De Subitaneis Mortibus

XXI. Adult Onset Syncope, with Comments on the Nature of Congenital Heart Block and the Morphogenesis of the Human Atrioventricular Septal Junction

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SUMMARY A black male nurse first began having syncope at the age of 30 years and when heart block was documented, a permanent electronic pacemaker was inserted. He died nine days later of a massive pulmonary embolus. There was a family history of sudden death. Special examination of this patient's heart demonstrated the following anatomical findings in the cardiac conduction system: (1) There was such diffuse fibrosis in the midportion of the His bundle that only a few tenuous connecting strands of fibers remained; the local blood supply appeared adequate. (2) The atrioventricular (A-V) node was located centrally in the interatrial septum, rather than under the right atrial endocardium as is normal, and was poorly formed with several separated fragmentary components. (3) The central fibrous body contained multiple faults and discontinuities, including a portion underlying the malformed A-V node. (4) The dorsal endocardial cushion was eccentrically located to the right and may have contributed to the malformation of the central fibrous body of which it normally comprises the midportion. (5) The left bundle branch originated by a narrow stem (1.5 mm maximal dimension) from a right-sided His bundle, a variation found in only fifteen percent of normal human hearts. (6) Fibrinous pericarditis involved the epicardial margin of the sinus node. Because of the similarity of many of these abnormalities to previously reported ones having a familial incidence, we interpret this case as an example of late-onset congenital familial heart block.

DEATH OF NATURAL CAUSES is a meaningful legal term. While it is also useful medically, it carries no specific etiological diagnosis and is particularly lacking when applied to examples of sudden unexpected death. In the latter circumstances it means only that foul play is not suspected. We have recently dealt with an example of death due to natural causes in which the fatal terminal event (massive pulmonary embolus) was completely different from an earlier near cause of death (syncope and heart block) for which this patient was in the hospital. The findings at post-mortem examination not only clarified the pathogenesis of his failing atrioventricular (A-V) conduction, but they also permit some useful observations concerning the morphogenesis of the A-V septal junction in the human heart and some comments about the classification of congenital heart block.

Case Report

A 30-year-old male nurse from the Virgin Islands was visiting a friend in Lansing when he first had a bout of syncope. After this occurred the next day, he sought medical advice and was hospitalized. Except for a past history of mild hypertension once treated with reserpine, he had no previous cardiovascular complaints and was considered in good general health. A son had died at the age of one year of unknown cause, his mother had died during cardiac surgery in another city (presumably for valvular disease) and his father died of undetermined cause in middle life, although it was known that he had diabetes mellitus. Physical examination on admission was entirely normal except for a blood pressure of borderline diastolic hypertension (126/90 mm Hg). Cardiac examination in particular was entirely normal. Numerous screening laboratory examinations were negative or within normal limits.

Both the chest X-ray and echocardiogram were suggestive of minimal left ventricular hypertrophy. An electrocardiogram showed slight A-V conduction delay plus right bundle branch block with normal sinus rhythm (fig. 1). While hospitalized he was initially monitored and these records revealed several episodes of transient A-V block during which the patient did not complain of symptoms. He had no syncopal episode while in the hospital. A right and left heart catheterization was within normal limits except for the electrophysiological studies (fig. 2). Atrial pacing produced increasing A-V block which was exclusively at the A-H interval with no associated H-V prolongation. Abrupt cessation of rapid atrial pacing was followed by normal sinus escape. No higher grade A-V block could be produced than the Wenckebach periods and transient A-V dissociation observed at an atrial rate of 140/min. Both in the monitor strips and the electrophysiological studies the non-conducted beats were usually preceded by progressive Wenckebach type A-V delays, but occasional episodes of block occurred with little or no preceding P-R interval prolongation. Carotid sinus massage did not cause progressive A-V nodal or sinoatrial block.

Because of the patient's obvious concern, the recent onset of syncope and the family history, a permanent demand-mode electronic pacemaker was implanted on the left ventricular epicardium via a left thoracotomy. Postoperative recovery was uneventful except for low grade fever until the sixth day, at which time the patient complained of pleuritic
chest pain and the pulmonic closure sound became palpable. The right calf was tender, with an equivocal positive Homans' sign. Heparin therapy was begun for a diagnosis of thrombophlebitis and pulmonary embolism, following which the patient's general status improved. At that time he received word from home that his brother of approximately the same age had died suddenly and unexpectedly, and the patient asked to be discharged so he could go there. Discharge was delayed on medical advice because of his condition. On the ninth postoperative day he experienced a sudden cardiac arrest from which he could not be resuscitated.

At necropsy examination a large saddle-shaped embolus occluded the bifurcation of the main pulmonary artery. All other findings were within normal limits except the heart. The heart weighed 300 grams and was covered with a fibrinous pericarditis. The epicardial pacemaker was well placed and intact near the left ventricular apex. The left ventricle was normal in size, shape and thickness. There were no mural thrombi, no areas of infarction, no septal defects and no occlusions of the main coronary trunks. Special examination of the cardiac conduction system was performed; methods for this purpose have been described previously in this series.

Except for the pericarditis which incorporated the entire epicardial surface of the sinus node, it was essentially normal. The region of the septal atrioventricular junction was removed intact, extending from (and including) the root of the aorta to the epicardium overlying the crux and coronary sinus. This block was then cut into seven slices each oriented perpendicular to the plane of the A-V valves, with each slice about 4 mm in thickness. Screening sections of 8 micron thickness (minimum of fifteen from each block) were then followed by complete serial sectioning of selected blocks, with every tenth section mounted and stained with the Goldner trichrome method. A total of 658 sections were studied from the region of the A-V node and His bundle.

In this heart the His bundle coursed to the right of the crest of the interventricular septum (figs. 3 and 4), a variation found in only 15% of normal human hearts. As is usually the case in such hearts, the left bundle branch (fig. 3) originated by a narrow stem (1.5 mm maximal diameter in this heart) rather than as the characteristic broad sheet found in 85% of human hearts. At the region of the bifurcation of the His bundle there was edema and scattered fibrosis, but no definite interruption of either bundle branch was observed. For most of its course the undivided His bundle was the site of disruptive focal fibrosis, in some areas so extensive that continuity of the His bundle was maintained only by "frayed strands" (figs. 4–8). Near the posterior margin of the undivided His bundle, where its junction with the A-V node became identifiable, the upper half of the bundle's cross-section was comprised of typical transitional

**FIGURE 1.** ECG on admission (above) and three representative monitor strips for heart block (below). See text for discussion.

**FIGURE 2.** Electrophysiological records during cardiac catheterization studies. Rapid atrial pacing prolongs the A-H interval but not the H-V interval. More rapid atrial pacing produced Wenckebach type A-V dissociation, and some periods of interference. Configuration of the first His complex (H-1) is different from the three other ones (H-2), but each is about the same distance from the ventricular complex. Because of interference with atrial response beginning with the third electrical stimulus (S), all of the last three ventricular beats are most likely of A-V junctional escape origin.
cells interweaving as they do in the A-V node, while the lower half consisted of Purkinje cells characteristic of the His bundle. The line of separation of these cell groups was more distinguishable than normal, although there did appear to be tenuous intercellular continuity when examined in serial sections.

Except in the region of junction between A-V node and His bundle, the anterior portion of the central fibrous body and the entire membranous interventricular septum were normally intact. Just at the junction area there was an irregular fault in the midportion of the central fibrous body through which strands of separated A-V nodal tissue passed toward the His bundle (fig. 8). As one examined posteriorly, toward the coronary sinus, subsequent serial sections demonstrated a thinner rim of anatomical union between the base of the tricuspid valve and the mitral annulus than would be expected. The A-V node lying directly above this thinned-out central fibrous body was not only poorly formed but actually comprised of separated cellular aggregates. Numerous groups of A-V nodal cells clustered into two general clumps (figs. 9–11). One of these lay against the mitral annulus and at its posterior margin appeared to be connected with A-V nodal transitional cells streaming to it from the eustachian ridge, the normal course of the posterior inter-nodal pathway. The second clump of A-V nodal cells was on the opposite side of the central fibrous body, and lay against the tricuspid annulus. From this latter group of A-V nodal cells there were several clusters streaming through the central fibrous body toward the His bundle. Cellular continuity between these two groups of A-V nodal cells was fragmentary and consisted at most of a few single-cell strands.

Near the anterior margin of the poorly formed A-V node, in the region where the central fibrous body was more or less continuous, one could identify a mass of collagen which was round in cross section (figs. 9 and 10). In serial sections it was possible to follow this collagenous cylinder posteriorly and see it separate from the central fibrous body at approximately the same area where the central fibrous body had a

**Figure 3.** These two photomicrographs demonstrate the narrow origin of left bundle branch (arrow in A) and the right-sided course of the His bundle (two arrows in B). The section in A is about 3 mm anterior to the one in B. A shows the His bundle and the left branch origin directly beneath the membranous interventricular septum, while the undivided His bundle in B is to the right of the muscular interventricular septum and well posterior to the membranous septum. TV = tricuspid valve.

**Figure 4.** These two sections of the right-sided His bundle (arrows in A and B) illustrate its disruptive fibrosis and focal degeneration, e.g., the area in B with an asterisk. Note the absence of inflammatory cell response. These two sections are cut exactly 256 microns apart and are about 2 mm posterior to the section in figure 3B.
conspicuous second large fault in its midportion (figs. 9-11). The collagen cylinder could have been the tendon of Todaro,6 but we do not believe so because it was too large in diameter, too far to the right, too low in this portion of the atrial septum, and did not continue back into the eustachian ridge as would normally be expected. It more likely represents a poorly fused dorsal endocardial cushion which normally forms the midportion of the central fibrous body. Not only was the dorsal endocardial cushion poorly fused to the central fibrous body (actually separated from it) as examination progressed posteriorly, but its anatomical relationship to the A-V node was reversed, since the node normally lies to its right. Failure of the dorsal endocardial cushion in the formation of the central fibrous body in this case did three things. (1) It left a gap in the midportion of the central fibrous body, making it abnormally discontinuous. (2) It caused abnormal thickening of the tricuspid annulus by being laterally displaced to the right, and may have pulled that portion of the tricuspid valve upward. (3) By deforming the central fibrous body it disorganized the normal collagen template in which the A-V node develops, and it may have actually displaced the node from its usual right subendocardial location to this abnormal position centrally in the atrioventricular septal junction.

**Discussion**

As more is learned of the functional anatomy of the A-V node and His bundle, it leads to a keener appreciation of the ontogenetic importance of the central fibrous body and closely adjacent structures. Embryological development of the A-V septal junction has often been investigated with these thoughts in mind.7-10 What has seldom been adequately considered, however, is how much of this developmental relationship remains dynamic in the postnatal period and may continue into adult life. Not only does a dynamic interplay exist during the postnatal molding and shaping of this

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**Figure 5.** This portion of His bundle is passing through the middle of the central fibrous body (CFB) and contains both interweaving transitional cells typical of A-V node and the Purkinje cells of the His bundle. There is extensive fibrosis of the His bundle particularly in A. RA = right atrium, MA = mitral annulus, RV = right ventricle, LV = left ventricle. A is about 0.8 mm posterior to the sections in figure 4, and B is exactly 240 microns posterior to A.

**Figure 6.** These higher power photomicrographs illustrate the extent of fibrosis within the undivided His bundle (arrows in A and B). The section in A is 224 microns anterior to the one in B, which is from the same section shown in figure 5A except here at higher magnification. The upper half of the His bundle in B is comprised of interweaving slender transitional cells characteristic of the A-V node (AVN) while the lower half more closely resembles His bundle Purkinje cells. Still higher magnifications of these two cell groups are presented in figure 7.
region, but those fibroblasts must remain pluripotential in nature for a much longer time than the postnatal period alone. Some of the fibroblasts have been found to undergo metaplasia to cartilage or even bone, and it is pertinent to note that many of these findings were made during examinations conducted because of sudden unexpected death. In the absence of metaplasia it still appears that activity of these fibroblasts may account for disruptive fibrosis within the His bundle, although usually at an earlier age than the present case. If one thinks of the central fibrous body as a sort of collagenous template in which the newly forming A-V node and His bundle normally develop, then the present case and similar previous ones may represent ontogeny gone awry. Instead of a normally distinct A-V node connecting to a smoothly cylindrical His bundle, what one sees in the present case is nests or clusters of meandering A-V nodal cells which connect poorly to the His bundle. It is not so surprising that A-V conduction should fail under such circumstances, but more surprising that it should remain relatively normal for as long as it does. Assuming that functionally satisfactory A-V conduction (and absence of clinical symptoms) means good anatomical continuity, or conversely, that failing A-V conduction in many examples means deteriorating anatomical continuity, then what can account for such an anatomical change as late in life as the present case?

One possible explanation for progressive fibrotic destruction of the His bundle in adult life is the development of local ischemic degeneration due to impaired arterial perfusion. This can be on the basis of main coronary disease or because of more precisely located arterial narrowing lesions, as within the A-V node artery itself, and may occur either in childhood or adult life. While there were a few narrowing lesions in small branches of the A-V node artery in this case,
none was so severe as to be a logical explanation for the rather extensive fibrosis seen in the midportion of the His bundle.

Some of the anatomical fault here was in embryological development, particularly that dealing with malformation of the central fibrous body and the eccentric location of the dorsal endocardial cushion toward the right side (tricuspid annulus) rather than more centrally. The poorly formed and abnormally placed A-V node is very logically considered as part of this same embryological developmental malformation. But if one were to attribute the His bundle fibrosis to this as well, then it is difficult to explain why clinical evidence of failing A-V conduction (syncopal attacks, ECG evidence of heart block) was so late in appearing, first becoming clinically manifest in the fourth decade of this patient’s life.

We believe that the developmental fault in the central fibrous body and the malformation of the A-V node were directly related to each other: the A-V nodal cells of the embryonic and postnatal period not having the appropriate collagenous template for guidance to form the usual adult A-V node. If the fundamental problem was thus in the organization of the primitive central fibrous body, it would be the fibroblasts which must be the culprits, whether their misbehavior was genetically programmed defect or an acquired misdirection, although the positive family history suggests a genetic fault. On that same reasoning one would deduce that the eventual union of separately forming A-V node and His bundle must also be related to proper cell-to-cell interface recognition processes between the conduction system and its surrounding fibrous tissue. Whether the disruptive fibrosis seen in the present case was then the consequence of “overgrowth” by unruly fibroblasts, or simply the orderly replacement secondary to a developmental failure of cells in either the distal A-V node or the proximal His bundle, the visualized end result would be the same. Since the functional evidence (syncope) was so late in appearing, it would seem more plausible to blame the fibroblasts, postulating that some sort of metaplastic influence caused them to turn on their neighbors. Previous distinct evidence of metaplasia developing in fibroblasts of the central fibrous body would support such a hypothesis,
although it gives no clue as to what the influence was which led to metaplasia. In fact, metaplasia may not be exactly the correct term in the present case, where misbehavior leading to disruptive fibrosis was not associated with the formation of anything but normal appearing collagen (i.e., no cartilage or bone appeared).

A corollary observation on the normally dynamic relationship between fibroblasts of the central fibrous body and neighboring cells of the A-V node or His bundle is nearly a mirror image of the situation in the present case. Instead of an unruly overgrowth by fibroblasts causing disruptive fibrosis, there is sometimes a much delayed or even completely absent molding and shaping activity of these fibroblasts, producing an abnormal persistence of fetal dispersion of the A-V node and His bundle within the central fibrous body. In the present case and similar others,14,25,26 the fibroblasts were too active, whereas in other hearts21 they may not be active enough. This hypothesis assigns an important dynamic functional role to cells of the central fibrous body, and this role which normally is played out in the first year or two of postnatal life may not only be delayed in appearing (or fail altogether), it may also be played for the first time surprisingly late in life and then be overdone.

Although our discussion has focused on the syncope, heart block and anatomic abnormalities in the A-V junctional tissues, this patient died of a massive pulmonary embolus. What his brother or his infant son actually died of in a sudden fashion is completely unknown. Whether the present patient would have died of episodic heart block, or a concurrent further disorganization of cardiac rhythm (such as ventricular fibrillation), is uncertain although that would seem likely. Since it is probable that the anatomical fault was developmental in nature, a familial incidence could not only be suspected but the family history supports that likelihood. In this series of studies on sudden death one previous report dealt with familial congenital heart block.26 The histopathological basis for that example was totally different from the present case, since it appeared to be a primary caseous degeneration of A-V junctional and bundle branch cells similar to the process previously described by Le-negre.27 In the present case the postulated misbehavior of the fibroblasts resembles more the lesion described by Lev.14 An identical disruptive fibrosis of the His bundle has been observed in a fatal familial form of paroxysmal tachy-
cardia. We believe the fundamental fault in these circumstances to be in the behavior of the fibroblasts, rather than there being local mechanical trauma to the A-V node or His bundle by excessive fibrosis at the crest of the ventricular septum or its environs.

This brings us finally to a more general consideration of congenital heart block. It is now generally recognized that heart block caused by a congenital defect in development need not be fully manifest at birth, or even very early in life. Two forms of heart block which are in a sense congenital in nature are due to mesothelioma and that caused by progressive fibromuscular dysplastic narrowing of the A-V node artery. Either of these may first become clinically manifest in adult life as well as during childhood. Whether they have a familial incidence is not presently known.

In addition to these two forms of heart block there are four others which we believe are congenital in nature. The first of these is failure of union of the A-V node with the atria, or of the A-V node with the His bundle. This represents an embryological fault rather than a postnatal development, and clinical manifestation is usually apparent at birth or on first examination. The second is a failure of maturation by cells in the A-V node although the node is present in its normal location and by light microscopy appears abundantly connected both with the atria and with the His bundle. This unusual lesion, a form of partial maturation arrest, is also an embryological fault probably occurring very early in development, and represents failure in cellular differentiation rather than histological location. The inadequate differentiation may be the cause of A-V conduction failure by cells which are properly located and organized but abnormal in appearance (and presumably in function). The third form of congenital heart block is caused by progressive caseous noninflammatory degeneration of any or all portions of the distal A-V node, entire His bundle and proximal bundle branches. This may begin in infancy or later in life and probably progresses at unpredictable rates. It has been shown to occur in families and may represent a genetic example of programmed self-destruction of special cells. There is no present evidence of any toxic, mechanically traumatic, ischemic or infectious cause for this degenerative lesion, and the surrounding myocardium is conspicuously spared and normal in appearance. There is no abnormal infiltration, such as with fat or amyloid. The fourth form of congenital A-V block is exemplified by the present case, and others similar to it. We believe that the fault here is an abnormally transformed behavior of local fibroblasts which then destroy portions of the His bundle, some reasons for this hypothesis having been presented in the preceding discussion. With such a lesion the heart block can first become manifest early in life, which is probably more usual, or be delayed as long as to the third or fourth decade of life as in the present case. In addition to varying degrees of heart block, this same disruptive fibrosis may account for examples of re-entrant tachycardias (by anatomical production of longitudinal dissociation of A-V conduction), or for either the onset or termination of the Wolff-Parkinson-White syndrome.

For future studies on the normal and abnormal anatomy of the A-V node and His bundle, more careful attention should be given to the myocardial cell types and their histological organization than is usually done. For example, a very useful anatomical landmark in identifying the junction between A-V node and His bundle is the point at which the A-V node penetrates into the central fibrous body, and this is probably the most frequently utilized criterion for that purpose. However, careful examination of the component cells provides some other useful criteria as well. The most abundant cell in the human A-V node is the slender interweaving transitional cell, but some of these also appear for varying distances into the His bundle in different hearts. The architectural arrangement of the A-V node is one of densely interweaving randomly oriented fibers, while that of the His bundle is longitudinally oriented and precisely partitioned strands of typical Purkinje cells. In the present case some of the tissue within the central fibrous body had the histological appearance of A-V node. These pathological and histological considerations become especially relevant to two corollary forms of interpretation: electrophysiological and embryological. Where the A-V node begins and ends, and even whether it is present or not, depends very much on what is called A-V node histologically. Presence or absence of A-H or H-V prolongation or QRS distortion would be interpreted differently for correlative purposes if the A-V node or fragments of it were present than if they were not. Similarly, what the postulated embryological fault may have been, or what the normal embryological development of these structures is assumed to be, would also depend on accurate and correct interpretation of what is A-V node or His bundle.

References
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