen which is due to elimination of the drugs by a combination of hepatic metabolism and renal excretion. The half-time for elimination ($t_{1/2e}$) is 1.5 hours for lidocaine and 3.5 hours for procainamide.

At *right*, the plasma concentration during and after a 12-hour constant infusion of procainamide and lidocaine into a 70 kg patient. The infusion rate was selected so that after an infinite amount of time, the plasma concentration of each drug would be 4 µg/ml. For lidocaine, $t_{1/2e} = 1.5$ hours, $V_D = 120$ liters, and infusion rate = 52.8 µg/min/kg body weight. For procainamide, $t_{1/2e} = 3.5$ hours, $V_D = 140$ liters, and infusion rate = 26.4 µg/min/kg body weight. Primarily due to its longer elimination half-life, a much slower rate of procainamide infusion is required to produce a 4 µg/ml steady-state plasma concentration. Because of its longer $t_{1/2e}$, procainamide takes longer to achieve 90% of its steady-state plasma concentration (11.6 hours) than lidocaine (5.0 hours). Also, the plasma concentration of procainamide falls slower after discontinuing the infusion.

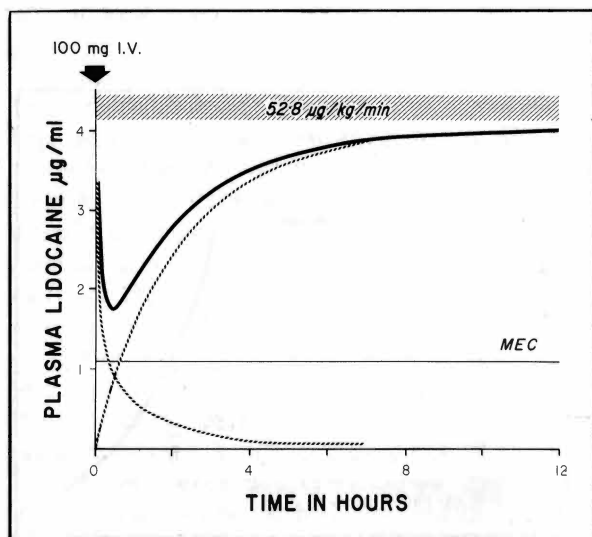


Fig. 3—Combined lidocaine dosage in a 70 kg patient with an initial IV injection of 100 mg followed immediately by an infusion of 52.8 $\mu\text{g}/\text{min}/\text{kg}$ body weight. The thin solid line shows the minimum effective concentration (MEC) for antiarrhythmic action. The thick solid line shows the concentration-time course resulting from combined therapy. The two interrupted lines show the concentration-time course which would have resulted from either mode of dosing alone. Note that this method maintains the plasma concentration in the effective range.

reduced rate of lidocaine elimination. Also, lidocaine elimination can be reduced when hepatocellular function is severely impaired. When congestive failure or another condition reducing metabolism of the drug is present, infusion rates must be reduced accordingly—sometimes by as much as two or three-fold.

Intramuscular injection. This route of administration is still being studied for its therapeutic usefulness. The plasma concentration achieved after intramuscular injection seems to depend on the formulation and concentration injected, the particular muscle used for injection, activity in the muscle after injection, and general circulatory status. Using a special 10% solution and a 4 mg per kg body weight given in the deltoid muscle, we usually achieve a 1 μg per ml plasma concentration by 5 minutes, an average peak level of 3.3 μg per ml at 15 minutes, and the concentration exceeds 1 μg per ml for 90 to 120 minutes (fig. 4).

Oral doses. When lidocaine is given orally, it is well absorbed, but this route of administration has at least two disadvantages which severely limit

its usefulness. First, the liver metabolizes an incredible proportion of an oral dose when the drug is presented to the liver via the portal circulation, and very low plasma concentrations of lidocaine are achieved. Second, oral doses tend to produce significant abdominal discomfort and, very frequently, nausea. There is evidence to suggest that the nausea may be caused by the central action of a metabolite rather than local gastrointestinal irritation.

Procainamide. Procainamide is a more versatile drug than lidocaine not only because of its broader antiarrhythmic spectrum but also because it can be administered by more routes, including the oral route which permits long-term therapy.

IV injection. There is a great deal of conflicting data in the literature regarding IV injection of procainamide. Many reports would lead one to believe that precipitous arterial hypotension is almost the rule after IV procainamide. This is true if large injections are given. We have devised a simple method of IV injection which allows rapid control of ventricular rhythms but circumvents hypotension. We give 100 mg IV every five minutes. This leads to a linear rise in plasma drug concentration and progressive decrease in VPD's until they finally disappear. This usually takes 4 to 8 doses and is not accompanied by clinically significant hypotension (fig. 5). Another advantage is that the physician knows immediately whether or not a par-

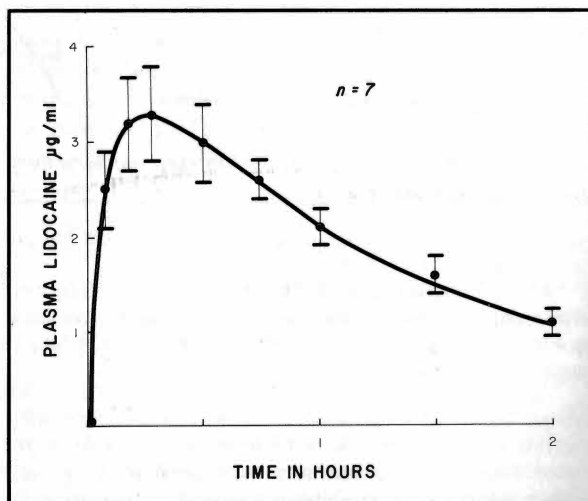


Fig. 4—Average plasma lidocaine as a function of time in seven patients with acute myocardial infarction. Four mg/kg body weight of 10% lidocaine was injected in the deltoid muscle of seven patients during the initial eight hours of acute myocardial infarction.

ticular arrhythmia will respond to this agent and whether high or low concentrations will be required. Like lidocaine, procainamide plasma concentration falls rapidly after a single IV injection because of an initial rapid distribution of the drug into a large apparent volume (fig. 2). The late phase of decline in plasma concentration is due to elimination and has an average $t_{1/2}$ of 3.5 hours. A large proportion of procainamide is excreted unchanged into the urine (about 60%), but a significant amount is acetylated, presumably by the liver (25-30%).

Intravenous constant-rate infusion. We have used this method for many years, particularly in the intensive care unit when a stable plasma concentration is desired. Figure 2 shows the plasma concentration of procainamide during and after an IV infusion. Because the MEC of procainamide is higher than lidocaine and the elimination $t_{1/2}$ is longer (± 3.5 hours), infusions may not yield therapeutic concentrations until about 6 hours have elapsed, and 90% of steady-state concentration is reached at 12 hours (3.3×3.5). Because the elimination $t_{1/2}$ of procainamide is about twice as long as that of lidocaine, the former drug takes longer to achieve a new steady state after a change in infusion rate and falls much slower when an infusion is stopped. Figure 4 shows the combination of intermittent IV injection therapy with constant-rate infusion.

Intramuscular injection. Procainamide is fairly well absorbed after IM injection and when given by this route rapidly produces antiarrhythmic plasma concentrations which decline as expected from its elimination $t_{1/2}$. The rate at which a MEC is achieved is not a great deal faster than after an oral dose. Therefore, unless the patient is unable to take the drug by mouth, there is little indication for IM administration.

Oral doses. Procainamide can be given by mouth which is a major advantage over lidocaine. The drug is not well absorbed from the stomach when the pH is acid, and delay in gastric emptying can cause a delay in onset of absorption. However, this drug is quickly absorbed from the alkaline small intestine; after adequate doses, effective plasma levels are achieved in 15 minutes or so, and the peak level is achieved between 45 and 75 minutes after a dose. Absorption is virtually complete after 90 to 105 minutes, and elimination takes place with a $t_{1/2}$ of 3.5 to 4 hours. Renal excretion of procainamide is greatly reduced when the urine is alkaline,

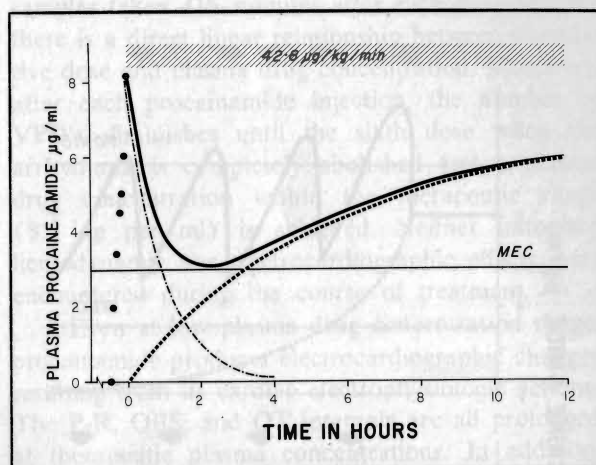


Fig. 5—Plasma procainamide concentration plotted as a function of time when drug is given by incremental intravenous dosing and/or constant intravenous infusion. The minimum effective concentration, MEC, is represented by the thin solid line. Six 100 mg doses of procainamide are given every 5 minutes, black dots, until the arrhythmia is completely suppressed at a plasma drug concentration of 8.2 $\mu\text{g}/\text{ml}$ within 30 minutes. The dash-dot line shows the concentration-time course which would have resulted if incremental doses were stopped and no other mode of dosing started. Without prior injection, when a constant intravenous procainamide infusion (42.8 $\mu\text{g}/\text{min}/\text{kg}$ body weight) is started, dashed curve, the plasma drug concentration would be above the MEC at 3 hours and is 6.5 $\mu\text{g}/\text{ml}$ at steady state. The thick black line represents the plasma procainamide concentration which would be obtained by initially giving the six 100 mg injections and, then, immediately beginning a constant IV infusion of 42.8 $\mu\text{g}/\text{min}/\text{kg}$ body weight. Note that the procainamide concentration never falls below the MEC.

and in instances of congestive failure or renal failure. In these situations, a larger proportion of a given dose is acetylated by the liver. In congestive failure, procainamide, like lidocaine, has a smaller apparent volume of distribution, which means the same amount of drug in the body will result in a higher plasma drug concentration. Some years ago we noted procainamide toxicity occurring during the change from intravenous constant-rate infusions of procainamide to an oral regimen, even though the total 24-hour doses were identical. Our error is shown in figure 6 (upper panel). Since an oral dose produces a rapid rise in plasma concentration, an initial oral dose given immediately on stopping the infusion causes a high (toxic) plasma concentration. It is apparent that an oral dose of a rapidly absorbed drug is tantamount to an IV injection. This unfor-

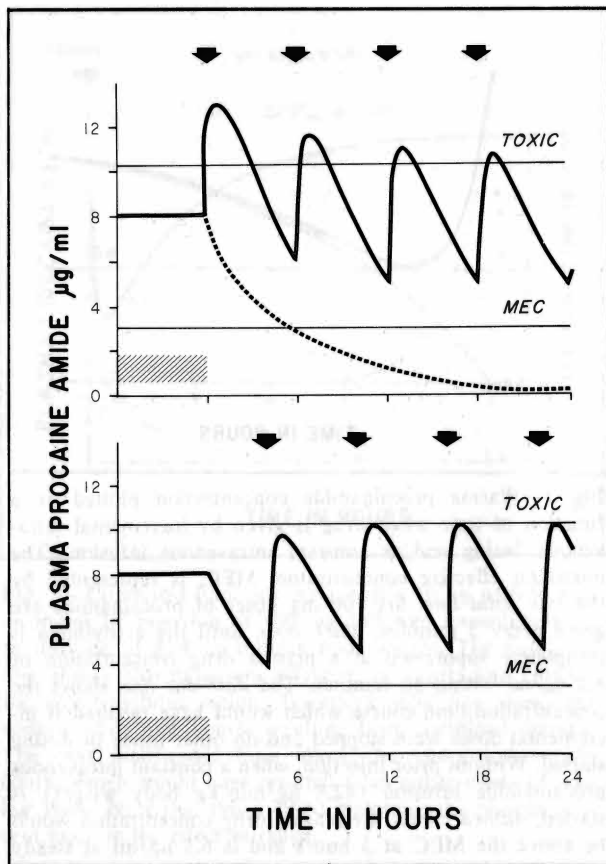


Fig. 6—Changing from continuous intravenous infusion to an oral dose regimen of procainamide $V_D = 140$ liters, $t_{1/2e} = 4.0$ hours.

The upper graph shows the termination of an intravenous infusion which for three days had maintained a stable plasma procainamide concentration of 8 $\mu\text{g/ml}$. At time = 0, the infusion was discontinued and a regimen of 1,000 mg oral doses every 6 hours was begun. Note that toxic concentrations are obtained after each of the first four oral doses although this will ultimately be a satisfactory regimen at steady state.

The lower graph shows an identical patient, given an identical infusion and oral dosage regimen with only one exception—four hours were allowed to elapse between cessation of infusion and beginning the oral drug. Note that the plasma procainamide concentration never reaches toxic concentrations.

unfortunate sequence can be avoided completely by waiting for about four hours after discontinuing the infusion before giving the first oral dose (fig. 6, lower panel).

Toxicity. While antiarrhythmic drugs have considerably decreased mortality from arrhythmias seen following acute myocardial infarction and open heart surgery, improper use of these agents is as

potentially life-threatening as the presence of the arrhythmia itself. A considerable incidence of toxicity is still encountered in using these drugs and impairs their general usefulness. Toxicity usually results from insufficient attention to the general physiologic state of the patient, the functional impairment of the organs which metabolize these drugs, or pharmacodynamic considerations. However, even when errors in judgement are made using these drugs, a thorough knowledge of their toxic effects and a continuing careful search for early toxic signs can often prevent more severe and serious toxicity.

Lidocaine. Clinical toxicity of lidocaine appears to be related to size of dose and rate of administration. Ordinary doses, however, may produce undesirable effects when there is severe hepatic disorder, acidosis, severe congestive heart failure, low cardiac output, and shock. If lidocaine is infused at usual rates where these conditions exist, toxicity may ensue and, in fact, where blood levels have been measured in these cases, they are frequently two or three times higher than those needed for effective therapy.

Lidocaine usually produces signs of central nervous system (CNS) involvement before any subjective or objective cardiovascular effects are observed. The early symptoms may be extremely subtle. Blood levels greater than 6 μg per ml have been associated with dizziness, drowsiness, numbness of lips and tongue, speech disturbances, and psychosis. At present we suspect that many of the minor CNS symptoms of lidocaine toxicity go unrecognized as such and are treated with diazepam or a similar agent. More severe CNS manifestations such as tremor, convulsions, respiratory depression, and areflexia occur most commonly when venous blood levels of lidocaine are higher than 10 μg per ml but may be seen at lower concentrations. Signs of CNS toxicity may be treated by stopping lidocaine infusion and, as a rule, symptoms will improve within 15-30 minutes, but may take several hours to completely abate. Lidocaine-induced convulsions may require treatment with small intravenous doses of short-acting barbiturates. High doses of barbiturate should be avoided since their CNS depressant effects may potentiate those of lidocaine and may result in respiratory arrest.

The hemodynamic effects of 1 mg per kg of lidocaine injected intravenously have been measured by several groups. While hypotension may result

from larger doses of lidocaine, in therapeutic doses, there appears to be little effect on systemic arterial pressure, ventricular contractile force, cardiac output, heart rate, or stroke volume in man. Thus, it would seem that lidocaine given in this way exerts remarkably few if any adverse effects of clinical significance. The hemodynamic effects of lidocaine in the shock state or after a constant intravenous infusion are as yet unknown.

Finally, lidocaine has been suspected of producing cardiovascular toxicity. Clinical observations, largely unsubstantiated by conclusive evidence, have implicated lidocaine as the cause of: 1) rapid ventricular response to an atrial arrhythmia, 2) production of ventricular arrhythmia, or increase in number of ectopic beats, 3) heart block, and 4) asystole. The use of lidocaine is not advised in the presence of heart block.

Procainamide. Procainamide is more prone to produce direct cardiac toxicity expressed as alterations in electrical and mechanical behavior of the heart than lidocaine. As with lidocaine, many of the toxic reactions seen with procainamide are related to size of dose and also to the route of administration. Rapid intravenous administration, particularly when given faster than 50-75 mg per minute, has been associated with undesirable electrocardiographic and hemodynamic effects. Because of this, oral and intramuscular use of procainamide has been advocated. However, even with these routes of administration and recommended dose size, toxicity may be encountered in congestive heart failure, renal disease, or shock.

In our experience, therapeutic effectiveness and toxicity of procainamide are closely related to plasma drug concentration. We consider the effective antiarrhythmic plasma drug concentration range to be 3 or 4-10 μg per ml and have observed electrophysiologic and hemodynamic toxicity at concentrations greater than 12 μg per ml. Notwithstanding the bad reputation of intravenously administered procainamide, we have found that antiarrhythmic plasma drug concentrations are attained rapidly, safely, and predictably when procainamide is given intravenously. We recommend 100 mg of procainamide be given intravenously every 5 minutes with electrocardiographic and blood pressure monitoring. An example of this method is shown in figure 4; the electrocardiogram was continuously monitored and patient P.B. was given 100 mg of procainamide every 5 minutes until VPD's were abolished. Plasma

samples taken 4½ minutes after each dose indicate there is a direct linear relationship between cumulative dose and plasma drug concentration. Moreover, after each procainamide injection, the number of VPD's diminishes until the sixth dose when the arrhythmia is completely abolished and a plasma drug concentration within the therapeutic range (8.3 μg per ml) is achieved. Neither untoward hemodynamic nor electrocardiographic effects were encountered during the course of treatment.

Even at low plasma drug concentration range, procainamide produces electrocardiographic changes resulting from its cardiac electrophysiologic actions. The P-R, QRS, and QT intervals are all prolonged at therapeutic plasma concentrations. In addition, toxic drug concentrations have been associated with progression of these or appearance of more dramatic electrophysiologic effects such as: 1) suppression of cardiac automaticity, including the S-A node, leading to asystole, 2) impairment of A-V conduction, leading to heart block, and 3) slowing of intraventricular conduction greater than 30%. Another noteworthy undesirable electrocardiographic change stems from the fact that toxic concentrations of procainamide almost invariably cause increased automaticity and multifocal pacemaker activity in isolated cardiac Purkinje fibers. Thus, the appearance of ectopic ventricular beats, ventricular tachycardia, or fibrillation in a patient who presumably has achieved therapeutic drug concentration may not represent arrhythmia breakthrough but rather procainamide toxicity. If the physician is unaware of this complication, he may continue to administer procainamide or even increase the dose, not realizing that the drug is responsible for evoking the arrhythmia. Since therapeutic and toxic drug effects are so well correlated with electrocardiographic changes, the electrocardiogram is an excellent way to monitor procainamide efficacy and, when carefully used, the incidence of toxicity is likely to be reduced. Because of its depressant effects on A-V conduction and ventricular automaticity, procainamide is contraindicated in heart block, and cautious use has been advised in patients with wide QRS intervals and bundle branch block.

Procainamide may produce hemodynamic changes by depressing myocardial contractility and the cardiac output and thereby produce hypotension. While the severity of these hemodynamic alterations appears to be related to dose size and rate of administration, they may be further intensified by heart

disease and congestive heart failure. Although procainamide should be used cautiously in these conditions, they do not preclude therapy. We have noted that the probability of untoward hemodynamic effects is minimized by intermittent intravenous injections and by careful monitoring of blood pressure. If necessary, doses higher than 1000 mg may be given by this technique without evidence of cardiac toxicity or hypotension. Procainamide-induced hemodynamic or electrocardiographic toxicity may be treated by molar sodium lactate and the catecholamines, norepinephrine or isoproterenol.

Extracardiac toxic reactions to procainamide are most commonly seen during chronic oral therapy. Gastrointestinal disturbances (nausea, vomiting, diarrhea), and CNS disturbances (mental depression, psychosis, and convulsions) have been reported. Other toxic effects include skin rash, fever and chills, and agranulocytosis. Most of these extracardiac reactions subside almost immediately with

discontinuation of the drug, but some may persist a few days to a few weeks. A syndrome resembling systemic lupus erythematosus (SLE) characterized by arthralgia, fever, pleuropneumonic involvement, and hepatomegaly has occurred frequently in patients on long-term maintenance therapy. Rarely, adrenal corticosteroids have been required to control unusually tenacious symptoms of SLE. It should be pointed out that, unlike SLE, the drug induced SLE-like syndrome produces no permanent damage in any vital organ system. This and the fact that aspirin or steroids may control symptoms are important considerations in planning the management of a patient who has a life-threatening arrhythmia for which other drugs are ineffective, and who has developed the SLE-like syndrome. In such a case, one reasonable course of action is to continue procainamide and control symptoms of the SLE syndrome with salicylates or adrenal corticosteroids.

The Evaluation of Sinoatrial Node Function in Man*

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The function of the sinoatrial node is complex. In nearly all hearts, this small bit of tissue is responsible for spontaneously generating the impulse which will be distributed to the remainder of the heart, maintaining coordinated electrical and mechanical function. In recent years, it has become clear that S-A node dysfunction is not rare, can cause disabling symptoms, and often presents difficult management problems. The challenges presented by the "Sick Sinus Syndromes" have increased our desire to know more about normal S-A node function and about function in disease states.

The intimate mechanisms of sinus node function remain a mystery despite the "prying eye" of the microelectrode and modern anatomical and chemical methods. At least the time-voltage course of spontaneous activity in the sinus node cells has been elucidated. After self-excitation, a pacemaking sinus node cell slowly depolarizes to zero potential differ-

ence with the extracellular fluid and often shows some overshoot, that is, the inside of the cell may become slightly positive relative to the extracellular potential. After reaching this peak inside-positive value of transmembrane voltage (V_m), the sinus node cell slowly repolarizes to a maximum inside-negative value—so-called maximum diastolic voltage. Then, the transmembrane voltage spontaneously begins to decrease (phase 4 depolarization) until a critical value of V_m , threshold voltage, is reached and self-excitation recurs. The rate of recurring self-excitation could theoretically be altered by changes in: 1) maximum diastolic voltage, 2) threshold voltage, and 3) rate of phase 4 depolarization. Changes in firing of a sinus node cell are most often mediated by changes in rate of phase 4 depolarization. We still do not know the precise sequence of membrane permeabilities as a function of time and voltage which are responsible for the normal automatic behavior of the S-A node.

Sinus node rate is sensitively adjusted to most suitably meet the needs of the body as a whole. These adjustments are usually mediated through autonomic reflexes which change the rate and pattern of firing on sympathetic and/or parasympathetic nerves terminating at or near the sinus node. Release of norepinephrine from sympathetic nerve terminals in the vicinity of a sinus node cell will accelerate phase 4 depolarization and the spontaneous firing rate of the S-A node while acetylcholine released from cholinergic terminals has the opposite effect.

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Once the normal automatic mechanism has generated an impulse in the S-A node itself, the impulse must be transmitted to the ordinary and specialized atrial fibers in order to effect atrial and, ultimately, total cardiac excitation. The action potential of the S-A nodal cell is of a type associated with slow conduction and vulnerability to block or fragmentation in transmission, that is, phase 0 is small in amplitude and extremely slow rising. Also, the S-A nodal pacemaker cells are small, have multiple connections with their neighbors, and are entangled in a dense connective tissue stroma. These anatomical features undoubtedly contribute to slow conduction in the sinus node. In addition, the sinus node is surrounded by a group of cells which are intermediate in time-voltage course between S-A nodal cells and atrial specialized cells. These cells, called "perinodal fibers" are not automatic under normal circumstances but do have electrophysiologic properties which promote slow conduction and block; "perinodal cells" represent a barrier to conduction into the S-A node and a region where "organization" and amplification of impulses leaving the S-A node might occur.

All of the events discussed above—impulse generation in the S-A node and its transmission to the atrium—are invisible both on the body surface electrocardiogram and in local extracellular atrial electrograms. Analysis of the behavior of the S-A node in man is even more complicated than analysis of the A-V node. We have been able to study the A-V node in man by recording local electrograms from the atrial margin of the A-V node and, on the other side, the nearby bundle of His. Programmed stimulation of the atria or ventricles and analysis of the electrical responses allow a rather complete characterization of the A-V node. The S-A node is somewhat analogous to the A-V node in that the impulse generated in the S-A node must pass through the "perinodal fiber" (analogous to the A-V node) in order to reach specialized atrial fibers (analogous to the bundle of His). However, this analogy is very incomplete in that the S-A node itself is an area of slow conduction and, in addition, spontaneously generates impulses.

Experimental and clinical observations made in the first decade of the twentieth century established that second degree S-A block could occur in animal and human hearts. In fact, second degree sinoatrial block was well established clinically from analysis of the jugular venous pulse well before this

abnormality was recorded electrocardiographically. Since that time there has been a great increase in our knowledge of the electrocardiographic features of second degree S-A block. More recently, the use of electrical pacemakers as a therapeutic device has led to an increased interest in and understanding of a variety of clinical patterns of S-A nodal dysfunction. These clinical patterns include:

1. severe sinus bradycardia, not induced by drugs or inappropriately severe for the type and amount of drug administered.
2. periods of second degree S-A block, inappropriate for drug therapy.
3. long pauses in sinoatrial rhythm caused by sinus arrest, repetitive concealed sinus exit block or third degree S-A exit block.
4. chronic atrial fibrillation with a slow ventricular rate in the absence of drugs which slow A-V conduction, and inability of the heart to resume stable sinus rhythm after electrical cardioversion.
5. the tachycardia-bradycardia syndromes.

Several features of these syndromes deserve comment. The first three listed have been recognized for a long time and if accompanied by heart failure or central nervous system symptoms are often treated, and successfully, with implanted electrical pacemakers. For a long time we recognized that patients with atrial fibrillation who had a slow ventricular rate without drug treatment were prone to develop very slow ventricular rates when treated with digitalis and often had severe sinus bradycardia, sinus pauses and other rhythms of sinus dysfunction when cardioverted. Recently, we have learned that this is due to the fact that many patients with severe S-A node dysfunction also have impaired A-V conduction and sluggish ventricular pacemakers. The tachycardia-bradycardia syndromes (fig. 1) have been recognized for about twenty years, but they presented difficult, often insurmountable, management problems until combined treatment with drugs and an electrical pacemaker became available.

It is easy to recognize S-A nodal dysfunction when it presents as one of the five syndromes listed above. However, it can be difficult to know whether S-A node dysfunction is present. Two examples which present clinical difficulty are: 1) moderate sinus bradycardia which may or may not indicate intrinsic malfunction of the S-A node and portend a series of difficult rhythm problems and their

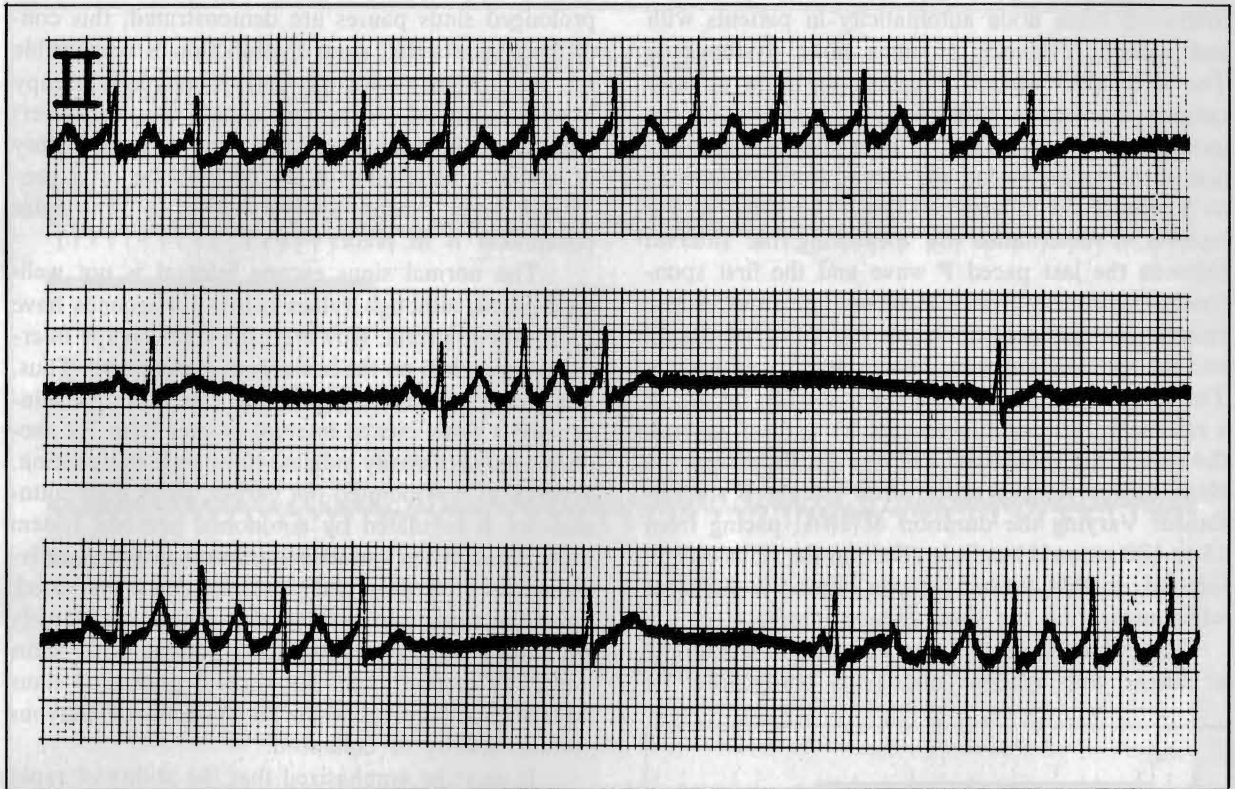


Fig. 1—The tachycardia-bradycardia syndrome. A 67-year-old man referred for evaluation of recurrent syncope, dizziness, and weakness. Lead II of his admission electrocardiogram shows a repeated change in rhythm from atrial flutter to sinus bradycardia. He was treated with a permanent transvenous pacemaker and digitalis and has been symptom-free for more than a year.

sequelae and 2) drug-induced sinus bradycardia or S-A block which improves to normal or near-normal when the inducing drug is removed. We need clinical applicable tests to evaluate patients who demonstrate such events. Ideally, these tests would separate patients with intrinsic S-A nodal dysfunction who require careful follow-up observation and have a high probability of need for early therapeutic intervention from those who merely have a slow sinus rate or those in whom a combination of extrinsic factors caused a temporary impairment in function of an essentially normal S-A node. Recently, two techniques have been used in the attempt to evaluate sinus node function in man: 1) rapid atrial pacing and 2) premature atrial stimulation. We will discuss briefly the use of these techniques in analyzing S-A nodal function.

Rapid Atrial Pacing. Out of a group of patients with syncopal attacks who presented to the National Heart Hospital in England, four were noted to have periods of sinus bradycardia alter-

nating with periods of atrial tachyarrhythmias. In these patients the sinus rate usually ranged between 22 and 50 per minute. The episodes of atrial tachyarrhythmias were of variable duration, and in one patient, syncope associated with the termination of the tachyarrhythmia was documented. The episodes of syncope in these patients were due to a long period of cardiac standstill that followed the sudden termination of the atrial tachyarrhythmia (fig. 1). The extra long pauses that followed the termination of the tachyarrhythmia were a manifestation of depressed sinus node automaticity. That this was the case is suggested by the effects of quinidine hydrochloride on the sinus rate, that is, atrial standstill was observed in all four patients. Recent experimental studies reporting on the sinus node response to atrial pacing have obtained data that is somewhat analogous to the clinical observations on the sinus node response following sudden termination of an atrial tachyarrhythmia. These reports also have speculated on the ability of this technique to

determine sinus node automaticity in patients with and without evidence of sinus node dysfunction. The technique consists of pacing the atria at rates ranging between a rate slightly in excess of the spontaneous sinus rate and 170 per minute. The duration of the pacing period has ranged from 15 seconds to 5 minutes in different studies. The sinus escape interval is determined by measuring the interval between the last paced P wave and the first spontaneously occurring sinus P wave. The sinus escape interval is dependent upon the rate of atrial pacing and the spontaneous sinus heart rate prior to pacing. The longest sinus escape interval usually occurs at a rate near 130 per minute (fig. 2) and, in general, the slower the spontaneous heart rate, the longer the sinus escape interval after atrial pacing is discontinued. Varying the duration of atrial pacing from 15 to 180 seconds has little effect on the sinus escape interval, so that pacing for one minute is sufficient when measuring the sinus escape interval.

Rapid atrial pacing is most useful in evaluating a patient with syncope and sinus bradycardia. If

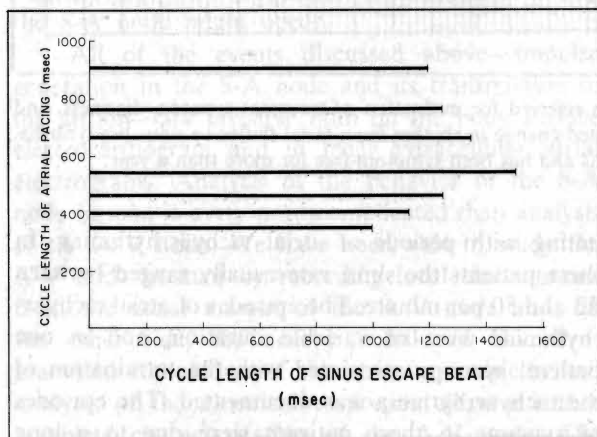


Fig. 2—The effect of atrial pacing on sinus escape interval. The patient's mean spontaneous sinus cycle length was 1050 msec (57/min). The right atrium was paced at each cycle length for 60 seconds and the interval between the last paced P wave and the first sinus P wave measured (plotted on the abscissa). As the paced atrial cycle length shortened, the sinus escape interval lengthened to a maximum of 1510 msec at a pacing cycle length of 540 msec (110/min). Thereafter, the cycle length of the sinus escape beat paradoxically decreased as the pacing rate increased. This finding suggests that, due to entrance block, the sinus node is actually being discharged more slowly at faster atrial pacing rates so that the decreasing cycle length of the sinus escape beat reflects the slower rate of sinus node discharge. The progressive shortening of the sinus escape interval as the rate of atrial pacing increases above 110/min probably reflects increasing degrees of sinoatrial entrance block.

prolonged sinus pauses are demonstrated, this condition suggests that sinus malfunction is responsible for the patient's syncope and pacemaker therapy is recommended. Also, one should not cardiovert patients with atrial fibrillation who have a history of either clinical sinus node dysfunction or a prolonged sinus escape interval unless a ventricular pacemaker is in place.

The normal sinus escape interval is not well-established, although values below 1.4 seconds have been called normal. However, the sinus escape interval is dependent on the basic sinus cycle length. Thus, in a young athlete, neither a heart rate of 43 per minute nor a sinus escape interval greater than 1.4 seconds need necessarily indicate sinus node dysfunction. Second, as was pointed out earlier, sinus node automaticity is regulated by autonomic nervous system tone. Thus, when sympathetic nervous system activity is increased, sinus node automaticity is enhanced. Since the sinus escape interval is determined largely by sinus node automaticity, a patient with sinus node dysfunction might not show a prolonged sinus node escape interval when his sympathetic nervous system activity is enhanced.

It must be emphasized that the ability of rapid atrial pacing to adequately assess sinus node automaticity is dependent upon 1:1 conduction from the atrium to the sinus node without excessive conduction delay between the atrium and sinus node. Should conduction from the atrium to the sinus node fail during atrial pacing, then the sinus node must be depolarized at a rate that is, in fact, much slower than the rate of atrial pacing. This entrance block could explain why the sinus node escape interval at 150 per minute was shorter than the escape interval at 130 per minute (fig. 2).

In patients with diseased sinoatrial nodes and sinoatrial junctional tissue, conduction from the sinus node to the atrium and from the atrium to the sinus node may be prolonged (fig. 6). In this circumstance, atrial pacing may fail to adequately assess sinus node automaticity since conduction from the atrium to the sinus node may become less than 1:1 even at very low pacing rates.

It is of interest that prolonged secondary sinus pauses are seen after discontinuing atrial pacing at 170 per minute (fig. 3). Secondary sinus pauses can recur many times during the first 20 seconds following termination of rapid atrial pacing. The duration of the secondary sinus pauses can even be greater than the duration of the sinus escape interval. This

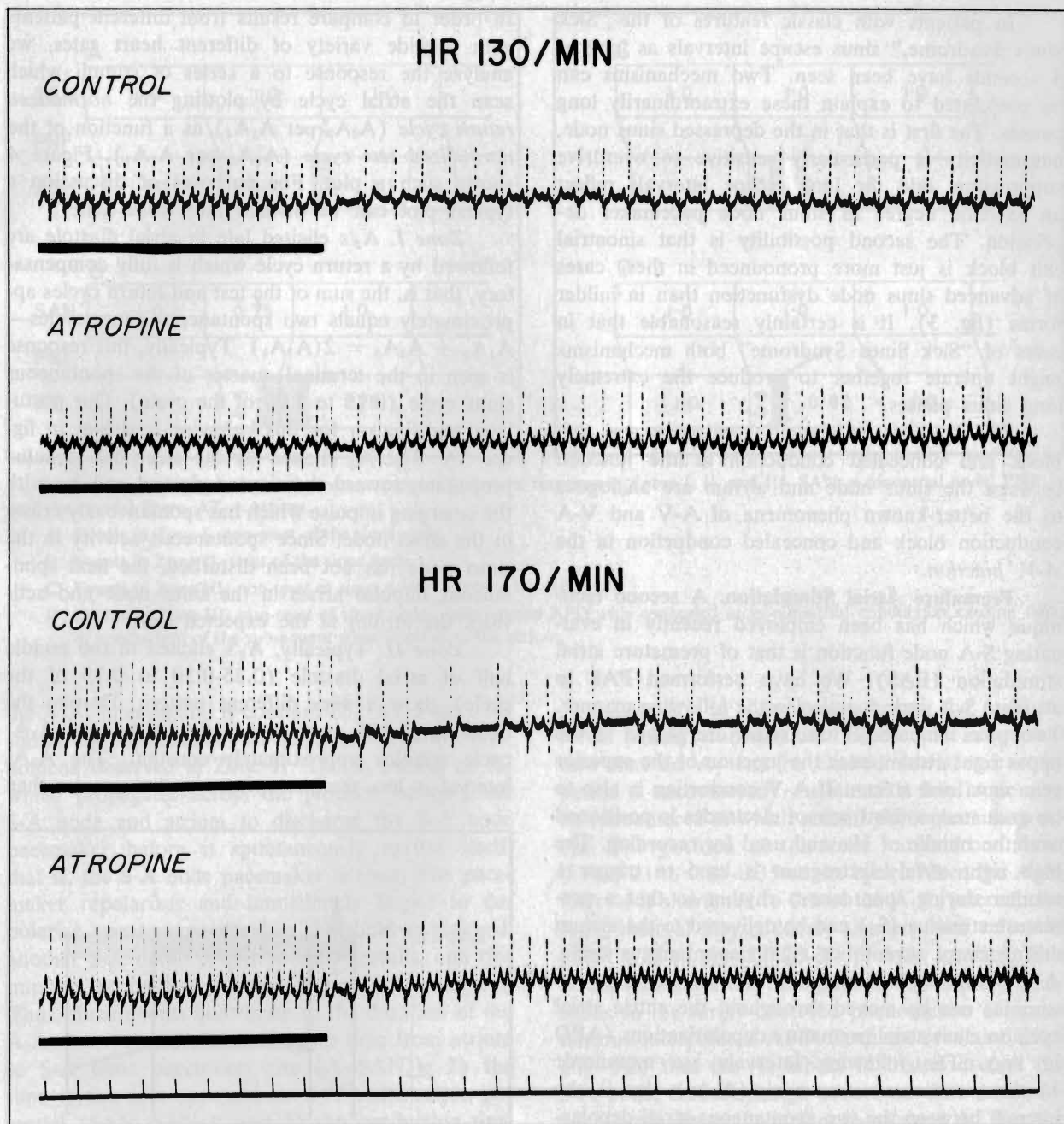


Fig. 3—Secondary sinus pauses occurring during the measurement of sinus escape interval. A 53-year-old woman with angina pectoris, and normal coronary arteriograms was referred for evaluation of sinus bradycardia. In this patient, the longest sinus escape interval was seen after an atrial pacing rate of 130/min. At a pacing rate of 170/min, the sinus escape beat interval was shorter than at 130/min, and prolonged secondary sinus pauses were noted following termination of rapid atrial pacing. These secondary sinus pauses may reflect pacemaker malfunction or advanced degrees of sinoatrial exit block. Atropine caused shortening of the sinus escape interval at all paced rates and abolished secondary sinus pauses. See text for discussion.

pattern of beating is compatible with repeated short periods of sinoatrial exit block (repetitive concealed exit block). Secondary sinus pauses seen

after discontinuing atrial pacing are abolished by atropine, suggesting that they may be encouraged by cholinergic influences (fig. 3).

In patients with classic features of the "Sick Sinus Syndrome," sinus escape intervals as long as 5 seconds have been seen. Two mechanisms can be postulated to explain these extraordinarily long pauses. The first is that in the depressed sinus node, automaticity is particularly sensitive to overdrive suppression, and the long escape intervals reflect an extreme degree of sinus node pacemaker depression. The second possibility is that sinoatrial exit block is just more pronounced in these cases of advanced sinus node dysfunction than in milder forms (fig. 3). It is certainly reasonable that in cases of "Sick Sinus Syndrome" both mechanisms might operate together to produce the extremely long sinus pauses.

The episodes of sinoatrial entrance and exit block and concealed conduction at the junction between the sinus node and atrium are analogous to the better-known phenomena of A-V and V-A conduction block and concealed conduction in the A-V junction.

Premature Atrial Stimulation. A second technique which has been employed recently in evaluating S-A node function is that of premature atrial stimulation (PAS). We have performed PAS to evaluate S-A node function in the following manner. Two pairs of catheter electrodes are placed in the upper right atrium, near the junction of the superior vena cava and atrium. If A-V conduction is also to be evaluated, a third pair of electrodes is positioned over the bundle of His and used for recording. The high right atrial electrogram is used to trigger a counter during spontaneous rhythm so that a premature stimulus (S_2) can be delivered to the atrium during every seventh or eighth spontaneous cycle. A programmable stimulator is used so that the stimulus can be moved throughout the entire atrial cycle to elicit atrial premature depolarizations (APD or A_2). The following intervals are measured: 1) *the spontaneous sinus cycle* (A_1A_1), that is, the interval between the two spontaneous atrial depolarizations immediately preceding A_2 , 2) *the test cycle* (A_1A_2), the interval between the atrial premature depolarization (A_2) and the immediately preceding spontaneous atrial depolarization (A_1), and 3) *the return cycle* (A_2A_3), that is, the interval between A_2 and the subsequent spontaneous atrial depolarization (A_3). In order to check the stability of atrial cycle length and evaluate the feasibility of normalizing, we measure the spontaneous atrial cycle immediately following the return cycle (A_3A_1).

In order to compare results from different patients with a wide variety of different heart rates, we analyze the response to a series of stimuli which scan the atrial cycle by plotting the *normalized return cycle* (A_2A_3 per A_1A_1) as a function of the *normalized test cycle* (A_1A_2 per A_1A_1). Figure 4 shows such a plot. For purposes of discussion a typical plot can be divided into three zones.

Zone I. A_2 's elicited late in atrial diastole are followed by a return cycle which is fully compensatory, that is, the sum of the test and return cycles approximately equals two spontaneous sinus cycles— $A_1A_2 + A_2A_3 = 2(A_1A_1)$. Typically, this response is seen in the terminal quarter of the spontaneous sinus cycle (0.75 to 1.00 of the cycle). Our postulated mechanism for this behavior is shown in figure 5A. The A_2 elicited by the electrical stimulus propagates toward the sinus node and collides with the emerging impulse which has spontaneously arisen in the sinus node. Since spontaneous activity in the sinus node has not been disturbed, the next spontaneous impulse arises in the sinus node and activates the atrium at the expected time.

Zone II. Typically, A_2 's elicited in the middle half of atrial diastole (0.25-0.30 to 0.75 of the cycle) show a very different pattern. Despite the decreasing A_1A_2 per A_1A_1 , the A_2A_3 per A_1A_1 cycle remains approximately constant. The A_2A_3 interval is less than compensatory but greater than

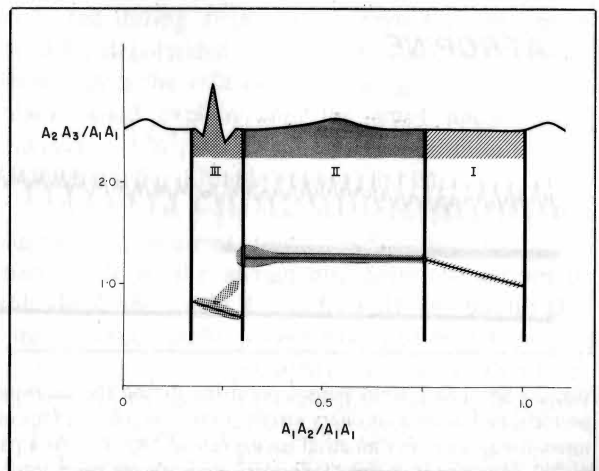


Fig. 4—The three zones of the atrial cycle revealed by premature atrial stimulation. Every seventh spontaneous atrial cycle, a stimulus (S_2) evoked a premature atrial depolarization. Here, the normalized return cycle (A_2A_3/A_1A_1) is plotted as a function of the normalized test cycle (A_1A_2/A_1A_1). The atrial zones are referenced to the electrocardiogram above. See text for detailed explanation.

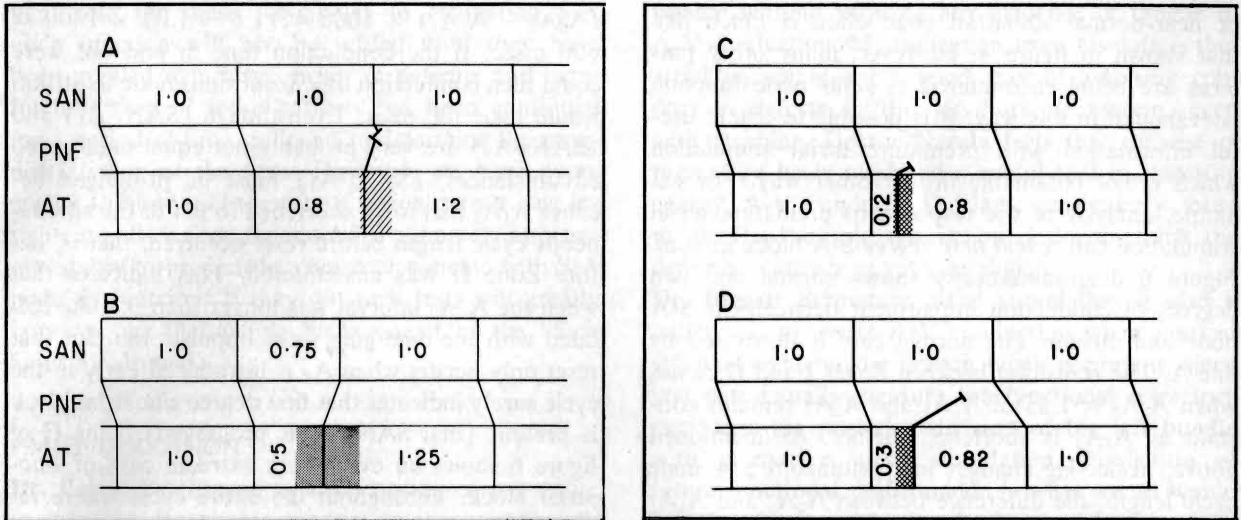


Fig. 5—Ladder diagrams depicting the events responsible for the response in Zones I, II, and III. SAN = sinoatrial node, PNF = peri(sinus)nodal fibers, AT = atrium.

- A. Events in Zone I: non-reset of the sinus node
- B. Events in Zone II: reset of the sinus node
- C. Events in Zone III: non-reset of sinus node—interpolated APD
- D. Events in Zone III: non-reset of sinus node—interpolated APD with concealed atrial-sinoatrial conduction causing delay of conduction of the subsequent sinus impulse to the atrium.

the A_1A_1 interval and is constant (fig. 4). Figure 5B shows the mechanism we postulate for this phenomena observed in Zone II. The S_2 evokes an A_2 which propagates across the junction between the S-A node and atrium to discharge the S-A node pacemaker before it spontaneously excites itself, that is, the S-A node pacemaker is reset. The pacemaker repolarizes and immediately begins to depolarize spontaneously; when threshold is reached, another S-A nodal action potential results, and this impulse propagates to the atrium producing A_3 . Thus, three events contribute to the duration of the A_2A_3 interval: 1) the conduction time from atrium to S-A node pacemaker site (A_2-SAN_2), 2) the time to the next spontaneous S-A nodal action potential (SAN_2-SAN_3), and 3) the conduction time from the S-A nodal pacemaker to the atrium (SAN_3-A_3). The A_2A_3 interval remains almost constant throughout Zone II, indicating that the sum of these three events remains almost constant. If the spontaneous S-A node cycle following reset (SAN_2-SAN_3) is equal to the basic sinus cycle length (SAN_1-SAN_1), then the difference between A_2A_3 and the spontaneous atrial cycle (A_1A_1) represents the sum of conduction into and out of the S-A node— $(A_2A_3)-(A_1A_1) = (A_2-SAN_2) + (SAN_3-A_3)$.

Zone III. In some human hearts, the A_2A_3 interval remains constant until S_2 becomes so premature that no A_2 can be elicited (atrial refractory period is encountered). In others, a third zone may be encountered in which several phenomena may occur. The position of this zone varies from about 0.18-0.23 to 0.25-0.35 of the cycle. When the A_1A_2 interval is shortened to 0.3 of the A_1A_1 interval, the A_2A_3 interval may suddenly shorten from values of about 1.25 to about 0.70 of the A_1A_1 interval. This would indicate a true interpolated A_2 , entirely analogous to the rarely observed phenomenon of spontaneous interpolated APD. Such an event indicates (fig. 5C) that the A_2 blocks in tissues around the S-A node; S-A discharge occurs on time and conducts normally to the atrium to produce A_3 . For the SAN_3-A_3 conduction time to remain normal, the perinodal tissues must recover from the refractoriness engendered by the blocked A_2 before the SAN_3 impulse arrives. If the perisinus node zone is still refractory when SAN_3 propagates through this region on its way to the atrium, SAN_3-A_3 and A_2A_3 will be prolonged; A_2A_3 might be 0.8 to 0.9 of A_1A_1 at $A_1A_2 = 0.3$ rather than 0.7, the value expected if SAN_3-A_3 remains equal to SAN_1-A_1 (fig. 5D).

In general, the response in patients with normal

or near-normal sinoatrial conduction is much like that shown in figure 4. However, many other patterns are being encountered as sinus node function is evaluated in this way. It is possible to obtain useful information with premature atrial stimulation which is not obtainable in any other way. For example, analysis of the response to premature atrial stimulation can reveal *first degree* S-A block in man. Figure 6 diagrammatically shows normal and two degrees of conduction impairment between the S-A node and atrium. The normal case is illustrated by line A. The transition between Zones I and II comes when A_2A_3 is 1.25 of A_1A_1 and A_2A_3 remains constant as A_1A_2 is shortened further. As mentioned above, neglecting changes in spontaneous S-A node cycle length, the difference between A_2A_3 and A_1A_1 represents the sum of conduction into (A_2 -SAN₂) and out of (SAN₃-A₃) the S-A node. In this example with a cycle length of 1,000 msec, the total conduction time—(A_2 -SAN₂) + (SAN₃-A₃)—would be 250 msec ($[1.25 - 1.00] \times 1000$). Line B in figure 6 shows the transition between Zones I and II at 0.4 the spontaneous atrial cycle length. In this instance, total conduction time would be 600 msec—

$(A_2A_3 - A_1A_1) \times 1000 = (1.6 - 1.0) \times 1000 = 600$ msec. If the conduction time in and out were equal then conduction time from sinus node to atrium would take 300 msec. Even though (SAN₁-A₁) and (SAN₃-A₃) are very probably not equal under such circumstances, (SAN₁-A₁) must be prolonged because A_1A_2 had to be shortened to 0.4 of the spontaneous cycle length before reset occurred, that is, before Zone II was encountered. This indicates that when the A_1A_2 interval was longer than 0.4, A_2 collided with the emerging sinus impulse; the fact that reset only occurs when A_2 is introduced early in the cycle surely indicates that first degree sinoatrial block is present (that SAN₁-A₁ is prolonged). Line C of figure 6 shows an even more extreme case of sinoatrial block. Throughout the entire cycle where responses could be elicited, A_1A_2 per A_1A_1 from 1.0 to 0.3, A_2A_3 was fully compensatory. This pattern of response indicates that A_2 never reached the S-A node pacemaker to reset it; therefore, the conduction time between the S-A node and atrium must be very long or unidirectional block must be present. The total conduction time is 700 msec—($A_2A_3 - A_1A_1$) \times 1000 = $(1.7 - 1.0) \times 1000 = 700$ msec. Thus, premature atrial stimulation can be used to detect first degree sinoatrial block in man, a feat not possible with any other technique.

Also, a variety of behavior has been observed in the early part of Zone II. When A_2 is placed early in Zone II, for example, 0.30-0.40 of A_1A_1 , A_2A_3 may depart from its usual constant value. If the perinodal tissues are more refractory than usual, an A_2 in this portion of the cycle may conduct into the S-A node with great delay (A_2 -SAN₂ greatly prolonged); even if SAN₂-SAN₃ is constant, A_2A_3 will be prolonged in direct proportion to the increase in A_2 -SAN₂. If the S-A node pacemaker is unstable, then the spontaneous cycle length of the sinoatrial node pacemaker may not recover immediately after being reset by A_2 , that is, SAN₂-SAN₃ may prolong. Even if A_2 -SAN₂ and SAN₃-A₃ are not increased, A_2A_3 will prolong. An increase in A_2A_3 caused either by changes in conduction or automaticity would cause early Zone II responses to curve upward and be readily apparent in a plot of A_2A_3 vs. A_1A_2 . Finally, in Zone III, the effects of concealed conduction can be so marked as to cause A_2A_3 to vary from 0.7 to values exceeding 1.0.

Thus, it is apparent that there is a great deal that can be learned from analyzing the responses to atrial pacing or premature atrial stimulation. The

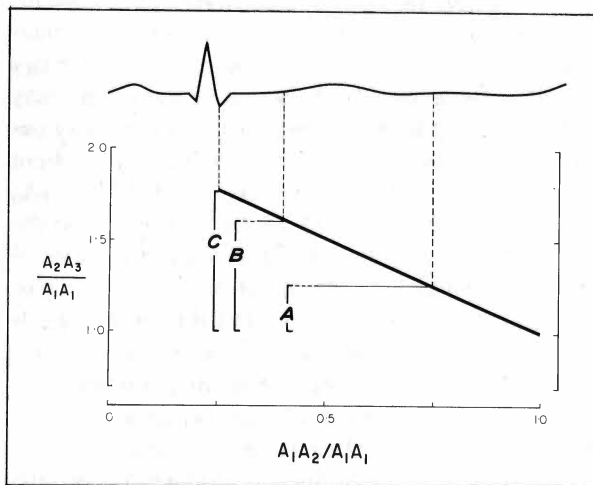


Fig. 6—The diagnosis of first-degree sinoatrial block in man by premature atrial stimulation. The abscissa is the normalized test cycle (A_1A_2/A_1A_1), the ordinate the normalized return cycle (A_2A_3/A_1A_1). The heavy diagonal line represents responses without reset (Zone I). Line A shows the transition from Zone I to Zone II in the usual portion of the cycle. Line B shows transition from Zone I to Zone II at 0.4 of the cycle indicating marked sinoatrial conduction delay. In C, a transition from Zone I to Zone II was never obtained, indicating either extreme sinoatrial conduction delay or, much less likely, unidirectional S-A block throughout the cycle.

final role for these techniques in evaluating S-A node function will not be settled until they have been applied to a large group of patients and careful follow-up of these patients has been continued for a period of time sufficient to determine the prognostic value of the tests. However, we have every reason to hope that these tests which permit new insights into S-A node function will ultimately improve our ability to predict the course of patients with S-A node dysfunction. If they do, such tests will greatly improve our therapeutic management of the "Sick Sinus Syndromes."

PANEL DISCUSSION

Dr. Baird: Dr. Bigger, is atrial pacing of any value in stressing ventricular conduction in patients with bilateral bundle branch block?

Dr. Bigger: Do you mean rapid atrial pacing?

Dr. Baird: Yes.

Dr. Bigger: Very little, I think. In such cases, rapid atrial pacing usually produces block at the A-V node. It is more than useful to use premature atrial stimulation, a technique which often permits one to demonstrate transmission through the A-V node but block in the bundle branches, if a His bundle recording is also made. This is a better technique for demonstrating bundle branch disease. In A-V nodal disease, of course, you may get second degree A-V block at an unduly low rate during fixed rate atrial pacing.

Dr. Scherlag: As I think most people know, there are patients who show periods of complete heart block and then periods of sinus rhythm with normal conduction. Doctor (Onkar) Narula has alluded to the fact that these patients, after complete heart block and subsequent sinus rhythm, sometimes will show 1:1 conduction up to rates of 150 or 180 per

minute without showing any evidence of fatigue in A-V conduction. My indication from his data is that atrial pacing is not a good way of assessing conduction defects in the His-Purkinje system, even with atropine. Doctor Narula feels that the use of premature beats might be a useful tool in assessing critical A-V conduction delays, particularly those in the His-Purkinje system, but I do not think the definitive data are as yet available.

Dr. Bigger: Premature atrial stimulation is also a better test to assess A-V conduction when marked left axis right bundle branch block is present, since you can actually measure the functional refractory period of the posterior division of the left bundle with premature atrial stimulation. Prediction of future functional performance is what we all would like, but I am afraid that is the pot of gold at the end of the rainbow. As we have emphasized so many times, the heart under test conditions may not relate to the heart under conditions not related to the test or predict the future. Much remains to be learned about the prognostic significance of functional testing.

Dr. Moe: Years ago I used to demonstrate this phenomenon to students in the open chest dog as an attempt, in effect, to estimate refractory period of the sinus node. If you deliver a premature atrial stimulus at a time when the S-A node is refractory, the node will not discharge. Thus, the next expected sinus beat arrives almost on schedule and is, therefore, an almost interpolated atrial beat. Later premature beats will, of course, discharge the pacemaker although with a delay attributable to delayed conduction. The sum of the test cycle plus the "return" cycle, when plotted against the duration of the test cycle, will exhibit a sharp break. I wonder if you ever saw this break in the human heart.

Dr. Bigger: Yes, we have seen that quite often.

Mechanisms of A-V Block*

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Within recent years an abundance of information has become available concerning the pathology, electrophysiology, anatomy, and clinical significance of disturbances of atrioventricular (A-V) conduction. Interest on this subject apparently began in 1827 with a description by Adams (1) of syncope associated with a slow heart rate and subsequent observations by Stokes (27) in 1846. Wenckebach (36) (1899) and Hay (7) (1906) described atrioventricular conduction block and ushered in the era of eponyms and synonyms in the classification of atrioventricular conduction disturbances. The issue heated up intensely in 1924 when Mobitz (15) classified A-V block according to rather precise criteria. In the following years, numerous clinical and experimental studies appeared in the medical literature. In 1941, Katz (9) attempted to describe the clinical correlation in the presence of various types of A-V block. Uhley and Rivkin (28, 29) first described the ECG pattern following the interruption of the main and peripheral branches of the canine right (1961) and left (1964) bundle branch system, and in 1963, Lenègre (11, 12, 13) and Lev (14) initiated the intense anatomical studies that led to the more recent concepts of intraventricular conduction disturbances. Precise experimental studies by Lenègre (11, 12, 13), Lev (14), Pruitt (22), and Rosenbaum (23) offered a logical classification of block within the fascicles of the Purkinje system. By the mid-1960's, Hoffman and Cranefield (8), Paes de Carvalho (20), Watanabe and Dreifus (30, 31), and others had

explored the electrophysiologic mechanisms of atrioventricular conduction delay at the cellular level. Studies in man using His bundle electrograms by Damato and associates (2) and Narula and co-workers (17, 18, 19) confirmed the findings in earlier animal experiments. However, the importance of a more precise classification of A-V block came into sharp focus with the development of electronic pacing and the dramatic lifesaving results which followed. Unfortunately, too little is known about the life expectancy in patients with A-V block, and the medical literature is often distorted by a few scattered cases with unusually long survival or by including cases of A-V block engendered by an acute myocardial process (5). It is our intention to review the present anatomic, electrophysiologic, and clinical knowledge in an attempt to define A-V conduction disturbances. It is probably wise to consider first the classical definitions set forth by Wenckebach (36) and Mobitz (15, 16).

In his original paper in 1899, Wenckebach (36) described a progressive prolongation of the a-c interval (interval between atrial and ventricular contractions) until one ventricular contraction dropped out. Following a pause, the a-c interval was shortest, which suggests improved conductivity. Impairment of conductivity as judged from the increment of the a-c interval was most marked in the second conducted beat and much less in subsequent beats. This resulted in a quickening of the radial pulse. However, the increment of a-c interval was often again greater immediately before the dropped beat in the presence of higher conduction ratios, resulting in a slowing of the pulse. When Mobitz (15) for the first time classified incomplete A-V conduction disturbances in 1924, he termed the above

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variety Type I, which subsequently became known by the name of "Wenckebach periodicity."

In contrast, Mobitz (16) called a block Type II when a ventricular complex dropped out without any change in the P-R interval of the electrocardiogram in immediately preceding beats. He also mentioned that, in the Type II variety, often many successive ventricular beats dropped out causing prolonged asystole, despite preceding periods of 1:1 conduction with a normal P-R interval. Hence, it must be reemphasized that the original classification of the two types of "partial heart block" was based entirely on variation or constancy of the A-V conduction time.

Clinical Findings. First Degree Atrioventricular Block. First degree block does not itself produce any symptoms. From a physical standpoint the presence of this type block may be suspected by the finding of a soft first heart sound. Levine and Harvey (1949) provided us with an explanation of this finding. These workers reported that the intensity of a first heart sound depended upon the position of the cusps of the A-V valves at the onset of systole. If ventricular systole occurs shortly after atrial systole, the A-V valves are open wide and will be closed violently and abruptly during systole producing a loud first sound. When the interval between atrial and ventricular systole is longer, the cusps will tend to return to their original position so that the sound produced at the time of ventricular systole would be much softer. This suspicion may be confirmed when inspection of the jugular pulse discloses a delay between the A and V waves.

Second Degree and High-Grade Atrioventricular Block. Second degree and high-grade atrioventricular block may or may not produce symptoms. Second degree A-V block with Wenckebach periods must be differentiated from the pause following an extrasystole. This can usually be done with auscultation. In block there is ventricular acceleration before the pause. Difficulty may arise in diagnosis because occasionally a blocked atrial premature beat may cause a pause in the sinus rhythm. If the P wave is hidden in the T wave, interpretation may be quite difficult. From the physical standpoint, however, the extrasystole will produce a cannon wave in the neck. More advanced second degree block with 2:1 A-V ratio produces a marked bradycardia.

Electrocardiographic Findings. The traditional classification of atrioventricular block involves three

major types. In first degree, there is merely a prolongation of the P-R interval, and every atrial impulse is conducted into the ventricle. Second degree A-V block has been divided into two sub types: Mobitz Type I which is equated with the traditional Wenckebach (15) periodicity, in which the P-R interval is gradually prolonged and eventually the QRS complex drops out (figs. 1 and 2), and Mobitz Type II second degree block, characterized by the sudden dropping out of a QRS complex without progressive prolongation of the P-R interval (figs. 3 and 4). Complete or third degree A-V block is identified by independent activation of atria and ventricles with no conduction seen when physiologic P-R intervals are possible. The ventricles beat independently, each with its own pacemaker. The difficulty with this traditional classification is that the site of the A-V block is not specifically identified. In addition, it cannot be utilized in 2:1 conduction or in any rhythm other than sinus (figs. 5 and 6). Hence, more precise identification of the type and site of conduction block is mandatory, as specific clinical programs must be organized. There is no problem with first degree block; however, with second degree block, classification based on the width of the QRS interval will apply to all conduction ratios including 2:1, high grade A-V block, and in certain instances of atrial fibrillation (figs. 3, 4, 5, and 6).

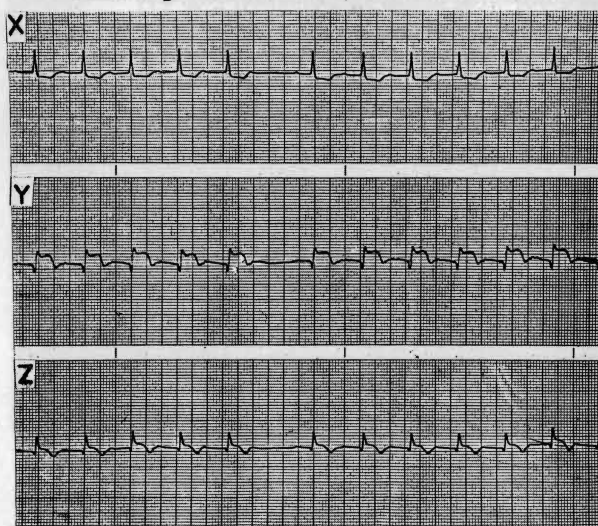


Fig. 1—Orthogonal leads X, Y, Z. A sinus rhythm is present at a rate of 75/min. The P-R interval becomes progressively prolonged with 0.22 sec to 0.32 sec before the 6th P wave fused with the T wave is dropped. This is a Type I block (Wenckebach) associated with an acute inferior wall infarction.

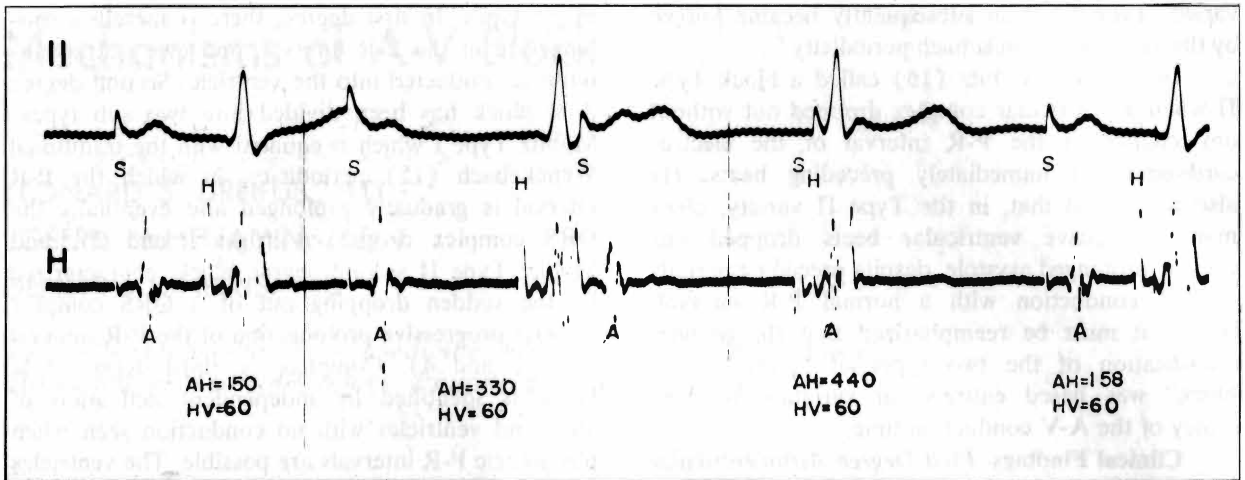


Fig. 2—Second degree block Type I, produced by atrial stimulation, lead 2 and His bundle electrogram shown. The A-H interval increases from 150 to 440 msec before the 4th atrial impulse is not conducted to the ventricles.

Confusion occurs when one talks exclusively of the progressive or sudden increase of the P-R interval before the dropped beat in attempting to classify the two types of block, as this criteria can be applied only in the presence of regular supra-ventricular rhythm and second degree A-V block associated with conduction ratios greater than 2:1 (33) (fig. 7). Furthermore, instances of atrial fibrillation and higher grades of A-V block cannot be considered in this classification (fig. 6).

In figure 7, taken from the same patient within a few seconds, both types of conduction block are demonstrated. In the upper strip (lead 3) sudden dropping out of a QRS complex is evident after beats 1, 6, and 7. The P-R remains constant at 0.20 seconds before the block occurs. This is Type II conduction block. However, in the lower strip, the P-R interval increases from 0.20 to 0.32 seconds before the third and ninth P waves are not conducted. This represents a Type I conduction block.

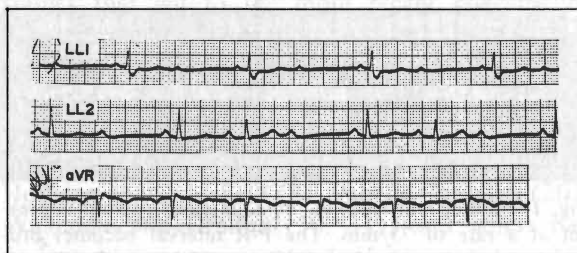


Fig. 3—Second degree block Type II variety. In lead 1, 2:1 conduction is seen; in lead 2, 3:2 conduction is present. AVR shows 1:1 conduction.

However, the QRS complexes are narrow, and block, in both instances, is most likely within the A-V node.

On the other hand, the QRS duration cannot always identify the precise site of conduction block. Type I or the Wenckebach variety can occur in all excitable tissue, and along the entire A-V transmission system (4). However, the nature of conduction delay usually localizes the block in the intranodal region of the A-V node (6). Further problems may arise when more than one region of block may be present in the same patient. From the clinical standpoint, it is the location of the block that largely determines the significance, rather than the variation or constancy of the P-R interval. Mobitz originally described the high incidence of Adams-Stokes attacks as well as complete heart block in cases of Type II variety. Later Katz (9) and Donoso and associates (3) confirmed the sinister prognosis associated with block and wide QRS complexes. Similar observations were made by Lenègre (12), Scanlon (24, 25), and Haiat (6) and their co-workers. In the latter study, major neurologic or cardiac symptoms were present in 86.2% of patients with A-V block associated with wide QRS complexes as contrasted to 37.5% of those patients with narrow QRS complexes. Furthermore, the incidence of sudden cardiovascular death was more than twofold in the group with wide QRS complexes. Second degree and high-grade A-V block offered a similar prognosis.

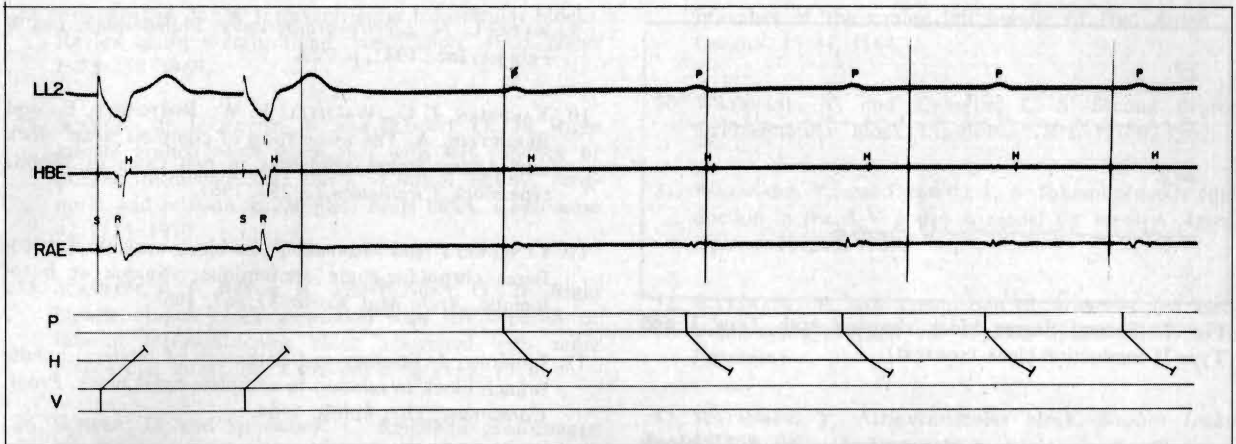


Fig. 4—His bundle electrogram, first two beats are produced by ventricular pacing. P waves are conducted to His bundle but are blocked below His. This type of conduction block is usually associated with Type II conduction.

With the development of cardiac pacemakers as well as the expanding knowledge in precise localization of the pharmacologic action of antiarrhythmic and cardiotoxic agents, the clinician must acquire a firm understanding of the nature of A-V transmission. Digitalis, acetylcholine, and ischemia appear to slow intranodal conduction, while procainamide, quinidine, propranolol, potassium salts, and lidocaine slow conduction above the A-V node and in the subjunctional region (21, 34, 35). For practical purposes, the site of block can be identified by the duration of QRS in most instances, and His bundle electrocardiography will add little to clinical management. If progressive P-R prolongation

is seen with a wide QRS complex, two levels of block may be present, but therapy is predicated on the lowest level of block. Conduction delay of the Wenckebach variety is most common in the "N" region of the A-V node but can be seen in the subjunctional region of the A-V transmission system (19) and even between contiguous ventricular fibers (4), but offers little as a prognostic sign alone.

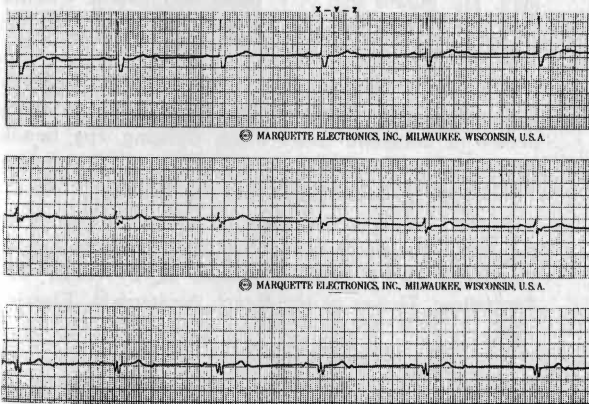


Fig. 5—Orthogonal leads X, Y, Z. 2:1 conduction is present and QRS complexes are wide. This type of conduction cannot be classified, block probably exists in the fascicles and is subjunctional in location.

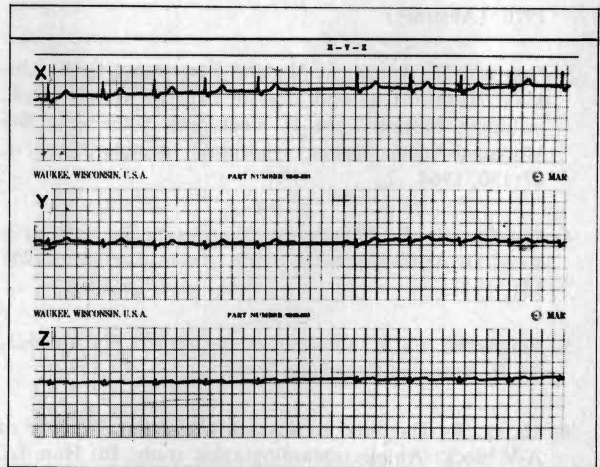


Fig. 6—Orthogonal leads X, Y, Z. QRS complexes are wide and show a right bundle branch system block configuration with an S wave appearing in lead X. A QRS complex fails to appear following the 6th P wave. P-R interval had become progressively longer from 0.18 sec to 0.32 sec before dropping out of QRS. Two levels of block may be postulated, the first within the A-V node, causing Wenckebach periodicity, and second, a subjunctional block in the fascicles of the right bundle branch system.



Fig. 7—Second degree block showing both Type I and Type II conduction block (see text).

Determination of the varieties of A-V block is predicated on the precise identification of the site(s) of conduction delay as prognosis, and therapy must follow on this basis. Further electrophysiologic and pharmacologic studies will undoubtedly reveal other mechanisms on the nature of A-V transmission.

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Microelectrode and His Bundle Studies on Type I and II Second Degree A-V Block*

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Mobitz classified second degree A-V block into two categories. Mobitz type I, or Wenckebach block, is characterized by a gradual prolongation of the P-R interval preceding the dropped ventricular beat. In Mobitz type II block, the dropped beat occurs without preceding prolongation of the P-R interval. Bundle branch block usually is present in patients with Mobitz type II block. The importance of distinguishing between these two types of A-V block lies in the usual irreversibility and higher mortality of patients with type II A-V block, as contrasted with type I or Wenckebach block. Also, Mobitz type II block frequently progresses to complete A-V block and Adams-Stokes attacks, thus necessitating a cardiac pacemaker (1, 2, 3).

Using only electrocardiographic recordings, it is not possible to define the location within the A-V conduction system where A-V block actually develops. The need to distinguish between conduction failure above or below the bundle of His is important since dropped beats occurring from block within the

A-V node would not carry as serious a clinical prognosis as would block within the ventricular specialized conduction system (VSCS or His-Purkinje system). The following figures are presented to demonstrate the use of the microelectrode technique and His bundle electrogram recording technique to localize the site of A-V block in type I and II block.

Figure 1 is an example of Wenckebach or Mobitz type I second degree A-V block. Electrograms were recorded simultaneously from the right atrial appendage (RA), bundle of His (BH), and right ventricles along with a lead II electrocardiogram. The bundle of His electrogram contains three deflections: an atrial deflection, His bundle spike, and a ventricular septal complex. Each of the His bundle depolarization complexes is designated by a small letter *h*.

In the lead II ECG, it can be noted that the first three P-R intervals progressively increase until the fourth P wave is not followed by a ventricular response. This 4:3 Wenckebach cycle then repeats again. An approximation of the conduction time through the A-V node can be determined by the interval between the atrial deflection in the RA electrogram to the His bundle spike (*h*) in the BH electrogram. The fact that the progressive increase in the P-R interval in this typical example of Mobitz

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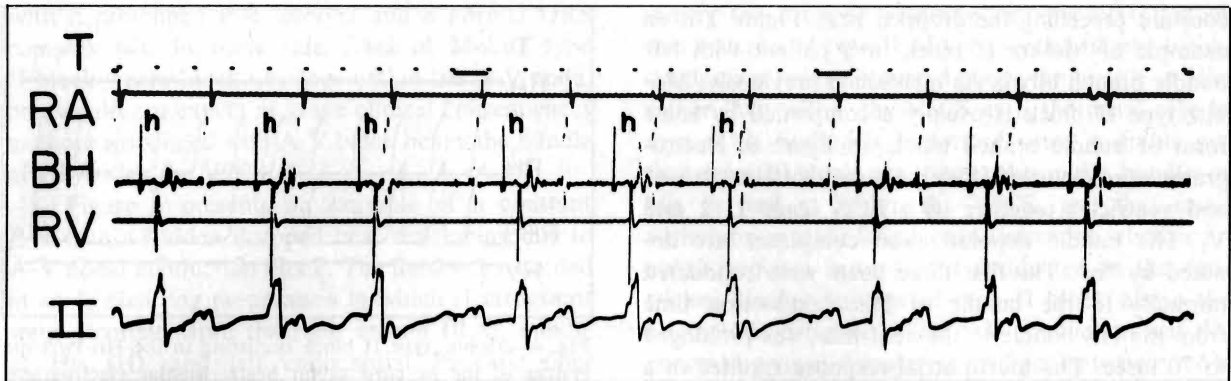


Fig. 1—Mobitz type I block due to conduction failure within the A-V node of the *in vivo* dog heart. Bipolar electrograms were recorded from the right atrium (RA), bundle of His (BH), and right ventricle (RV) together with the lead II electrocardiogram (II). The timing signal (T) denotes 100 msec. The h indicates the His spike in the BH electrogram.

I block is a reflection of a progressive increase in A-V nodal conduction time as demonstrated by the atrial to His conduction time between the first and third beats. The fourth atrial deflection is not followed by a His bundle spike. Therefore, A-V block of this atrial beat occurred at a site above the bundle of His recording site, that is, within the A-V node. Note that the interval between His bundle depolarization and ventricular depolarization did not change in any of the conducted beats, thereby indicating that ventricular conduction in Mobitz type I block is normal. Type I Mobitz block can be a functional type of A-V block when associated with rapid atrial pacing. Most normal human hearts will exhibit Wenckebach type block upon rapid atrial pacing. Again, this type of second degree A-V block is nearly always due to conduction delays and block within the A-V node.

Figure 2 is presented to further demonstrate that the prolongation and block of A-V conduction in type I block occurs within the A-V node. Atrial (RA) and ventricular (RV) electrograms were recorded simultaneously with transmembrane potentials from two single A-V nodal fibers (N and NH) during 3:2 Wenckebach. Ten msec and 100 msec time dots are indicated in the top trace, T. The first atrial response was conducted to the upper A-V nodal fiber (N) with little conduction delay. Conduction time from the upper nodal fiber (N) to the lower A-V nodal (or upper bundle of His) fiber, labeled NH, required 110 msec. Conduction from the NH fiber to the RV extracellular electrode required only 58 msec. The increase in atrial (RA) to ventricular (RV) conduction time of the second beat resulted

from slowed conduction within the A-V node as demonstrated by the increased time for the excitation wave to be transmitted from the upper to lower A-V node, that is, the N-NH interval (A-V conduction time) for the second response is 60 msec longer than for the first beat. Conduction time between the NH fiber to RV extracellular electrogram was 12 msec longer than for the first beat. The third atrial response (RA) failed to be conducted to the ventricles as shown by the absence of a ventricular depolarization complex in the RV electrogram. Block of this atrial beat occurred within the A-V node at a location between the impaled upper and lower A-V nodal recording sites. Clearly, this example of 3:2 Wenckebach resulted from block within the A-V node.

In Mobitz type II second degree A-V block, the P-R interval is usually normal and remains

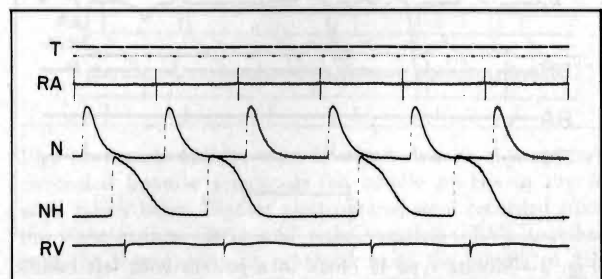


Fig. 2—Mobitz type I block due to conduction failure within the A-V node of the *in vitro* rabbit heart. Bipolar electrograms were recorded from the right atrium (RA) and right ventricle (RV) together with transmembrane potentials from the high A-V node (N) and low A-V node (NH). The timing signal (T) denotes 10 msec and 100 msec intervals.

constant preceding the dropped beat. Figure 3 is an example of Mobitz II block in a patient with left bundle branch block. As mentioned previously, Mobitz type II block is usually accompanied by some form of bundle branch block. In figure 3, electrograms were recorded from the bundle of His, atrium, and ventricles together with ECG leads 1, 2 and V_1 . His bundle depolarization complexes are denoted by "h". The first three beats were conducted normally to the bundle of His; conduction time from the His bundle to the ventricles was prolonged to 70 msec. The fourth atrial response resulted in a bundle of His depolarization complex, but was not accompanied by ventricular depolarization. The atrial to His bundle conduction time for the dropped ventricular beat was normal. Therefore, in this typical case of Mobitz type II block, conduction failure occurred within the ventricular specialized conduction system at a site below the A-V node and bundle of His. The fourth ventricular beat is an idioventricular escape beat. The P-R intervals before and after the "dropped" beat are identical and within normal limits. On a routine ECG, the presence of an intraventricular conduction defect accompanying second degree A-V block would be highly suggestive that block developed below the A-V node.

Figure 4 demonstrates type II Mobitz block in the isolated rabbit heart. In this experiment the heart was paced from the atrium at a constant rate

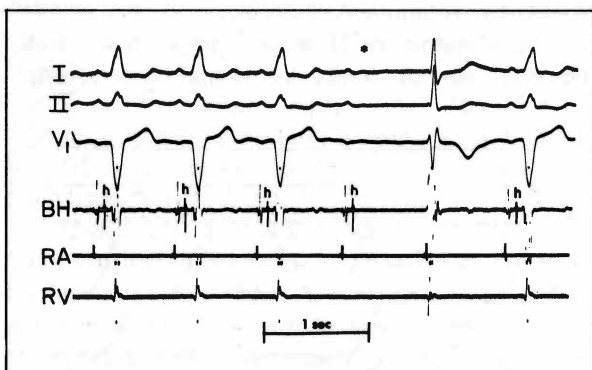


Fig. 3—Mobitz type II block in a patient with left bundle branch block. Catheters were used to record from the bundle of His (BH), the right atrium (RA), and right ventricle (RV) together with three simultaneous electrocardiographic leads (I, II and V_1). The h in the BH record indicates the His spike. (Reproduced with permission from B. N. Goldreyer and from *Annals of Internal Medicine* 77:132, 1972.)

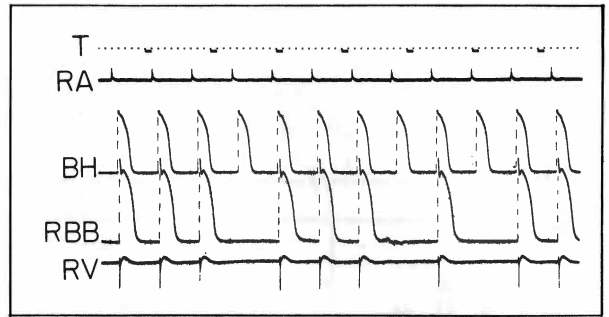


Fig. 4—Mobitz type II block occurring in the His-Purkinje system of the *in vitro* rabbit heart. Bipolar electrograms were recorded from the right atrium (RA), and right ventricle (RV) together with transmembrane potentials from the bundle of His (BH) and right bundle branch (RBB). The timing signal (T) denotes 100 msec and 1 sec intervals. (Reproduced by permission of The American Heart Association, Inc. from J. F. Spear and E. N. Moore, "Electrophysiologic Studies on Mobitz Type II Second Degree Heart Block," *Circulation* 44:1090, 1971.)

of 99 per minute; this rate caused some beats to be dropped abruptly. Electrograms were recorded from the right atrium (RA) and right ventricle (RV) simultaneously with transmembrane action potentials recorded from a bundle of His fiber (BH) and right bundle branch fiber (RBB). Time marks (T) denote 100-msec and 10-sec intervals. Notice that each right atrial electrogram was accompanied by an action potential recorded from the bundle of His, and that the atrial-to-His bundle conduction time (RA-BH) and His-to-right ventricular conduction time (BH-RV) remained constant. The bundle of His action potential was not accompanied by a right bundle branch action potential when the atrial impulse failed to be conducted to the ventricles (fourth, eighth, and tenth RA responses). Therefore, in this example of Mobitz type II block, conduction failure occurred below the bundle of His somewhere above the impaled bundle branch fiber. Figures 3 and 4 confirm studies completed in man where the sudden dropped beat in type II second degree block results from block within the ventricular specialized conduction system.

Figures 3 and 4 demonstrate the usual site of conduction failure in Mobitz type II block, that is, block within the VSCS below the A-V node and bundle of His. However, in some rare instances a constant P-R interval with sudden dropped beats may result from block within the A-V node. These cases of Mobitz type II block are usually associated

with a prolonged P-R interval and a normal QRS complex (4). In these rare cases of Mobitz type II block where block develops within the A-V node, one would not expect as grave clinical consequences as those associated with A-V block below the bundle of His within the VSCS.

Figure 5 presents an example of a constant P-R with a sudden dropped beat developing due to A-V nodal conduction block. The data was recorded in an *in vivo* dog preparation in which electrograms were recorded from the right atrium (RA), bundle of His (H), and left endocardial Purkinje fiber (LPF) simultaneously with the lead II electrocardiogram (II). Time marks denote 100 msec intervals. The right atrium was paced at a basic cycle length of 258 msec (heart rate of 234 per min). At this rapid rate, conduction time through the A-V node was somewhat prolonged, but the P-R interval of 0.14 sec is still within the normal range in the dog (0.06 to 0.15 sec). Every fourth atrial beat in figure 5 was made premature by 20 msec. In the standard electrocardiographic tracing, this would mean that every fourth response would have a variation in the P-R interval of 0.5 mm, that is, a sinus arrhythmia was present which would be barely perceptible in the routine ECG tracing. This small variation in the P-R interval resulted in 4:3 second degree block; it can be observed in the lead II ECG that the fourth atrial response is blocked. As so commonly occurs in clinical cases of type II block in man, the P-R interval following the blocked beat was slightly shorter than that for the responses preceding the blocked beat. The fact that bundle of His and left Purkinje electrograms were not recorded

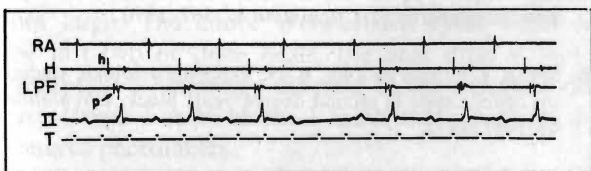


Fig. 5—Mobitz type II block due to conduction failure within the A-V node of the *in vivo* dog heart. Bipolar electrograms were recorded from the right atrium (RA), bundle of His (H), and left Purkinje fiber (LPF) together with a lead II electrocardiogram (II). The timing signal (T) denotes 100 msec intervals. The h in the H electrogram indicates the His spike, and the p in the LPF electrogram indicates the Purkinje spike. (Reproduced by permission of the American Heart Association, Inc. from J. F. Spear and E. N. Moore, "Electrophysiologic Studies on Mobitz Type II Second Degree Heart Block," *Circulation* 44:1091, 1971.)

during the dropped response demonstrates that in this instance of type II Mobitz second degree block, conduction failure occurred above the bundle of His, rather than within the VSCS as is the usual case in man. This finding is important since it points out that type II block can occur above the bundle of His as well as within the VSCS, and that small variations in cycle lengths can determine whether an atrial response is or is not conducted to the ventricles. Similar findings of type II block above the His bundle occurred when A-V conduction was depressed by vagal stimulation or digitalis toxicity (6).

Recent studies indicate that concealed His bundle extrasystoles or echo beats can cause pseudo-type II block (5, 6). Such findings have been dependent upon the chance occurrence of an extrasystole or echo beat blocking a regularly conducted beat. In our experiments we were able to demonstrate pseudo-type II block consistently by evoking extrasystoles in the bundle of His using a technique for intracellularly stimulating and recording through the same microelectrode. This technique allows precise localization of the site of stimulation as well as direct verification of activation of the same cell.

In figure 6, simultaneous atrial and ventricular electrograms are shown as well as a transmembrane potential recording from the bundle of His in an isolated rabbit heart. The ladder diagram is included

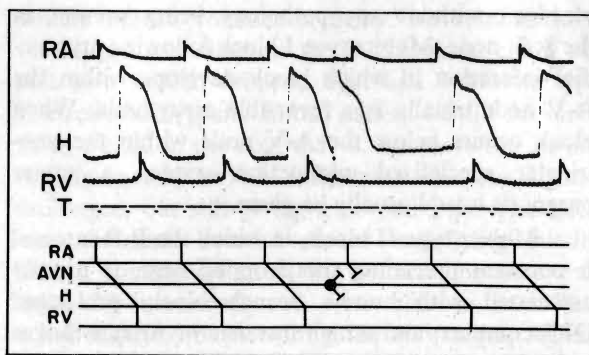


Fig. 6—Pseudo-Mobitz type II block due to a premature concealed impulse arising in the bundle of His in the *in vitro* rabbit heart. Bipolar electrograms were recorded from the right atrium (RA) and right ventricle (RV) together with the transmembrane potential from the bundle of His (H). The timing signal (T) denotes 100 msec intervals. The ladder diagram below demonstrates the conduction sequence through the right atrium, A-V node (AVN), His bundle and right ventricle. (Reproduced by permission of The American Heart Association, Inc. from J. F. Spear and E. N. Moore, "Electrophysiologic Studies on Mobitz Type II Second Degree Heart Block," *Circulation* 44:1093, 1971.)

TABLE 1. PATTERNS OF MOBITZ TYPE I AND TYPE II HEART BLOCK

DESCRIPTION	CLINICAL APPEARANCE		CAUSE OF CONDUCTION FAILURE		
	P-R interval	QRS duration	block in AVN	block in VSCS	"pseudo-block"
Mobitz I (increasing P-R interval)	increased increased	increased normal	possible likely	likely possible	possible possible
Mobitz II (constant P-R interval)	normal increased	increased normal	possible likely	likely possible	possible possible

below the analog tracings as an orientation to the sequence of conduction. Notice that after the third conducted beat a premature action potential is evoked in the bundle of His by stimulation through the recording microelectrode. The premature action potential is concealed both antegradely and retrogradely but has the effect of blocking conduction of the subsequent atrial activation (fourth atrial response). The electrocardiographic pattern that this intervention produces is "pseudo" Mobitz type II block with the site of block occurring within the A-V node.

Table I summarizes various possibilities for Mobitz types I and II second degree A-V block. Mobitz type I, or Wenckebach block, with progressive P-R prolongation is usually associated with a normal QRS complex and block within the A-V node. At rapid atrial rates, this can be a functional type of block without any pathology being present in the A-V node. Mobitz type I block following myocardial infarction in which block develops within the A-V node usually is a reversible arrhythmia. When block occurs below the A-V node within the ventricular specialized conduction system, a graver prognosis would usually be given.

Mobitz type II block, in which the P-R interval is constant preceding the dropped beat, is usually associated with bundle branch block, prolonged QRS complex, and a high instance of Adams-Stokes attacks. In these cases, the site of A-V block is nearly always below the A-V node within the ventricular specialized conduction system. In rare instances, a variation of Mobitz type II block in which the P-R interval is fixed but prolonged and the QRS complex is normal may be encountered where the site of block is within the A-V node. Thus, second degree A-V block is one instance where His bundle electrocardiography may be indicated. This is true since from the clinical standpoint it is predominantly the site of block rather than the P-R interval

which determines the significance of the block; block above the bundle of His is usually benign while block below His bundle is usually malignant.

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PANEL DISCUSSION

Dr. Baird: Dr. Bigger, if a patient presents with a Mobitz type II block and syncope, although you have not documented that the patient had third degree block, what would you recommend with regard to permanent pacemaker therapy, or would you recommend pacemaker therapy without documentation of third degree A-V block?

Dr. Bigger: With Mobitz type II block or even

with left axis deviation, right bundle branch block, and even one nonconducted beat and the history of syncope, I think there is sufficient indication for a pacemaker. I think there is almost unanimous agreement on that. There are groups now, however, who would put pacemakers in those patients with a vague history of dizziness, light-headedness, fatigue, and marked left axis deviation with right bundle branch block. I want to tell this audience that this is a highly experimental approach and not of proven benefit. People can carry the pattern of marked left axis right bundle branch block and, if they have never dropped a beat, they may carry that pattern for 20 years without experiencing difficulty. In my view, it has by no means been proven that you should put in a pacemaker unless you have seen dropped beats. However, it is very clear in several prospective studies that once you have seen one drop beat in a patient with marked left axis deviation and a right bundle branch block type pattern on the electrocardiogram, then a very high percentage of those patients will be in complete heart block within one year to 18 months.

Dr. Moore: Would you put a pacemaker in a patient with Mobitz type I block in which a His bundle electrogram demonstrates that type I block is due to progressive delay in the His-Purkinje system?

Dr. Bigger: I have studied only three such patients myself. All of them had marked left axis with right bundle branch block and subsequently showed Wenckebach phenomenon with the H-V getting longer and longer in the His bundle study. One characteristic of the body surface electrogram is that the increments in P-R interval prolongation are not large. The entire Wenckebach cycle tends to be just two or three beats; the beat drop is more abrupt. It is strikingly different to the eye than the usual type I A-V block. I think these patients do deserve pacemakers.

Dr. Scherlag: Dr. (Onkar) Narula and Dr. (Philip) Samet have published a paper on Wenckebach not only below the His bundle but also within the His bundle itself. I think one uses the well-accepted clinical criteria that if one sees a drop beat and one knows it is in the His-Purkinje system, certainly that is a strong indication for pacemaker therapy. The problem, and I think this is an important one that others have not really dealt with, is that the natural history of such cases is not well known. I do not know if any physician would want to chance

just following a case of that type because of the possibility that Stokes-Adams might occur a short time afterwards. So, in general, most people want to be safe and would put a pacemaker in under those circumstances. I believe that is what happened to those patients who were described by Narula, *et al.*

Dr. Bigger: I would have to agree with that last statement except that I think it is possible to follow natural history such as when using a demand pacemaker. You can see when the pacemaker starts to stimulate or how often it is active by the usual ambulatory monitoring techniques. If the pacemaker activates, you could bring them in and with temporary transvenous catheters inhibit the demand pacemaker for study. I do not think we completely lose our opportunity for studying the natural history of a patient by introducing therapy.

Dr. Moore: I personally would want a pacemaker just to be sure.

Dr. Bigger: I do not think it is reasonable to implant pacemakers in left axis right bundle branch block. No such indication is evident in second degree A-V block. Yet in some places every patient with that pattern gets a pacemaker. I am not sure all of those physicians are carefully following the patients as a study to see what happens in real life. This is clearly a very experimental type of program to be carrying on.

Dr. Moore: Recently, in a patient with a right bundle branch conduction delay, we demonstrated that slight variations in the P-P interval could result in a sudden dropped beat and a Mobitz type II electrocardiogram. In this patient we did the same thing we did in the dog; that is, we drove the atrium rapidly so that the A-V conduction time was slightly prolonged, but still giving a normal P-R. The QRS was abnormal because of the underlying bundle branch conduction problem. By bringing in one P wave 20 msec early we were able to have this atrial response block within the A-V node. Again, this would look like a Mobitz type II with a sudden drop beat due to the slight prematurity of the atrial response. However, the dropped beat was blocked within the A-V node and, thus, probably should not require a pacemaker.

Dr. Baird: Dr. Bigger, how would you manage a patient with left bundle branch block and syncope that was presumably a recent onset?

Dr. Bigger: How old is this man?

Dr. Baird: He is sixty-seven.

Dr. Bigger: Well, this electrocardiogram, as I see

it of course, is left bundle branch block, and the P-R is probably 19 or 20, clearly prolonged. Did the left bundle branch block just come on about the time of the syncope?

Dr. Baird: It was a persistent left bundle.

Dr. Bigger: Of known duration or just encountered?

Dr. Baird: It was at least two months in duration. A previous tracing was taken two months before he had the syncope and, at that time, during his routine physical examination, the electrocardiogram appeared to be completely within the normal limits.

Dr. Bigger: It is difficult to be sure syncope had anything to do with his heart. It would require a work-up involving the extracranial vascular system and possible CNS causes of syncope.

Dr. Baird: He was lying down one Sunday night and suddenly developed seizure-like activity. He then awoke in about 10 or 15 seconds and resumed normal activity for the evening. We did just as you suggested and had the neurology service evaluate him. They found nothing neurological. We did Holter monitoring, and there was no evidence of A-V block or any dropped response. The patient felt, like Dr. Bigger, that there was possibly no justification for a pacemaker. The question is, would a His bundle recording be of any benefit in a patient of this type in determining whether he deserves consideration for demand pacing, particularly in the presence of the history of recurring syncope?

Dr. Bigger: This is a question Dr. Ken Rosen has been particularly interested in, the H-V time in left bundle branch block. The probability of developing complete heart block may relate to whether or not the H-V interval is long when the body surface cardiogram shows complete left bundle branch block. I think his hope is that H-V time will become a criteria that will be helpful in pointing to those who should and those who should not have pacemaker therapy. I have not been entirely convinced, but it seems a fruitful area for study.

Dr. Scherlag: I can appreciate the perplexity of the problem, and it is rather important because of the studies in Miami. There they have done several hundred cases, and they feel that with an H-V time of 70 or more and with this kind of history, such a patient is possibly going to have another seizure. I think that the H-V time would be an important objective measure to get.

Dr. Baird: Our patient refused pacemaker therapy, so we taught his wife cardiopulmonary resuscitation. However, with recurrent attacks he agreed to have a pacemaker and while waiting in the clinical center, he again had syncope. On this occasion, his wife successfully resuscitated him. The following day during elective pacemaker surgery, he developed complete A-V block. At this time, he has done relatively well, but A-V block was finally documented.

Recent Studies in the Pre-Excitation Syndrome*

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The Wolff-Parkinson-White syndrome has held an unusual fascination for cardiologists ever since its original description in 1930. Over 60 different theories have been postulated to describe the mechanism of pre-excitation. The recent development of epicardial mapping techniques to define the sequence of ventricular activation, and the introduction of His bundle electrocardiography have provided valuable procedures for studying pre-excitation. This presentation will discuss some of the insights into the mechanism of pre-excitation that have been derived from these two electrophysiological procedures.

Epicardial Mapping. Epicardial mapping of the sequence of ventricular activation is usually accomplished in the following way. First, a monopolar recording electrode is fixed within the ventricular cavity, or else bipolar electrodes are attached to the ventricular free wall. This permits recording of a consistent activation time which remains stable at a fixed time during ventricular activation and the inscription of the QRS complex. The standard ECG cannot be used as an indication of onset of ventricular activation due to the variations that result from moving the heart within the chest cavity to facilitate mapping both the right and left ventricular free walls. In addition to a fixed reference electrode, a second bipolar electrode (roving electrode) is placed at multiple sites on the ventricular epicardium; the time for onset of activation at each site is measured against the activation time of the fixed reference electrogram. By determining

the activation times at many epicardial sites, for example, 40 sites would be very minimal for constructing an activation map of the right ventricle, it is possible to construct a map of the sequence of epicardial activation. Detailed methods for determining the sequence of cardiac activation have been reported previously (1).

Figure 1 presents an ECG and bipolar electrograms recorded from a dog having spontaneous WPW. The Lead II ECG has a prominent delta wave without a visible isoelectric P-R segment. The uppermost electrogram labeled "Bipolar Electrograms Post. RV" was recorded from the earliest site on the ventricular epicardium where activation was recorded. Note that this ventricular electrogram occurs at the end of the P wave and before the initiation of the delta wave. In any normal heart, ventricular activation at the posterior right ventricular base would occur at least 50 msec later than shown in figure 1. In addition to the epicardial electrode, multipolar intramural electrodes were used to record from the right and left ventricular septum, in this case of spontaneous WPW in a dog. Purkinje spikes (labeled P) were recorded at the beginning of both septal electrograms. In a normal heart, septal Purkinje activation develops just before, or at the initiation of the QRS complex. In this WPW heart, early activation in the right ventricle began before the end of the P wave and preceded activity in the right Purkinje system by 10 msec. The right Purkinje system was activated prematurely by retrograde spread from the adjacent pre-excited myocardium. The impulse that spread over the normal A-V pathway was recorded in the left Purkinje network 30 msec after the onset of activity in the right Purkinje system and occurred 40 msec after pre-excitation of the posterior right ventricle. Since

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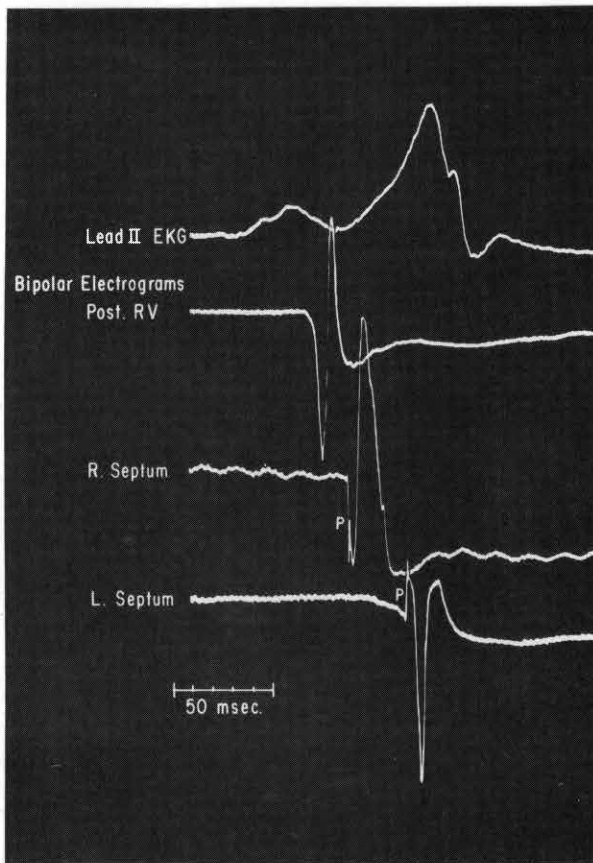


Fig. 1—The degree of ventricular fusion during activation in a dog with spontaneous WPW. Bipolar electrograms recorded from the site of pre-excitation in the posterior right ventricle and from the right and left septal surfaces are shown in relationship to the lead II ECG. P denotes Purkinje potentials. Pre-excitation begins in the posterior right ventricle during the P wave and before onset of the delta wave in the ECG. The pre-excitation wave spreads to the right septum and activates the right Purkinje system prematurely. The left Purkinje system is activated normally over the A-V conduction system. (Modified from J. P. Boineau and E. N. Moore, "Evidence for Propagation of Activation Across an Accessory Atrioventricular Connection in Types A and B Pre-excitation," *Circulation* 41:386, 1970. Reproduced by permission of The American Heart Association, Inc.)

the QRS duration was 65 msec, 60% of ventricular activation must have occurred due to activation over the accessory pathway before the impulse was propagated over the normal A-V conduction system to the left Purkinje system.

Figure 2 presents the sequence of ventricular epicardial excitation and the lead II ECG recorded at the time of surgery in a patient with type B

Wolff-Parkinson-White syndrome. It was decided to perform surgery since this patient had recurrent bouts of tachycardia and had to be resuscitated from a bout of ventricular fibrillation while in the hospital for evaluation. The subject's preoperative ECG (left tracing labeled "Pre-excitation") shows the absence of a P-R segment, the presence of a delta wave, and a marked prolongation of QRS. The initial or delta forces are oriented toward the left, and the principal QRS forces are directed posteriorly, superiorly, and to the left. The time sequence key below the maps of the heart indicates the times in milliseconds that the various areas of the heart were activated during the inscription of the ECG. Earliest activity at time 0 was recorded from the region of the sinus node. The atrial activation wave spread radially to the lateral right ventricular free wall with earliest activity being recorded at 100 msec at the A-V sulcus. The spread of ventricular activation then progressively spread radially from the right lateral A-V sulcus towards the apex. Once the sequence of ventricular activation was mapped in this WPW patient, the region of pre-excitation was sectioned along the right A-V sulcus. Following sectioning of this region, pre-excitation disappeared. Postoperatively, the ventricular activation sequence became completely normal, with activation occurring first at the medial aspect of the right ventricle near the anterior descending coronary artery. Activity then spread toward the A-V groove and into the pulmonary conus region in a normal manner. The patient's ECG has remained normal and no further bouts of tachycardia have been recorded since interruption of the presumed lateral accessory bypass tract.

The surgical interruption of a region of pre-excitation resulting in normalization of the ECG is strong supportive indirect evidence for the existence of a lateral accessory bypass tract (bundle of Kent). However, direct proof that lateral accessory bypass tracts actually can conduct and pre-excite the ventricles resulting in pre-excitation in the ECG was obtained in the dog with spontaneous WPW. Rather than surgically section the region where pre-excitation was demonstrated by electrophysiological activation mapping procedures, the region was removed for serial histological sectioning. An atrioventricular accessory bundle was demonstrated histologically at the precise location where pre-excitation was found by activation mapping procedures. This study provided the first direct demonstration that a lateral

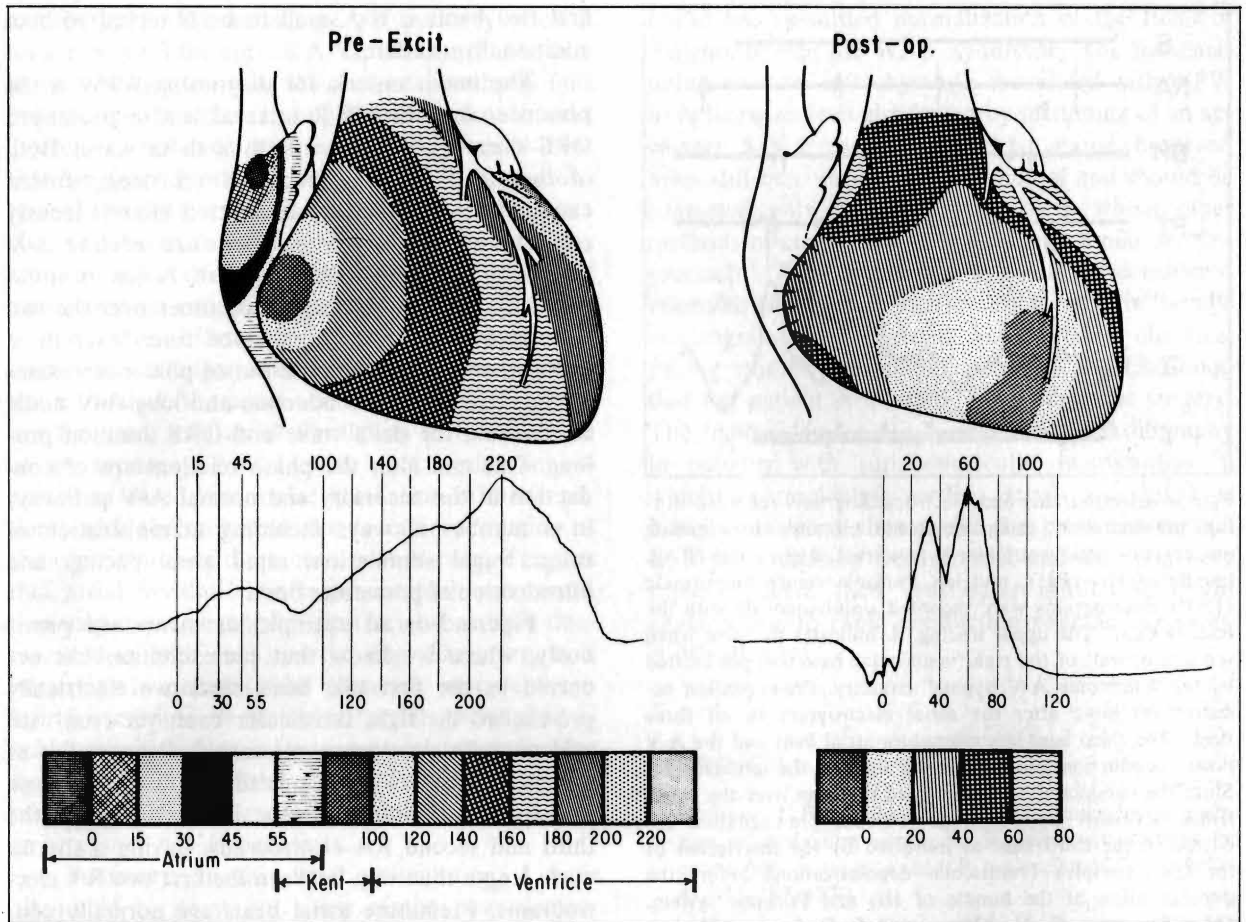


Fig. 2—Ventricular epicardial activation sequence map in a patient with type B WPW syndrome. On the left is the activation map and lead II ECG recording during pre-excitation, and on the right is the map of epicardial excitation and the ECG following surgical interruption of the A-V region where pre-excitation was recorded. The sequence key below each map indicates the relative activation times. During pre-excitation (left map) a focal region at the lateral right A-V sulcus is activated first and closely follows atrial activation of the adjacent atrial muscle. Following surgical interruption earliest activation occurs at the region of the ventricular septum. (Modified from J. P. Boineau and E. N. Moore, "Evidence for Propagation of Activation Across an Accessory Atrioventricular Connection in Types A and B Pre-excitation," *Circulation* 41:382, 1970. Reproduced by permission of The American Heart Association, Inc.)

accessory bypass tract (bundle of Kent) can produce an electrocardiogram exhibiting the Wolff-Parkinson-White syndrome (1).

Bundle of His Electrograms in Pre-excitation.

The other development in cardiac electrophysiology that has contributed recently to our better understanding of the pre-excitation syndrome is His bundle electrocardiography. The electrogram recorded from the bundle of His contains three complexes recorded from the lower right atrial septum (A), the His bundle (H), and the ventricular septum (V). The atrial-to-His bundle activation time (A-H interval) is roughly equal to A-V nodal conduction time and the His-to-ventricular septal activation time (or to

the earliest ventricular depolarization represented on an electrocardiogram) reflects conduction time within the ventricular specialized conduction system (H-V interval). Sufficient numbers of studies in normal patients and in dogs have provided us with normal A-H (50-120 msec in man) and H-V (25-55 msec in man) values.

Figure 3 presents electrograms recorded simultaneously from the right atrium (RA), bundle of His (BH), left Purkinje fiber and left ventricular muscle (LPF) together with a lead II electrocardiogram (3). The tracing labeled S is a recording denoting the time that an electronically simulated lateral accessory A-V bypass pathway pre-excited the

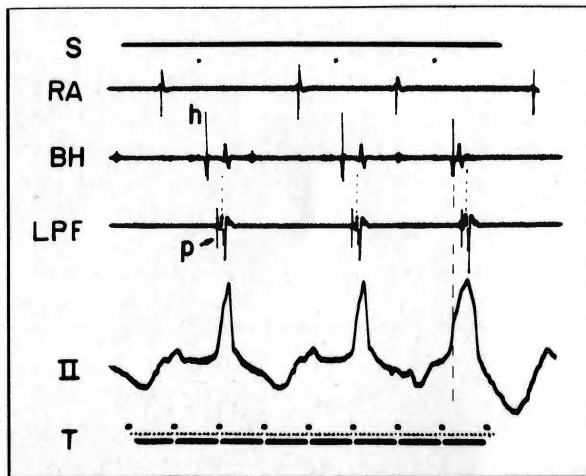


Fig. 3—Electrograms and electrocardiograms recorded during pre-excitation using electronic circuitry to simulate an accessory atrioventricular bypass tract. Right atrial (RA), bundle of His (BH), and left Purkinje ventricular muscle (LPF) electrograms were recorded simultaneously with the lead II ECG. The upper tracing, S, indicates the time when the lateral wall of the right ventricular base was pre-excited by the "electronic A-V bypass" circuitry. Pre-excitation occurred 80 msec after the atrial electrogram in all three beats. The third beat is a premature atrial beat and the A-V nodal conduction time increased due to the prematurity. Since the conduction time remained constant over the "electronic accessory bypass" tract, obvious pre-excitation occurred in the third beat as indicated by the inscription of the QRS complex (ventricular depolarization) before the depolarization of the bundle of His and Purkinje system. (Modified from E. N. Moore and J. F. Spear, "Electrophysiological Studies on Pre-excitation in the Dog Using an Electronically Simulated Atrioventricular Bypass Pathway," *Circulation Res.* 31:174, 1972. Reproduced by permission of The American Heart Association, Inc.)

base of the right ventricle at the middle of the right A-V sulcus. It can be noted that the electronically simulated accessory bundle excited the right ventricular base at a constant interval following the RA electrogram in all three beats. The atrial-to-His bundle interval is normal in the first two beats reflecting normal conduction time through the A-V node. The His bundle-to-ventricular septal interval is short, but within normal limits. Both His bundle and Purkinje excitation precede the initiation of the QRS complex in the ECG tracing. Therefore, the presence of pre-excitation is not suspected, that is, the P-R interval is normal and a delta wave is not present. However, there is no question about pre-excitation being present since we have electrically pre-excited the right ventricular base. The amount of ventricular fusion caused by pre-excitation in the

first two beats is too small to be observed without additional procedures.

The major criteria for diagnosing WPW is the presence of a short P-R interval, and a prolonged QRS duration associated with a delta wave. Both of these reflect the presence of ventricular fusion caused by activity being conducted simultaneously over the accessory A-V pathway and normal A-V conduction system. The degree of fusion is influenced by the relative conduction times over the two A-V pathways; as the conduction times over these two pathways become more out of phase, for example, short accessory conduction and long A-V nodal conduction, the delta wave and QRS duration prolong. One can alter the phase relationships of conduction in the accessory and normal A-V pathways in a number of ways including administration of drugs, vagal stimulation, rapid atrial pacing, and introduction of premature beats.

Figure 3 is an example, as mentioned previously, where we know that pre-excitation has occurred in the first two beats since we electrically pre-excited the right ventricular base; yet even with a His bundle electrogram we cannot diagnose this as an example of WPW. The third beat is a premature atrial beat as denoted by the interval between the third and second RA electrograms having a shorter cycle length than that between the first two RA electrograms. Premature atrial beats are normally conducted with an increased conduction time through the A-V node. If the conduction time over the accessory pathway does not increase, or increases less than that through the A-V nodal conduction system, we can anticipate a greater degree of ventricular fusion. The third beat in figure 3 shows marked fusion in the ECG. The fact that an accessory bundle should be strongly suspected is also shown by the BH and LPJ electrograms. Both the His bundle (R) and Purkinje (P) depolarization complexes occur following the inscription of ventricular depolarization in the lead II ECG. This fact is emphasized by the dotted line which indicates when the bundle of His was excited during the third QRS fusion complex. Also, the H-V interval in the BH electrogram is too short for normal conduction to have occurred over the ventricular specialized conduction system. An abbreviation of the H-V interval and prolongation of the QRS following a premature atrial beat or rapid atrial pacing suggests that pre-excitation is present.

His bundle electrocardiography and atrial pacing have also demonstrated that the effective refrac-

tory period of the accessory A-V pathway often is longer than for the normal A-V pathway, that is, premature conduction over the accessory pathway fails before conduction fails through the normal A-V node. Therefore, an even earlier premature atrial beat than in figure 3 may result in complete normalization of the QRS complex if conduction over the accessory pathway fails, since, in this case the ventricles are normally activated only through the normal A-V conduction system and ventricular fusion is absent.

It is indeed fortunate that the accessory pathway usually has a longer effective refractory period than the normal A-V transmission system. If this were not the case, then atrial fibrillation in the presence of an accessory A-V bypass tract would be expected to cause ventricular fibrillation in many patients with pre-excitation due to rapid activation of the ventricles over the accessory A-V tract. The fact that atrial fibrillation in a patient with pre-excitation may cause ventricular fibrillation has been documented in both man and the dog. Therefore, it is important in patients with recurrent supraventricular tachycardias in which an atrial pacemaker is being considered as a treatment to terminate the dysrhythmia, that atrial pacing studies be undertaken to rule out the possibility of the presence of an accessory A-V bypass tract.

Summary. In this brief presentation, I have attempted to point out some of the new electrophysiological techniques used in studying the pre-excitation syndrome as well as some of the interesting findings which these techniques have provided. For more detailed particulars on the newer findings on the WPW syndrome, the reviews of Durrer *et al.* and Wallace *et al.* can be recommended (2, 4).

The technique for mapping the sequence of ventricular epicardial activation has provided a mechanism of defining the anatomical site of pre-excitation. Surgical interruption of the atrium and ventricle at the region where pre-excitation was

found has permitted normalization of the ECG of patients having the WPW syndrome. The incapacitating episodes of tachycardia associated with WPW have likewise been eliminated by sectioning of an accessory A-V bypass tract. This technique, however, must still be considered experimental and should be suggested only in WPW patients in whom other methods of controlling the tachyarrhythmias are unsuccessful. Prior to surgery it should be considered essential that other studies such as His bundle electrograms be recorded and suitable electrical pacing studies undertaken to assure the likelihood that the patient is a suitable candidate for surgery. The indications for His bundle electrocardiography in patients with supraventricular tachycardias in which an implanted cardiac atrial pacemaker is being considered should also be emphasized; that is, if pre-excitation were present and the atria were rapidly paced, then ventricular fibrillation might develop due to rapid conduction over an accessory A-V pathway.

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Workshop

Presiding: WILLIAM A. DICKINSON, JR., M.D.

Co-Director of Coronary Care Unit and Electrocardiography, General Hospital of Virginia Beach, Virginia Beach, Virginia

CASE 1

Dr. Dickinson: How would you manage this patient?

Dr. Dreifus: I do not believe that there is much to discuss in the first lead of ventricular fibrillation, and I would probably defibrillate the heart. The second one, however, reveals anteroseptal infarction. The exact age is not clear, but it is probably recent. The P-R interval appears to be normal; however, there is left axis deviation with right bundle branch block. Thus, I believe that this is sinus rhythm with bifascicular block and an anteroseptal wall infarction.

Dr. Baird: What are the criteria for the insertion of temporary pacemakers during an acute myocardial infarction?

Dr. Dreifus: The prognosis in patients with acute infarction complicated by bifascicular or trifascicular block is poor. The mortality may approach 60 or 70%, whether or not we utilize pacemakers. There is considerable work to show that patients who have two fascicles blocked with an acute process may eventually involve the third fascicle, and high grade block develops rapidly. I do not know whether I would put one in this patient unless there is associated first degree block. This can be either intranodal or block in the third fascicle. If it behaved like a basic Wenckebach, I would assume that it was in the A-V junction, but if the QRS suddenly dropped out, I would believe that the block is in the distal portion of the third fascicle or the posterior division. I would certainly put in the temporary pacemaker under these circumstances. However, I do not think I would recommend insertion of pacemakers in patients with mono- or bifascicular block alone in the electrocardiogram, even though two fascicles are blocked.

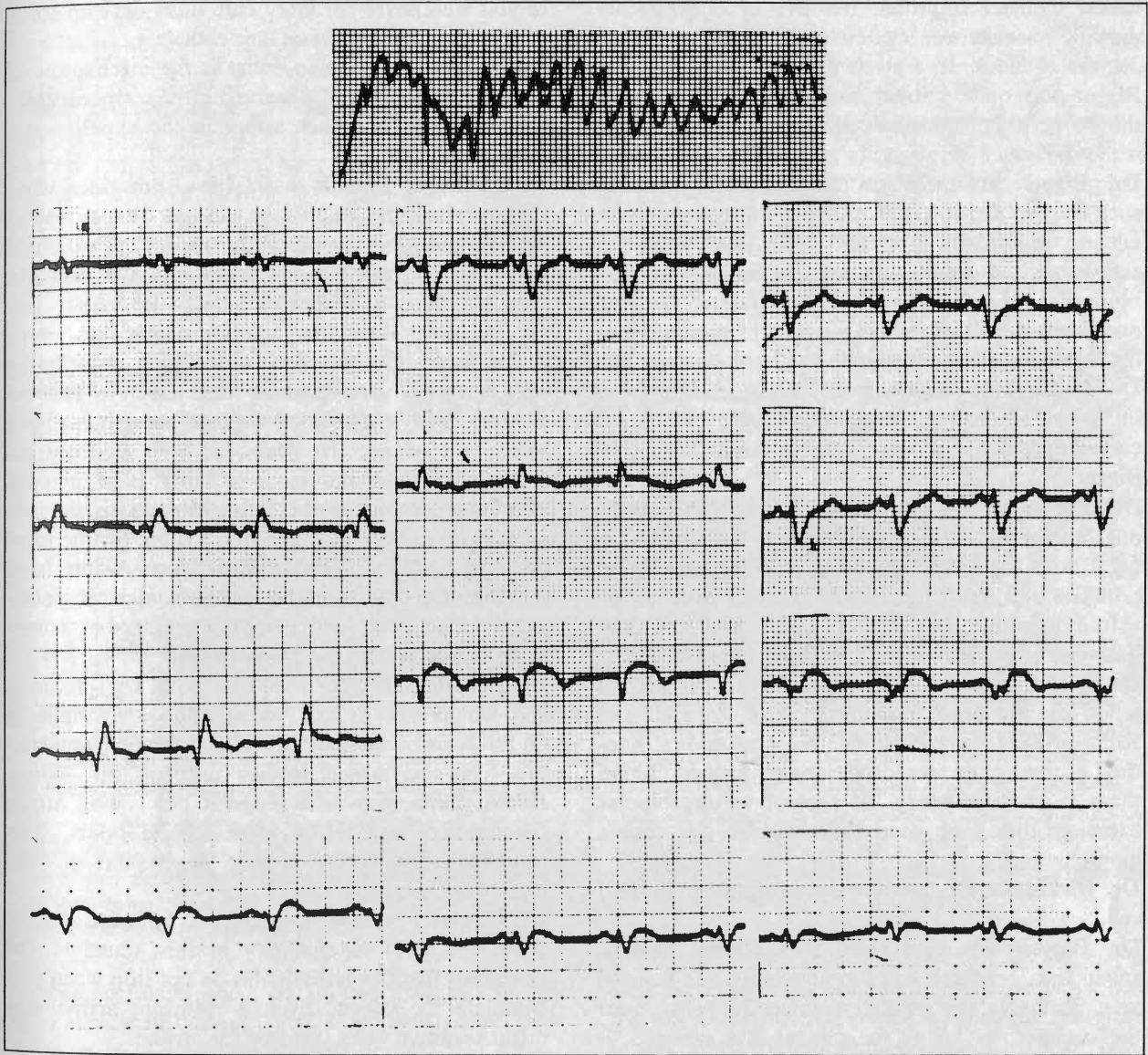
Dr. Dickinson: Are there any other comments regarding this?

Dr. Surawicz: I would like to make a comment. This kind of discussion always breaks down somewhat because we have two groups of people who manage such a problem, the university or teaching hospital with a house staff and the private hospital without house staff, which is quite different. The physician in a small private hospital knows that he has an hour's time and that later he will be busy. Aware of this, he will place in a pacemaker earlier, even though it may not be necessary. That is the situation frequently found in a small private hospital. To open the discussion in this case, I would not recommend temporary pacemaker insertion in a patient with a normal P-R interval, right bundle branch block, and left anterior hemi-block.

Dr. Bigger: At our hospital, Macken and Stock reviewed a series of cases of acute myocardial infarction with anteroseptal infarction and right bundle branch block. Nearly half of these cases developed sudden complete heart block or high degree A-V block without warning or Wenckebach periods.

Dr. Scherlag: I can report on studies that were done in a large series by Dr. Narula and recently published in the *American Journal of Medicine*. The patients with right bundle and left axis deviation, or what people term left anterior hemi-block, showed a 70% incidence of damage in all the "fascicles" of bundle branches, that is, the H-V times were prolonged, indicating bilateral bundle branch block. Twenty-eight to 30% showed that this was truly bifascicular, that is, the posterior "fascicle" was probably intact, and the H-V time was normal. The statistics are identical for both the infarcted as well as the noninfarcted.

Dr. Baird: I think it is interesting to note that the acute development of right bundle branch block during acute myocardial infarction has a mortality

**CASE 1:**

This 56-year-old white male painter was in excellent health prior to the development of substernal pain, diaphoresis two days prior to admission. During the ER evaluation, the patient had ventricular fibrillation and asystole. After defibrillation, a complete electrocardiogram demonstrated the following.

What would you recommend?

of close to 50%; therefore, I am sure Dr. Bigger and I, although we would insert a pacemaker catheter in this situation, realize the prognosis is extremely poor. It is possible that in the future, studies such as selective coronary arteriography with the consideration of emergency aorto-coronary surgery would be a more appropriate approach than the sole management of heart block with the insertion of a standby catheter.

Dr. Scherlag: I would like to make another comment. I agree that in patients with acute infarction and bundle branch block, pacemaker therapy does not appear to aid in terms of survival. However, we have been involved in studies with Dr. Clyde Schoenfeld in the intensive care unit utilizing His bundle recordings. Acute inferior myocardial infarction with Wenckebach phenomena is a situation in which most people do not recommend pacer-

maker catheter insertion, but five of our patients showing Wenckebach cycles have developed higher degrees of block. In a given patient I think that Dr. Bigger was quite correct since these patients may show a period of nonconduction, and the pacemaker is the difference between life and death.

Dr. Bigger: In these people with complications such as hypotension, congestive failure, pulmonary edema, or emboli, a period of asystole may be catastrophic. I think that an individual who has borderline compensation of pump failure because one-third of his ventricle is necrotic or nonfunctioning would not survive a minute or two of asystole.

Dr. Dickinson: The audience might be interested in your recommendations concerning types of catheters and the use of portable fluoroscopy, Dr. Bigger.

Dr. Bigger: We often utilize No. 5 Cordis® transvenous bipolar pacemaker catheters or the semi-floating USCI® catheter. We prefer bipolar pacemaker catheters and insert them using portable fluoroscopy in our intensive care unit. Up until two and one-half years ago we utilized a large number of the Davis and Geck floatable platinum probes with a teflon coating made popular by Drs. Kimball and Killip of New York Hospital. We used several hundred of these catheters for various reasons and found them to be satisfactory. At present we use bipolar catheters that have good characteristics for torque manipulation.

Dr. Dickinson: Do you use the brachial or femoral vein?

Dr. Bigger: We have used the external jugular, subclavian, brachial, and more recently, the femoral vein. Probably the most convenient place to insert the catheter, as far as the patient is concerned, is in the external jugular system because both the patient's arms and legs are left free. A cut down on the jugular vein may be difficult for inexperienced personnel because it is friable.

Dr. Dreifus: Dr. Dickinson, may I make one more remark before you leave the pacemaker discussion? We have been using the Swan-Ganz floating balloon catheter and have found it successful in these situations. I think it is an alternative for fluoroscopy, particularly if you want to insert one rapidly. It may be placed through a needle percutaneously. If you need to put in one on a more permanent basis, for example, a week to ten days, you may transfer the patient to a fluoroscopy room and replace it with a stiff catheter. I would recommend that those

of you who cover coronary care units develop some facility in using the Swan-Ganz catheters.

Dr. Baird: Dr. Hoffman, what is the mechanism of ventricular fibrillation observed after temporary occlusion of the coronary artery in the experimental animal?

Dr. Hoffman: I think that I have some idea what the mechanism would be in an experimental animal, and it is very straightforward. If you occlude a branch of the coronary artery and the ventricle does not fibrillate during ischemia—let us say you are fairly far down the anterior descending artery—you leave the artery occluded long enough for cells normally nourished by the vessel to become ischemic and lose a good deal of potassium. Then when you release the occlusion you suddenly reperfuse this bed and move a fairly large amount of potassium out of the ischemic area to the adjacent areas of the myocardium. I think for the most part the so-called “release fibrillation” results from the flushing out from the ischemic area of potassium, lactic acid, and everything else that comes out suddenly from ischemic cells.

Dr. Scherlag: I certainly agree with Dr. Hoffman and would like to ask whether the arrhythmia is on the basis of automaticity or a reentry phenomena. We have performed studies utilizing the Sidney Harris preparation with anterior descending artery tie-offs and reperfusion after several hours. The resultant arrhythmias appear to be due to enhanced automaticity.

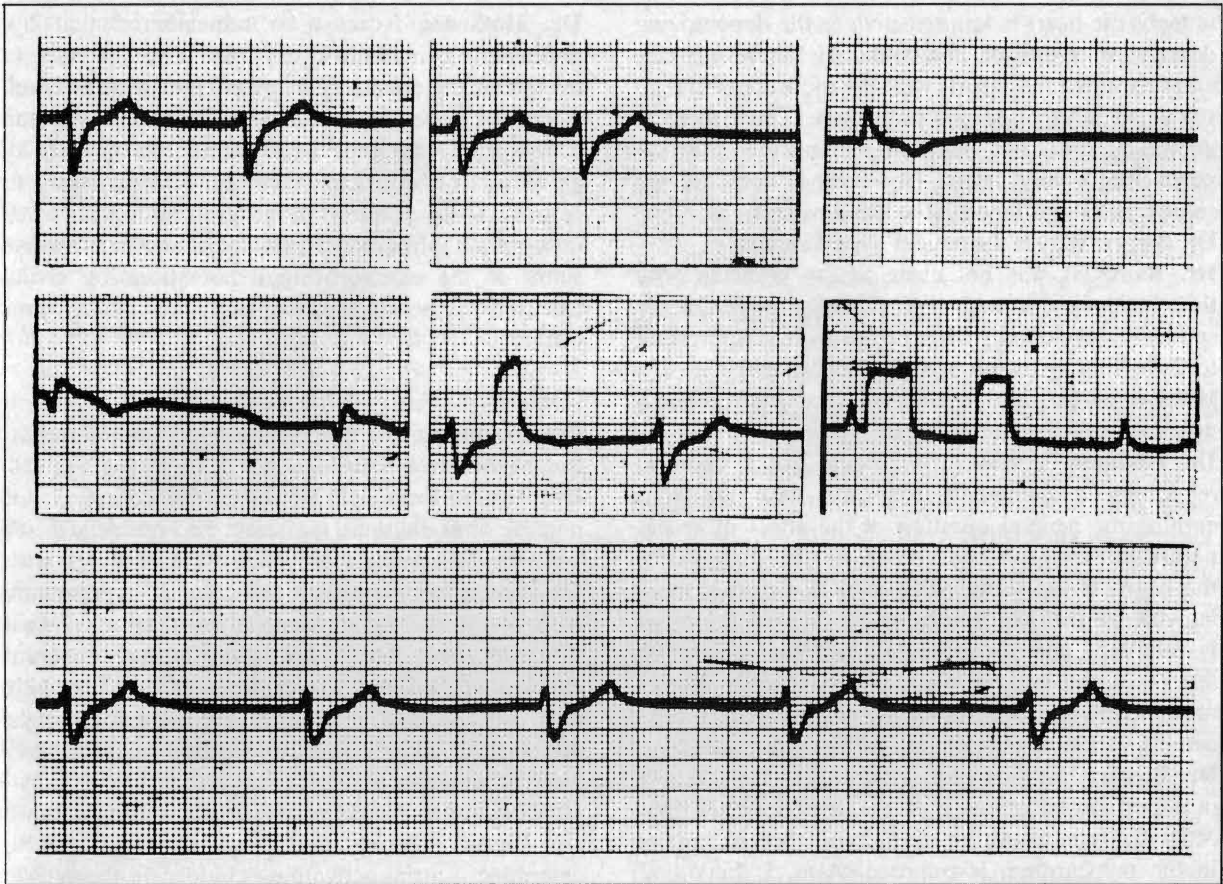
Dr. Bigger: I wonder if you would be more specific about the term automaticity in this situation. Do you mean that the arrhythmias do not stop when you stimulate the vagus? Even a reentrant arrhythmia might continue when you stop the atrium.

Dr. Scherlag: I think it is a good point, and it is difficult to differentiate between reentry and automaticity.

CASE II

Dr. Dickinson: Dr. Surawicz, we would like your interpretation of this, and any remarks regarding etiology and treatment.

Dr. Surawicz: I presume that this patient has severe hyperkalemia with the serum potassium above 8 meq/L because of the absence of P waves. The presence of chest pain and syncope raises the possibility of fibrillation and a diaphragmic myocardial infarction with peri-infarction block. I would probably get some clue from the electrocardiogram

**CASE II:**

This 67-year-old white male with arteriosclerotic heart disease, angina pectoris, and mild chronic renal disease developed chest pain and syncope associated with the following electrocardiogram.

How would you manage this patient?

preceding this episode, but if this diagnosis of hyperkalemia is correct, then I would treat it with glucose, insulin, and bicarbonate.

Dr. Dickinson: The potassium level was 9 mg/L. Would you like to be more specific as to how you would use the dextrose and insulin?

Dr. Surawicz: In a case like this, we can give 50% glucose and 1 unit of insulin per 2 g of glucose during a period of electrocardiographic monitoring. I would then give 1–2 ampoules of bicarbonate and see what is happening.

Dr. Hoffman: I agree with Dr. Surawicz. In most mammalian hearts, including the human heart, the atria seem to be more sensitive to hyperkalemia than the ventricles. I do not know why the atria are more sensitive to the potassium than the ventricles and the ventricular conduction system. Perhaps Dr. Surawicz can tell us.

Dr. Surawicz: No, but the question is, why does the rhythm remain regular? Is it an escape pacemaker or is it from the sinus node?

Dr. Hoffman: If I had not read a recent paper by Dr. Fred Pick, I might have said what you wanted. I think that in many instances, if you have a ventricular rhythm of this sort in a patient with hyperkalemia, it may be a sinus rhythm where there is sinoventricular conduction and sinoatrial block. Dr. Pick is a very careful investigator, and he has not been able to reproduce some of our studies. Thus, I have been hedging on it for awhile. To come back to the question of other electrolytes, I imagine that one might wonder about changes in the level of calcium. As the serum calcium is elevated, the only thing this will do to the heart is to antagonize the effects of high potassium. For any given level of potassium, if the serum calcium

is high, the heart is less sensitive to the depolarizing depressant effects of potassium. If the serum calcium is low, the heart will be more sensitive to the same level of serum potassium. Thus, there is an antagonism, but one can demonstrate this experimentally very easily. However, it does not assume much importance in the usual patient.

Dr. Bigger: Why is the patient hyperkalemic?

Dr. Baird: It was not clear to the clinician why this patient who had had chronic renal disease suddenly developed such a problem. It is interesting to note that a temporary pacemaker catheter was inserted as the initial therapy since hyperkalemia was not recognized until later.

Dr. Hoffman: I wonder if I could ask a question reiterating a comment from the audience concerning the general question of the effect of serum potassium level on the uptake of the digitalis by the heart. If the serum potassium is elevated, there is evidence that the uptake of digitalis by the heart is retarded, and therefore, digitalization might be less rapid and less complete. I wonder if Dr. Bigger or someone else could help my vague memory concerning variation among the digitalis compounds.

Dr. Bigger: The first part, I think, has been shown in experimental animals; if the hyperkalemia precedes the administration of digitalis, then its uptake in the myocardium is retarded. Also, I think that it is correct that there is a difference between compounds; however, I am not certain of this.

Dr. Dreifus: If you add magnesium, you can go even farther with digitalis, but this is very impractical from the clinical standpoint.

Dr. Hoffman: It must be remembered that hyperkalemia can result in asystole. If you attempt to overcome the effects of hyperkalemia with calcium, it must be done very carefully since you may develop a completely asystolic heart without atrial activity as well as no ventricular activity. I merely want to express some caution in general; although when interpreting physiologic principles one can reverse some of the effects of high potassium by giving calcium, it is not a completely innocuous procedure.

CASE III

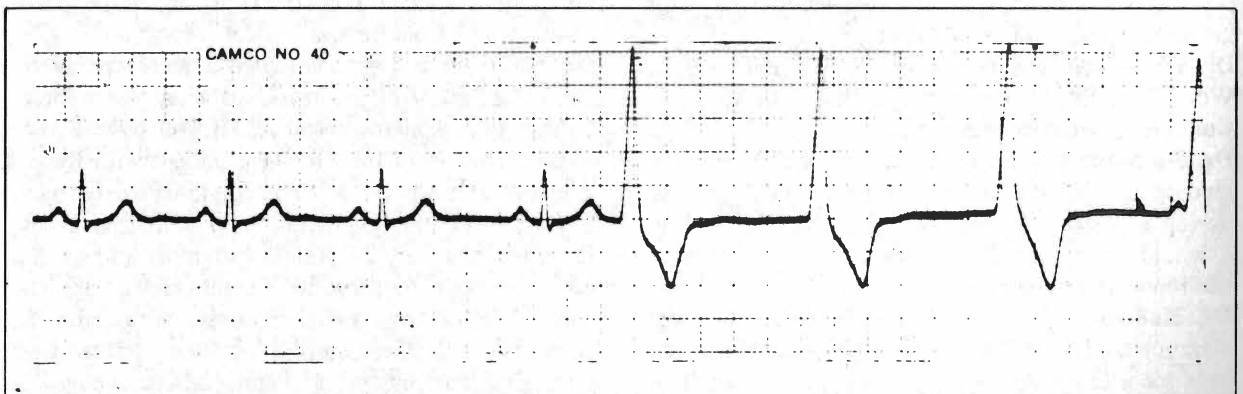
Dr. Dickinson: Dr. Bigger, what is your interpretation of this electrocardiogram?

Dr. Bigger: From left to right, four complexes of normal sinus rhythms are seen. The problem arises with the fifth beat, a tall wide QRS complex with the T wave in the opposite direction. It is premature with a shorter cycle length than that in normal sinus rhythm. Atrial activation is not apparent within the QRS and T complexes of that first wide beat. Atrial activation reappears at the extreme right of the slide. The reason for the depression of sinus node is not clear.

Dr. Dickinson: Would you treat this, and if so, how?

Dr. Bigger: I would first place an atrial lead to determine if atrial activation is hidden in those wide beats. I would not treat until the rhythm was diagnosed and the history, physical, and laboratory examination were satisfactorily completed.

Dr. Moe: In this situation I would like to observe a simultaneous record of the arterial pressure because



CASE III:

This 60-year-old alcoholic was admitted to the Rehabilitation Center and the routine electrocardiogram demonstrated left axis deviation with right bundle branch block. There had been several episodes of questionable syncope probably related to his alcoholism. Is provocative atrial pacing of any value in predicting which patients may be subject to Adams-Stokes seizures?

it is conceivable that this arrhythmia could be vagally induced. The last P-R interval in which the P waves are clearly visible is distinctly longer than the preceding one.

Dr. Dickinson: Dr. Dreifus, could this be ventricular tachycardia with exit block?

Dr. Dreifus: This is a possible explanation, but in my experience it is extremely rare. Inhibition of sinus rhythmicity and vagal influence are probably major factors in this situation. Acceleration of the sinus rate by the administration of atropine, or by raising the foot of the bed, may be an effective approach. I have observed their disappearance by the administration of lidocaine as well. In general, they are benign arrhythmias, and it is rare for them to develop repetitive ventricular tachycardia.

Dr. Hoffman: The fact that lidocaine was administered and that they disappeared does not mean anything. I believe that this type of arrhythmia might be observed off and on again for a few minutes or a half-hour, and then it is questionable whether lidocaine was effective as a therapeutic agent.

Questioner: In one of our patients we have observed that slow ventricular tachycardia was terminated by premature ventricular contraction. I would like to know whether you consider this evidence of a reentry mechanism.

Dr. Moe: This is a very broad question, and therefore, it will receive a very broad answer. Yes, it is possible, but one would have to have more definitive evidence than that to be able to make a diagnosis. I am sorry if I disappoint you, but that is how I feel.

Dr. Hoffman: Dr. Dickinson, I wonder if I might try to confuse the picture a little more. The temptation which I think confronts everybody is to assume that rate and the duration of the QRS complex provide an indication as to the site of the impulse initiation. If you have a normal QRS, it is stated to be above the bifurcation or in the common bundle. If you have a broad, bizarre QRS complex, then you assume that it arises distal to the bifurcation, and the ideal rate would be 40, let us say. I believe this is a

very imprecise set of guidelines because it is quite possible to have an impulse arise in the common bundle, to be conducted aberrantly, that is, to be delayed in one or another of the other fascicles of the conducting systems and to give you a wide QRS complex even though it is originating proximal to the bifurcation. The point is that aberration is usually associated with rapid rate. Yet, when the automaticity of the conducting system is increased, when the diastolic depolarization is fairly marked with long diastolic intervals, the depolarization of the conducting system proceeds farther. Then, even the impulse that originates in the common bundle will be conducted with aberration. In general, it is probably not permissible to use the association of a particular rate or the appearance of the QRS complex to decide that you have ventricular tachycardia or a junctional rhythm. I believe that you can have junctional rhythm with an abnormal QRS, and since the rate is 62, it cannot be stated that it represents accelerated activity in the distal portion of the ventricle. I do not know whether Drs. Bigger, Surawicz, or Dreifus would disagree with me, but I hope that one of them might try.

Dr. Moe: I doubt that all of the various antiarrhythmics act by suppressing automatic activity. All of these examples were from Purkinje fibers, and I think mainly in dogs. One might have the right to ask why, if these drugs all suppressed automatic activity and therefore ectopic automatic activity, do they not suppress all activity totally and thus cause cardiac arrest.

Dr. Hoffman: I cannot answer this in terms of "why." I think that Dr. Moe made a good point and that there are differences in the sensitivity of pacemakers in the various parts of the heart. When you are considering the sinus node, this is a special case, and it is quite insensitive to the slowing effect of any of these agents. In order to appreciably slow a healthy sinus node, you have to use very high concentrations. I do not have the vaguest idea why the sinus node is resistant to this effect of antiarrhythmic drugs, but I am glad that it is resistant.



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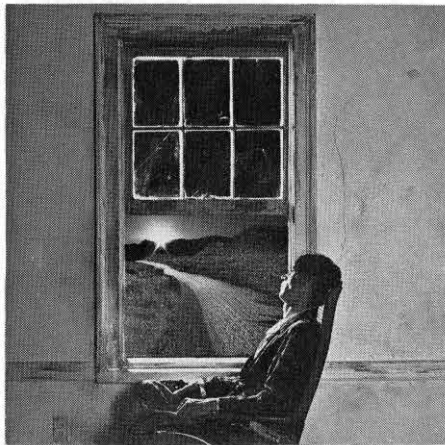
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Precautions: *Certain Respiratory Conditions.* Although respiratory depression has rarely been reported after oral administration of Talwin, the drug should be administered with caution to patients with respiratory depression from any cause, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Decreased metabolism of the drug by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects

of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract. **Patients Receiving Narcotics.** Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. **CNS effects:** dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations (see *Acute CNS Manifestations* under WARNINGS); and rarely tremor, irritability, excitement, tinnitus. **Autonomic:** sweating; infrequently flushing; and rarely chills. **Allergic:** infrequently rash; and rarely urticaria, edema of the face. **Cardiovascular:** infrequently decrease in blood pressure, tachycardia. **Other:** rarely respiratory depression, urinary retention.

Dosage and Administration: *Adults.* The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg.

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Duration of Therapy. Patients with chronic pain who have received Talwin orally for prolonged periods have not experienced withdrawal symptoms even when administration was abruptly discontinued (see WARNINGS). No tolerance to the analgesic effect has been observed. Laboratory tests of blood and urine and of liver and kidney function have revealed no significant abnormalities after prolonged administration of Talwin.

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

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Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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