CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

IX. Type A Wolff-Parkinson-White Syndrome

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SUMMARY
A twenty-two-year-old woman with type A Wolff-Parkinson-White syndrome had a long history of paroxysmal tachycardia and died of a stroke. Until the last two years of life the tachycardias responded to medical treatment, but thereafter they could only be terminated with electrical shock. During one such shock her sinus rhythm disappeared and for over a year she had only atrioventricular (A-V) junctional rhythm although paroxysms of tachycardia persisted.

Special studies of the heart after death included serial sections of the entire A-V ring. Nonspecific degenerative disease of both atria included the internodal pathways. Both the sinus node artery and the A-V node artery were narrowed by mural thickening. The sinus node was generally intact but virtually all atrionodal connections were degenerated. The A-V node was similarly detached from its atrial connections but was in direct continuity with the His bundle. The right bundle branch was interrupted at its origin. Within the central fibrous body there were numerous lacunae and one long cleft extending from atrial to ventricular septum parallel to the A-V node. Although the cleft contained cells, there was no direct A-V connection. At the right lateral A-V junction a long thin cylinder of Purkinje cells lay parallel to the tricuspid valve ring and connected to the atrium but not the ventricle. Beneath the left atrial appendage there was a fault in the mitral annulus through which there was a direct A-V connection. Most of this connection was composed of P cells and thus resembled the patient's own sinus node. The atrial connection was to Bachmann's bundle, which was extensively degenerated. The ventricular connection was to ordinary working myocardium midway between epicardium and endocardium. Some functional implications of these anatomical findings are discussed.

Additional Indexing Words:
A-V node  Pre-excitation  His bundle
Paroxysmal supraventricular tachycardia  Sinus node  Atrial degeneration
Internodal pathways  Sinus arrest

In the original study of eleven patients with the syndrome which now bears their name, Wolff, Parkinson and White emphasized that these were healthy young people and that the syndrome was not indicative of heart disease.1 There was good reason for their reassuring remarks, particularly in view of the rapidity of the tachycardias, the bizarre nature of the electrocardiogram, and the considerable mystery about the mechanism of the disorder. However, their remarks were for many years interpreted as meaning that the syndrome was a safe clinical condition with little or no hazard to life, although that was not exactly what they had said. After about a decade of increasing worldwide fascination with the Wolff-Parkinson-White (WPW) syndrome, it began to be apparent that the patients did not always do well and that some died during attacks of tachycardia.2 Subsequently, it has become widely recognized that exceptional patients with the WPW syndrome may indeed die suddenly and unexpectedly.3, 4

Because of certain remarkable surgical successes in treatment of carefully selected patients with the WPW syndrome at the Duke University Medical Center,5, 6 there has been a recent resurgence of interest in the anatomical substrate for the electrophysiological disturbance. Most of the few hearts carefully studied at necropsy have been from patients who died with type B of the WPW syndrome, which resembles left bundle branch block.7, 16 This report will describe findings from a detailed study of the heart of a young woman who died rather suddenly.

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and who had a variety of documented electrophysiological disorders which included the type A WPW syndrome.

**Case Report**

**Clinical Course**

A young white woman had enjoyed excellent health until the age of thirteen years when she experienced her first episode of paroxysmal tachycardia. No other members of her family had this problem. Over the next seven years she had frequent recurrences of the paroxysmal tachycardia and required repeated hospitalizations. In the attacks the cardiac rate was usually about 180/min with varying configuration of the QRS complexes, but between attacks there was sinus rhythm with QRS complexes resembling type A of the WPW syndrome (figs. 1 and 2). Most bouts of tachycardia were terminated by the intravenous administration of either ajmaline or procaine amide, and this treatment sometimes but not always abolished the pre-excitation to restore normal QRS complexes.

At the age of twenty years the paroxysmal tachycardia gradually became resistant to any pharmacological treatment and normal rhythm could only be restored by electrical cardioversion. All of the attacks remained supraventricular in origin as determined with both esophageal and intracardiac (right atrial) electrograms (figs. 1–3). Several months after the need for periodic use of electrical cardioversion, following one such shock treatment sinus rhythm disappeared and did not return, being replaced by a slow A-V junctional rhythm without pre-excitation (fig. 4). Paroxysmal tachycardias continued, however, exactly as previously. During this period of time there was a progressive increase in the size of the right atrium on chest X-rays.

At the age of twenty-two years the patient experienced a cerebrovascular accident due to an arterial embolus most likely originating in the heart. Because of the slow A-V junctional rhythm (35/min), a pacing catheter was introduced into the right atrium where the entire wall was found to be unexcitable despite maximal levels of stimulus intensity. The catheter was then advanced into the right ventricle, although with some difficulty due to the large size of the right atrium. Right ventricular pacing was effective until her death (of respiratory arrest thought to be of bulbar origin) on the third day after onset of hemiplegia.

**Postmortem Examination**

At necropsy the important findings for this report are limited to the heart. There was distinct enlargement of the

![Figure 1](http://circ.ahajournals.org/)

*Panel A shows the WPW syndrome during sinus rhythm. In Panel B the pre-excitation has disappeared after an intravenous injection of ajmaline. Panel C illustrates a period of tachycardia (at a rate of 170/min) with maximal pre-excitation, but the delta wave disappears after ajmaline in Panel D, where the supraventricular nature of the tachycardia is revealed.*

![Figure 2](http://circ.ahajournals.org/)

*These tracings show the supraventricular tachycardia in the presence of pre-excitation (Panel A) and in its absence (Panels B–D). The esophageal leads at four levels (E₁ to E₄) demonstrate 1:1 A-V conduction. Ajmaline caused the pre-excitation to disappear (Panels B–D) and the ventricular rate to slow (Panel D). Note from all four panels that the direction of atrial activation varies during the tachycardia, shown most clearly in the esophageal leads.*
Figure 3

The two upper tracings illustrate supraventricular tachycardia with pre-excitation, while the lower tracing (after ajmaline) shows persistence of the atrial tachycardia (P waves marked) plus second degree A-V block during which the pre-excitation has disappeared.

right atrium which had thin walls, but the other cardiac chambers were grossly normal in appearance and consistency. The cardiac values were normal in location and appearance and there was no defect in either the atrial or ventricular septum. The major coronary arteries were nor-

Figure 4

Permanent A-V junctional rhythm (at a rate of 45/min) characteristically present the last two years of the patient’s life is illustrated here. There is 1:1 A-V conduction and the retrograde P waves are marked.

Figure 5

A gross photograph of the heart shows the location of the left A-V connection which was beneath the left atrial appendage at approximately the point indicated by the asterisk. The location of the right paravalvular cylinder is marked by the cross-hatched strip. The thin right atrium (RA) is wrinkled. Other labels are left atrium (LA), aorta (Ao), pulmonary artery (PA) and right ventricle (RV).

Figure 6

The source of the blocks for serial sectioning is depicted above. The block containing the junction of atrial and ventricular septa (plus the A-V node and His bundle) is cut free, and Ao overlies the non-coronary sinus of the aorta. The upper portions of the two atria have been removed, and the asterisk and cross-hatched area correspond to the left A-V connection and the right paravalvular cylinder, respectively. In the lower photograph the three final blocks for serial sectioning of the entire A-V rings are shown, after the aorta and pulmonary artery outside the A-V junction have been cut away.
mally distributed and had no significant enroachment on their lumens at any point. The right coronary artery crossed the crux of the heart and thus supplied the A-V node, while the sinus node artery also originated from the right coronary about two centimeters from the aorta.

The heart was intact at the time of special examination except for a single incision from the inferior vena cava to the superior vena cava across the sinus intercavum, at all points a minimum of two centimeters from the crista terminalis, thus entirely sparing the region of the sinus node. The crista terminalis appeared pale but grossly normal, as did the first few millimeters of trabeculae extending laterally. However, the remaining portions of trabeculae over most of the right atrial free wall were thinned extensively and this gave the lateral right atrial wall a paper-like appearance. The crista supraventricularis was large and thick.

Special blocks were prepared for serial sectioning of four regions: the sinus node, the entire junction of atrial and ventricular septum, the entire left A-V ring and the entire right A-V ring. The nature of these blocks is illustrated photographically in figures 5-7. Each of the four blocks was carefully cut into serial slices from 5 to 10 mm in thickness to promote optimal fixation. Sectioning was done at 10 micron intervals. Every section was saved with 9 of every 10 being prepared with the Goldner trichrome stain and the tenth routinely being a Verhoeuff-Van Gieson elastic stain. For the three blocks representing the complete A-V junctional region a total of 13,065 slides were prepared and every slide was examined microscopically. About 300 sections were either damaged or distorted in processing, making them unsatisfactory for study, but there was no interval in the series where more than two such sections occurred in sequence.

Serial section study of the sinus node was limited to the node and a few millimeters of its direct environs, as initially defined from screening sections of serial blocks. Each of those blocks containing the sinus node was serially sectioned and a total of 1100 such sections were made. Samples of other portions of the heart were studied only with subserial sections and included the free right atrial wall, the left atrial wall, the eustachian ridge of the right atrium where it connected with the crista terminalis (the remainder was included in blocks of the right A-V ring), selected portions of the free right and left ventricular walls, and the course of the sinus node artery outside the sinus node blocks which were

Figure 7

These two photographs show the regions of the sinus node (SN) and of the A-V node and His bundle as they were studied in this case. The thin wall of the right atrium (RA) is apparent above, and the block serially sectioned for sinus node in the upper segment cut away. The block containing A-V node and His bundle in the lower photograph was completely serially sectioned. Labels there include right ventricle (RV), interatrial septum (IAS), interventricular septum (IVS), tricuspid valve (Tr Vtv), crista supraventricularis (CrS) and the coronary sinus (CS). The thebesian valve overlying the coronary sinus is fenestrated, forming part of a small Chiari net.

Figure 8

In these two photomicrographs of sinus node (arrows) its isolation by perinodal fat is apparent. A is near the anterior margin of the sinus node, while B is 4 mm closer to its midpoint. The epicardium is above in both A and B, but the orientation of the superior vena cava (SVC) is reversed. In B a fibroed old thrombus (Thr) is seen. Verhoeuff-van Gieson stain both sections.
The thickened sinus node artery is seen from a point just posterior to the sinus node in A. Note the extensive fibrosis and fat throughout the atrial wall (Goldner trichrome stain). Note the sharp discontinuity of the internal elastic lamina in an adjacent section in B, and the fact that most of the thickening is in the tunica media (Verhoeff-van Gieson stain).

The Sinus Node

At all its margins the sinus node was virtually disconnected from the right atrium (fig. 8). Where a few fibers could be found to leave the node in the direction of one of the three internodal pathways,19 their course was regularly interrupted after a distance of no more than a few millimeters. Near its midportion the sinus node appeared normal in architecture, although containing slightly more collagen in its framework than is usually present at this age. The sinus node artery encircled the superior vena cava in a counterclockwise direction, thus entering the node from its posterior margin, which is not an unusual variation.17 Just before entering the node, the artery was remarkably thickened with marked narrowing of its lumen (fig. 9). Both at this point and at another location about 8 mm into the sinus node, the internal elastic lamina of the sinus node artery was sharply discontinuous, being present for only about half of the circumference of the vessel.

The crista terminalis was virtually replaced with fat and a scattering of fibrosis or recent degeneration (fig. 10). This extensive degeneration continued into the eustachian ridge, where hemorrhage and recent necrosis of cells were even more extensive. Although a portion of these findings may have been attributable to the intracardiac catheter used in the last few days of the patient’s life, the lesions were not particularly endocardial in location and most appeared much older than could be attributed to such recent trauma. Furthermore, the fatty degeneration and other lesions virtually destroying the crista terminalis (and thereby interrupting the posterior internodal pathway19) were identical to the histopathological changes in the free walls of both the right and left atria.

The Internodal Pathways

All three internodal pathways had extensive focal degeneration, particularly within the interatrial septum and the region directly above the A-V node (figs. 11 and 12). There were areas of recent focal hemorrhage and necrosis but the most prevalent changes were fatty replacement and scarring.

Because of findings in the left A-V ring (see below), special attention was directed at Bachmann’s bundle as it continued into the left atrium. Here too there was extensive focal degeneration of the same nature as in the rest of the atrial myocardium, although a number of islands of normal-appearing Purkinje cells could be found. These islands were essentially isolated, in particular being unconnected to the sinus node.

The A-V Node and His Bundle

Just as with the sinus node, the A-V node was disconnected from the internodal pathways. Where there were scattered connecting fibers, these extended only for a
few millimeters up the interatrial septum before entering a blind pocket of collagen or fat. Within the A-V node there was focal fatty degeneration as well as small areas of active necrosis of nodal cells. Cells in the bypass tracts were as extensively damaged as those in the internodal pathways, thus leaving the A-V node essentially isolated from the rest of the atrium and in particular completely disconnected from the sinus node.

At its posterior margin the A-V node was supplied by the A-V node artery coming from the right coronary in the usual fashion. Before entering the AV node, this artery was markedly narrowed by mural thickening (fig. 13). Its histologic appearance differed from that seen in the sinus node artery; e.g., the sharply defined discontinuity of the internal elastic lamina was not found in the A-V node artery. Instead, the elastic tissue of the A-V node artery was widely reduplicated and frayed, making the entire process one of fibromuscular hyperplasia with interspersed elastic fibers. By contrast, the A-V node artery proximal and distal to this site of narrowing appeared normal in caliber, histology and lumen size.

At several points adjacent to the A-V node or His bundle, the central fibrous body was abnormally fenestrated, containing cysts and slits and areas of actual discontinuity (figs. 11 and 12). In fact, most of the central fibrous body was focally faulty, including an abnormally thin sheet near the posterior margin of the A-V node (fig. 14). In the vicinity of the junction of A-V node and His bundle the cystic faults of the central fibrous body contained isolated islands of A-V nodal cells, some of which were undergoing active recent degeneration with cellular infiltrate (fig. 12). These pockets of focal degeneration are exactly in the region where normal molding and shaping of the A-V node and His bundle actively occur in the first year or two of life but where similar changes are sometimes observed a decade or two later. It has been postulated that delayed activity of this type may be the explanation for some examples of WPW syndrome which persist through childhood or adolescence and then disappear.

Of special pertinence in the present case is the fact that

Figure 11

In A the A-V node (AVN) is shown adjacent to an area of lacunar faults in the body (CFB), two lacunae being marked with asterisks. The broken-line arrow marks the course of a paranodal fault through the CFB which was present in parts within many adjacent sections of this region (see also fig. 12). The base of the mitral valve is marked MV. The connections of the A-V node to the interatrial septum above it are virtually destroyed by fat and scarring. In B a cross section of the His bundle shows it relatively well preserved, and the central fibrous body at that point did not contain faults. B (Goldner trichrome stain) is about 1.5 mm anterior to A (elastic stain).
these islands of recent focal degeneration of A-V nodal cells within the central fibrous body are also located exactly in the region where Lev and his colleagues found a sole abnormal connection between atrium and ventricle in a case of WPW syndrome. 14

From the A-V node distally there was a minimal additional focal degeneration in the His bundle and its left branch, but cellular continuity into the left ventricle was not significantly interrupted. However, no connection between the His bundle and the distal right bundle branch could be found, the site of origin of the right bundle branch at all points ending in a blind pocket of collagen (fig. 15).

The Right A-V Ring

No connection could be found between the right atrium and right ventricle in any of these blocks of tissue. However, there were two significant findings. A node-like structure (on cross-sectional appearance) composed primarily of Purkinje-type cells (figs. 16 and 17), and a long slender strand of

The paranodal fault in the central fibrous body is shown more fully in A, and a focus of actively degenerating A-V nodal cells is bracketed, with a higher magnification shown outlined by arrows in B. Compare the area of the fault which is between curved arrows in A with the location of the broken-line arrow in figure 11A, a section made about 2 mm away. There was no direct A-V continuity through this fault, although the possibility that one may have existed at an earlier time cannot be excluded. Most of the input to the A-V node from the interatrial septum above is again interrupted by fat and collagen. RA and LA indicate the cavities of the two atria, and LV the cavity of the left ventricle. Goldner trichrome stain.

The A-V node artery is shown in A from a point near the posterior margin of the A-V node. Compare the frayed and disorganized internal elastic lamina with that in the sinus node artery shown in figure 9B. The internal elastic lamina is normal in B, at a point in the A-V node artery about half way from its right coronary origin to its entry into the posterior margin of the A-V node. Verhoeff-van Gieson stain in both.

Purkinje cells coursing from the atrium directly into the ventricle without making cellular connections in the right ventricle (fig. 18). The node-like right atrial structure, which had no connection with the ventricle, is identical to ones also described in the human heart by Stanley Kent in 1914,23 by Öhnell in 1944,7 and by Verduyn Lunel in 1972.24 However, only Kent claimed that there was connection by this "node" with the right ventricle. Öhnell and Verduyn Lunel specifically denied such a connection and none was found in the present case. The sliver of Purkinje cells which passed near the node-like structure without communicating with it, was noteworthy primarily because it penetrated so far into the region of the ventricular myocardium without attaching or being in continuity with ventricular myocardial cells.

Actually, this lateral "node" can more accurately be depicted as a thin tube or cylinder (figs. 5 and 6). On cross-section made perpendicular to the plane of the right A-V ring it measured about 0.5 by 1.0 mm in its ovoid dimensions, but it was present parallel to and just above the attachment of the tricuspid valve for a distance of over 25 mm. Each end gradually tapered into ordinary right atrial myocardium and its shape for most of its course (at least 20 mm) was exactly as depicted in figure 16. At its right atrial margin it was distinctly connected to right atrial cells, except for focal interruption by scarring or more recent dis-
ease. It contained no unusual innervation nor vascular supply, although the main right coronary artery was only a few millimeters away. The histologic organization being primarily Purkinje cells, it was distinctly different from the A-V node, where the principal cell is the slender transitional cell. A comparison of this cytology at the same magnification is provided in figure 17.

The Left A-V Ring

Probably the most important single finding in this heart was a direct connection between the left atrium and the left ventricle in the region just under the left atrial appendage (figs. 5 and 6). This connection passed directly through a fault in the mitral annulus and was in distinct cellular continuity with both left atrial and left ventricular myocardium (figs. 19–22). The fault in the annulus was thin, measuring 30 to 100 μ in the cross-sections perpendicular to the plane of the left A-V ring, and being present in 40 sections or for a distance of 400 μ the annulus was 1 mm thick between left atrium and left ventricle at this point. Because of its possible physiological importance in this patient with type A of the WPW syndrome, the left A-V connection was especially examined for its cellular composition and architecture.

At its left atrial margin the A-V connection continued directly into a large number of Purkinje cells extending for several millimeters before ending blindly in areas of scarring and recent degeneration. At its left ventricular margin the A-V connection was comprised almost exclusively of slender transitional cells which are characteristic of most of the human A-V node and much of the human sinus node, particularly at its margins. Between the atrial and ventricular margins the A-V connection filled the defect in the annulus plus several cyst-like cavities adjacent to it within collagen of the mitral annulus, all of these resembling spheroidal clusters. These multicellular clusters contained primarily P cells which in appearance and organization closely resembled those in the sinus node (fig. 23), where they are thought to be the site of origin of the sinus impulse. Coming from left atrium to left ventricle through the connection one encountered ad seriatim Purkinje cells and then a few transitional cells before coming to the abundant P cell clusters directly within the mitral annulus, then tapering of the P cell aggregates into a sheet of transitional cells which continued into the left ventricle to connect directly with what appeared to be ordinary working myocardial cells. The ventricular connection was about midway between epicardium and endocardium and distinctly did not enter any area of Purkinje cells.

There was no unusual blood supply for the left A-V connection, and it was in particular not organized about a cen-

Figure 14

The central fibrous body not only contained lacunar faults (asterisks in B), but at some points was abnormally thin, as indicated by the arrow just beneath the A-V node in A. B is a higher magnification of the photomicrograph seen in figure 11A. The solid black arrows point to the lower margin of the paranodal fault within the central fibrous body. Both Verhoeff-van Gieson stain.

Figure 15

Discontinuity of the right bundle branch is indicated with the open arrows, which overlie its usual site of origin. The left bundle branch (LBB) has normal continuity here. The cavity of the left ventricle is marked LV. These two sections are about 0.7 mm apart, with B anterior to A. Both Goldner trichrome stain.
Figure 16

Two cross sections of the right paracavalicular cylinder are shown here from points about 17 mm apart. Single cross sections of this structure (open arrows) falsely give it a "node-like" appearance, whereas its true geometric form more closely resembles a long thin cylinder. Labels include the right atrium (RA), right ventricle (RV) and tricuspid valve (TV). A is with Goldner trichrome stain and B Verhoeff-van Gieson elastic stain.

demonstrated remarkable variations in electrophysiological properties of the anomalous A-V connection. The entire WPW syndrome may cease on its own, especially in infants or children but occasionally in adults. More rarely it may begin in adults, but in such cases this may simply represent delayed recognition or late occurrence of symptoms; whether pre-excitation of the ventricular myocardium had been previously present, perhaps intermittently, is often impossible to know.

Much less attention has been given to the possibility that the anatomical substrate itself may vary within any given patient from one time in his life to another. This is probably because we all superficially think of normal anatomy as immutable. However, anatomical molding and shaping of the heart is a normal postnatal evolutionary process, illustrated among other ways by normal closure of the fossa ovalis, obliteration of the ductus arteriosus and relative regression of right ventricular mass. There is
These two photomicrographs contrast the typical slender transitional cells of the A-V node in A with the larger Purkinje cells which comprised the right paracardiac cylinder shown in figure 16. Neither the cellular composition, histological organization nor geometric shape of the cylinder could be interpreted as resembling A-V node. Focal fat and degeneration of the A-V node is apparent. Both Goldner trichrome stain.

in particular a normal maturation of the heart valves and the central fibrous skeleton of the heart which Maude Abbott emphasized some years ago. This maturation may be faulty in toto to produce dysplasia of all heart valves or it may be focal to produce lacunar gaps or slits in the normal structures. Such gaps, e.g., as may occur in the mitral annulus, could be the consequence of either abnormal embryonic development or faulty maturation, but both causes may coexist.

It has long been suspected that faulty development of the fibrous skeleton of the heart could permit the abnormal persistence of A-V connections, particularly in the hearts of patients with the WPW syndrome. Faults or gaps have been found especially in the mitral annulus and in the central fibrous body, but less often in the right A-V ring. Anomalous lateral A-V connections described for the right side have most often coursed through fat, but this is to be expected since the attachment of the tricuspid valve is normally much less bulky and into a smaller mass of collagen than is the case for the mitral valve. Both the mitral annulus and the central fibrous body are normally bulkier masses of collagen, making defects or faults in their continuity all the more conspicuous. In the present case there were faults in both the mitral annulus (figs. 19-21) and in the central fibrous body (figs. 11, 12 and 14).

Sinus rhythm disappeared permanently nearly two years before this patient’s death. At least four histological findings are relevant to this clinical observation: marked narrowing of the sinus node artery, extensive disease of the internodal pathways (including the atrionodal margins), a generous size and relatively normal appearance of remaining sinus node, and the presence of extensive old juxtanodal endocardial fibrosis typical of organized thrombi. The point of narrowing of the sinus node artery was proximal to its passage through the node, but distal to most of the branches supplying the general atrial myocardium.
Thus, any possible ischemia caused by this stenosed artery would have affected the sinus node and its atrial margins, but there was no suitable vascular pathology to explain the widespread fatty scarred degeneration of both atrial walls and the internodal pathways. Similar widespread atrial degeneration with a paper-thin right atrial wall has been described in conjunction with loss of sinus rhythm and sudden death. Although suspected to be congenital, the true etiology of this process remains uncertain.

Absence of any focal degeneration in the ventricular myocardium was in conspicuous contrast to the extensive disease in both atria. This makes a generalized process such as myocarditis (viral or other cause) an improbable explanation. Since both atria were equally affected by degeneration and fibrosis, it is puzzling why only the right atrium was appreciably enlarged by dilatation. Both the sinus node artery and A-V node artery were significantly narrowed, without much other arterial disease; the small ventricular arteries in particular were spared. One speculative explanation could be some undefined form of vagal influence, which would afflict both right and left atria, including especially the regions of the sinus node and A-V junction, but would spare the ventricles. Unfortunately, attributing any mysterious disease to some undefined vagal influence has been a popular gambit in medical history but has too infrequently been substantiated.

Although the sinus node was of a size and apparent histological condition to provide a regular pacemaking impulse, its communications with the neighboring atrial myocardium were virtually severed. Its appearance of anatomic isolation fits with the clinical observation in this patient of loss of rhythm control by the sinus node. The presence of old mural thrombosis adjacent to the sinus node in the atrium atrii dextri (fig. 8) further establishes the likelihood of previous and recurring degenerative changes at the atrionodal margins, for Söderström has demonstrated that mural thrombi are the most consistent consequence of atrial infarction, particularly in the vicinity of the sinus node.

Since it has long been known that abnormal supraventricular rhythm with or without tachycardia is one of the hallmarks of the WPW syndrome, the variation and then loss of sinus rhythm may be of special importance in the present case. The lack of responsiveness to all efforts at right atrial pacing with a catheter was likely due to paucity of viable or excitable atrial myocardium. During the A-V junctional rhythm, there were P waves suggesting retrograde activation of the atria (fig. 4), but they were of small magnitude and may have represented electrical potential originating in the atrial septum or a portion of the left atrium which would not have been accessible to the pacing catheter in the right atrium.

Changes in the A-V node, His bundle and their environs need to be considered in respect to the source of the A-V junctional rhythm, the nature of the paroxysmal tachycardias, and the pathogenesis of the delta wave during pre-excitation. Like the sinus node, the A-V node was disconnected from most components of the internodal pathways and it seems unlikely that any sinus impulse could have entered the A-V node for a long time before death. Where within the A-V
Two components of the left A-V connection are shown here in sections exactly 990 microns apart. In A the portion (upper arrow) connecting with the left atrium (LA) is separated from that coursing into the left ventricle (middle arrow); the attachment to ordinary myocardium in the left ventricular wall is seen at the lower arrow. The intraseptal fault and the cellular connection are indicated by the two black arrows in B, while the open arrow indicates the area of continuity of these cells with similar ones in the left atrium. Both Goldner trichrome stain.

It is now generally thought that most supraventricular tachycardias are re-entrant in nature, and in the WPW syndrome this re-entry loop has been shown to include the A-V junction. Because of the focal disease in the A-V node and in the His bundle, there was abundant anatomical substrate for physiological re-entry to occur within the A-V junction and lead to paroxysmal tachycardia both during the earlier periods of sinus rhythm and the later ones of A-V junctional rhythm. On the other hand, some of the paroxysmal tachycardias in our patient may have been automatic rather than re-entrant in nature, and could have originated either in the A-V nodal region or in the lateral left A-V connection. The fact that ajmaline and procaine amide both sometimes eliminated the delta wave without terminating the tachycardia suggests that those bouts were automatic rather than re-entrant in nature.

Beneath the A-V node and adjacent to it within the central fibrous body there were several cystic lacunae or faults. Some of these lacunae contained cells similar to the A-V node and others were empty, the emptiness possibly representing an artefact of fixation and preparation. Most of the cell-filled lacunae contained what appeared to be viable tissue, but at least one contained cells undergoing active necrosis (fig. 12). These changes are directly in the paranodal region,

Figure 19
within the central fibrous body described by Lev and his colleagues as a possible route for pre-excitation in a case carefully studied by them.\textsuperscript{14} Furthermore, all these lacunar faults and their contained cells are also in the region undergoing resorptive degeneration during the normal postnatal development of the heart,\textsuperscript{20, 21} and the possible role of such foci in the genesis of either re-entrant or automatic tachycardias has been the subject of previous discussions.\textsuperscript{22}

A remarkable narrowing of the A-V node artery proximal to its entry into the A-V node was an intriguing counterpart to the lesion in the sinus node artery, although their histological appearance differed. Focal ischemia secondary to the narrowed A-V node artery may have contributed to focal degeneration in and near the A-V node but could hardly account for the much more extensive degeneration of the internodal pathways and other atrial myocardium. It also seems improbable that the lacunar faults in the central fibrous body were themselves the consequences of ischemia, although degeneration of some of their cellular contents may have been. More plausibly, periodic malfunction of the A-V junctional tissues, without necessarily any morphological change, may be suspected as one of the more important effects of poor perfusion through the A-V node artery. If the paroxysmal tachycardias in our patient originated in or near the A-V node then loss of the previous response to therapy with procaine amide or ajmaline may have been due to progressive narrowing of the A-V node artery, precluding effective blood-borne delivery of these agents to the appropriate site.

In the right lateral A-V ring there were two significant findings, the structure which was node-like in cross-section (fig. 16) but actually a cylinder, and the separate strand of Purkinje cells coursing from the atrium to the ventricle. The latter were clearly connected to atrium but not to any identifiable ventricular myocardial cells. Whether they may have been connected at an earlier time is unknown, perhaps later being subjected to the same obscure degenerative process seen at a number of other sites; however, a right lateral A-V connection is not what would have been expected in type A of the WPW syndrome. Similar uncertainty attaches to the "node-like" cylindrical structure; but whatever the significance of that structure may be, it was at no point connected to myocardial cells in the ventricle.

What was clearly the most intriguing finding of all was the distinct connection between the left atrium and the left ventricle coursing through a fault in the mitral annulus beneath the left atrial appendage (figs. 5, 6, 19–21). Very recently Wallace and his colleagues\textsuperscript{8} have reported the successful surgical treatment of two patients with type A of the WPW syndrome, and both their electrophysiological and surgical findings supported a connection being present between left atrium and left ventricle at approximately the location demonstrated in the present patient.

But the location of the left lateral A-V connection is only an anatomically pertinent matter. An equally important one is the cellular composition and histological organization of the connection. This small structure distinctly connected the left atrium to the left ventricle, but its central component resembled P cells of the sinus node.\textsuperscript{28} In fact, the structure contained within the fault in the mitral annulus appeared very much like a small sinus node composed

Figure 20

The nature of the left transvalvular fault and its cellular content (arrows) are seen in A, while a blind pocket of similar cells enclosed within the mitral valve is indicated with the open arrow in B. The section in A is 110 microns from that in figure 19B, while that in B is 770 microns away. Both Goldner trichrome stain.
Details of the cellular composition and histological organization of the left A-V connection are shown here. The upper portion is composed almost exclusively of P cells, while the lower portion connecting to the ventricle is composed of parallel oriented transitional cells. This section is exactly midway between the sections shown in figures 19B and 20A and is 50 microns from each. Goldner trichrome stain.

In these two photomicrographs the cytology and histology of the left A-V connection (LA-LV CNX) is compared to that of Bachmann’s Bundle (BB) just above the connection. Bachmann’s bundle contains almost exclusively Purkinje cells at this point, while the left A-V connection is composed of the much smaller ovoid P cells. The cells from the left A-V connection shown here are also seen in figure 20B. Both Goldner trichrome stain.

This resemblance to the human sinus node is made the more intriguing by the recent demonstrations by Wit and his colleagues\(^{34}\) that cells possessing spontaneous automaticity are present in the mitral valve of the dog at locations similar to the one found here. If this structure containing cells with the appearance of specialized tissue, located in just the right place, would anticipate in a patient with type A of the WPW syndrome, was crucial in the pathophysiology of this patient’s problems, it would seem that the correlation is established. Unfortunately, the cells seen here and the ones studied by Wit and his colleagues are just the type of cells known to conduct very slowly.\(^{34-36}\) In other words, this left lateral A-V connection in just the right place may have truly been specialized but for the wrong electrophysiological function. What are the means for logical resolution of this paradox?

Although there is good evidence that P cells are the site of origin of automaticity in the sinus node (and in

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*Figure 21*

*Figure 22*
the A-V junctional region), the evidence is largely indirect in nature. For that matter, no one to our knowledge has yet demonstrated the precise functional characteristics of any single type of myocardial cell, which would require sophisticated microelectrode and electron microscopic studies on the same cell. It may therefore be that the left lateral A-V connection in the present case did in fact conduct rapidly and not slowly the way one would deduce from what is known about P cells and about latent automaticity in the mitral valve region. The exact cellular characteristics of previously studied lateral A-V connections in the WPW syndrome have seldom been clearly defined, although it is doubtful whether ones with an appearance of the type seen here would have escaped ready notice. Furthermore, others have demonstrated by pacing studies from the left atrium in patients with type A WPW syndrome that the anomalous pathway can be engaged by such pacing whereas it fails to function or functions poorly during sinus rhythm. Even though rapid conduction through the left A-V connection may have been present in our patient, the weight of deductive logic would lead one to doubt it.

For the left lateral A-V connection in the present case to account for abnormally early excitation of left ventricular myocardium and to produce a type A delta wave during sinus rhythm, it would have been more appropriate if it had been composed of longitudinally oriented Purkinje cells where extensive large gap junctions would be expected and conduction should have been rapid. That not being the case, there is another possible explanation for rapid excitation of the left ventricle at its lateral margin during sinus rhythm, and that is a closely coupled early discharge of an impulse from the structure within the mitral annulus. If this were regularly synchronized with a preceding sinus impulse, then in every cardiac cycle with a delta wave deformity of the QRS complex we would visualize the following chronological sequence: sinus impulse coursing across atrium through inter-nodal pathways to the A-V node and simultaneously via Bachmann’s bundle toward the left lateral A-V connection, followed by the discharge of a closely coupled second impulse from the site in the mitral annulus at a time earlier than the time when the sinus impulse would have entered the normal His bundle. This would in essence be a fusion beat, long held as one of the hypothetical explanations for the WPW syndrome. The fact that there was no longer a delta wave when sinus rhythm disappeared would suggest that automaticity within the left A-V connection per se could not have been of a high order, perhaps requiring regular triggering by the sinus impulse arriving there very early. With such a triggering relay, one would assume that activation of the adjacent left ventricular myocardium would produce a delta wave coinciding with the time of activation of the His bundle, or perhaps even preceding it; however, no His bundle electrograms were made in this case. It may be noted parenthetically that the left lateral A-V connection could represent the essence of a parasystolic focus.

Because of the histological organization and cytology of the left lateral A-V connection, one may question whether this site could have participated as a component of some re-entrant pathway during supraventricular tachycardias. It would have been more likely that such a re-entry path was entirely within or near the A-V node or His bundle and their immediate environs. Such an explanation would fit well with the persistence of bouts of tachycardia even after the disappearance of sinus rhythm in our patient, and with the fact that a delta wave was no longer present during the escape A-V junctional rhythm. It would not explain, however, why the paroxysmal tachycardia can apparently be abolished in some
patients by surgical cutting of appropriate laterally placed sites in patients with either Type B or Type A WPW syndrome.

In order to plan surgical procedures for patients with intractable tachycardias due to the WPW syndrome, it will be as important to assess the functional properties of any anomalous connection as it will be to determine its anatomical location. In our case, for example, cutting the lateral left A-V connection would almost certainly have eliminated the delta wave without significantly influencing the paroxysmal tachycardia — and this is in fact what happened because of the intrinsic disease even without surgery. On the other hand, there are dramatic successes due to cutting either right or left lateral A-V connections, and the success includes termination of both the pre-excitation and the paroxysmal tachycardias. One way to account for the successful surgery would be by assuming that there is an error in our own deductions. Another way would be by assuming that the histological organization and physiological function of the lateral A-V connections in those other cases was different from the present case, and we favor this hypothesis.

For the evaluation of future cases there are certain crucial factors to consider, and these would apply equally whether the anomalous connection were laterally placed or centrally located in the A-V junction. By espousing these principles we do not imply that accomplishing them will be easy, or in some cases even possible at the present time; however, they are logical goals. First, it should be determined if conduction in the connection is slow or fast. Second, it should be determined if the connection itself possesses properties of automaticity. Third, the speed of conduction from the sinus node to the connection and from the connection to the central His-Purkinje system should be assessed. It may be predicted that these physiological factors will depend on the following anatomical features: (1) Whether there are P cells interposed within the anomalous A-V connection (as there are in the normal route through A-V node and His bundle).35 (2) Whether the connection is via Purkinje fibers without P cells, wherein conduction would be rapid. (3) Whether either type of connection terminates at its ventricular end into or near the normal Purkinje network, or into ordinary ventricular myocardium.

This brings us finally to a consideration of the question of how sudden death occurs in patients with the WPW syndrome. Certain evident possibilities include a chaotically rapid ventricular rhythm as the consequence of unfiltered conduction through the anomalous connection. Whereas the A-V node normally functions to sort and delay most rapid atrial rhythms, it may be bypassed in some patients with the WPW syndrome. The pharmacological treatment of paroxysmal tachycardia in some subjects with the WPW syndrome occasionally requires the administration of large amounts of rapidly given drugs which themselves carry certain risk to the patient, and it is this hazard which has been one of the logical points favoring surgical correction of the problem when feasible. But perhaps insufficient attention has been given to the unstable and undependable basic rhythm of the heart in WPW patients, either as an important precursor to the development of paroxysmal tachycardia or of more serious disorganized rhythms which might themselves be lethal.

It is well known that premature beats and arrhythmias of supraventricular origin are general features of the WPW syndrome.44 In the present patient there were numerous histopathological abnormalities in the sinus node and its environs, and in the A-V node and its environs, suggesting that sinus rhythm may have intermittently failed either to originate or to be conducted properly, numerous times before it completely disappeared. A-V junctional rhythm on the other hand is far more dependent on normal adrenergic neural input than is sinus rhythm,44 and either local histological or pharmacological impairment of adrenergic neural control may lead to failure or disorganization of the only stable subsidiary rhythm of the heart. That lethal electrical instability is the final event in sudden death of patients with WPW syndrome is probably no less true than for patients who die suddenly and unexpectedly without having the WPW syndrome. In the present case there was an abundance of structural abnormalities which could have accounted for sudden death in this fashion.

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De Subitaneis Mortibus: IX. Type A Wolff-Parkinson-White Syndrome
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