CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

X. Familial Congenital Heart Block

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SUMMARY

Complete heart block was found shortly after birth in a brother and sister (not twins). Both were treated by electronic pacing because of symptoms attributable to inadequate cardiac output and electrical instability of the heart. The boy has done well with his artificial pacemaker and is now six years old. His sister died of complications due in part to the large size of her pacemaker and small size of her body. At necropsy special studies of her heart included the centers for normal impulse formation and conduction. The primary abnormalities were at the junction of atrial septum with atrioventricular (A-V) node, and at the origin of the two bundle branches from the His bundle. The A-V node was isolated by collagen at all its margins except its junction with the His bundle. The proximal His bundle was essentially normal, but from that point on through the initial portions of both the left and right bundle branches there was extensive caseous degeneration which interrupted any possible conduction. These findings are discussed in relation to fetal and postnatal development of the human A-V node, and the His bundle and its branches; and in the context of a recently observed mathematical relationship between sinus rate and two forms of experimentally produced A-V junctional escape rhythms.

Additional Indexing Words:

A-V node
Electronic pacing of newborns
His bundle
A-V junctional escape rhythms
Heritable necrosis of His bundle

In 1901 Morquio reported that sudden death had occurred in five of eight children in one family, and that all had had a slow pulse.1 Put in historical context this was eight years before the description of the His bundle, six years before the discovery of the sinus node, and two years before Einthoven's first publication on his 'new galvanometer.' That various disturbances of the rhythm of the heart could cause sudden death has been known for a very much longer time, but Morquio was one of the first to focus attention on the problem in infants and small children.

Familial congenital heart block has been the subject of a number of recent studies, including some which have comprehensively reviewed the pertinent literature.2, 3 Although there now seems little doubt that all degrees and forms of heart block may occur in different members of the same family, and that the victims must either be born with the defect or develop it from some congenital etiology, what actually happens in the conduction system is not too clear. Investigation of the question is clouded some by the fact that viral infections may be associated with heart block4 and such infections may be communicated from one family member to another. However, histological studies by Lev and his colleagues5, 6 make it more likely that familial congenital heart block is due to localized degeneration (not caused by infection) or absence of crucial portions of the conduction system such as the His bundle. What the basis of this degeneration may be is unknown.

With this report we wish to present the clinical findings in a brother and sister born with heart block, and the histopathological changes found in the cardiac conduction system of one of them at postmortem examination. The clinicopathological correlation will be discussed with a view of fetal and postnatal development of the atrioventricular (A-V) junctional region, and in the context of a recently observed

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mathematical relationship between sinus rate and two forms of experimentally produced A-V junctional escape rhythm.

**Case Reports**

**Case 1**

A baby boy weighing seven pounds was found to have a heart rate of 44/min about fifteen minutes after delivery. His mother was an 18-year-old prima gravida in good health and the pregnancy was considered uncomplicated. At her last prenatal examination a normal fetal heart rate was described. In addition to the postnatal bradycardia, there was mild acrocyanosis and a grade III systolic ejection murmur along the left sternal border. There were no diastolic murmurs or extra heart sounds, but there was some peripheral edema and the liver was enlarged.

Complete heart block was present with a ventricular rate of 44/min, atrial rate of 136/min, and QRS complexes 100 msec in duration (figs. 1 and 2). The ventricular rate did not increase with the administration of either atropine or isoproterenol. Fourteen hours after admission a syncopal episode occurred, following which a temporary transvenous pacemaker was introduced with satisfactory control of the ventricular rate. Prior to pacing, it was seen that the QRS configuration had changed from the previous day (fig. 2). There was no evidence of atrial capture during electronic ventricular pacing, so that both A-V and V-A block were present. Right heart catheterization and angiocardiography were performed and there were no intracardiac defects.

On the fourth day of life a fixed rate permanent pacemaker was implanted with the generator placed subcutaneously over the abdomen. Because of its size the generator caused poor healing and was eventually removed, to be left externally for the next eight months without complications. At that time purulent...
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was embedded en bloc. The specimen was oriented to make whole heart sections in a plane parallel to the A-V valve rings and perpendicular to the diaphragmatic surface of the ventricles (fig. 3). Sections were cut eight microns thick with every 10th section saved and every third one of these prepared with the Goldner trichrome stain. Except as influenced by the pericarditis, all the atrial and ventricular myocardium outside the conduction system was normal. The coronary arteries had patent lumens and normal walls. The important abnormalities were in the conduction system.

The sinus node was normally formed and located and contained its characteristic central artery. Pericarditis covered the epicardial margin of the sinus node (fig. 4). Evenly dispersed throughout the main portion of the sinus node there were clear spaces which probably represented normal P cells, but even less cell structure could be identified in these loci than normal, suggesting that groups of P cells may have been absent from their normal location.

The A-V node was slightly smaller than normal but was located in its usual site, was supplied by a normally developed nutrient artery, and exhibited normal histological architecture (fig. 5). However, it was completely isolated from the atrial septum above by dense walls of collagen, thus making electrical communication with the sinus node via cellular connections impossible.

The proximal portion of the His bundle was normally connected to the A-V node. As the His bundle penetrated the central fibrous body, there was some

drainage developed around the electrode fistula. At another operation the epicardial electrodes were replaced and the generator was reinserted into the subcutaneous tissue of the abdomen. Postoperative healing was satisfactory. Since that time he has had two elective replacements of the pulse generator and is now six years of age. He is apparently healthy and vigorous, being in the 50th percentile for height and weight.

Except for his sister (case 2) there are no other children. The electrocardiogram of the mother is entirely normal. That of the father shows a short P-R interval with normal QRS complexes. Neither parent has cardiac symptoms. No other family members have been studied.

Case 2

A baby girl, the only sibling of case 1, was born four and one-half years after him. There was again no apparent problem during pregnancy. This child weighed 5½ pounds at delivery during the 34th week of gestation. Apgar score was 7. Fetal heart rate was not only described as normal during the routine prenatal visits, but a rate of 100/min was recorded during labor. At delivery the infant was markedly edematous and tachypneic with acrocyanosis, hepatomegaly and a fixed heart rate of 46/min.

Complete heart block was present with a ventricular rate of 46/min, atrial rate of 160/min, and QRS duration of 110 msec with some slurring of the R wave (figs. 1 and 2). Because of her moribund state and heart block, a temporary transvenous pacemaker was inserted with satisfactory control of the ventricular rate. As with her brother, both A-V and V-A block were present. Right heart catheterization and cineangiography demonstrated no shunt or apparent structural abnormality.

Seven hours later a permanent implantable pediatric pacemaker was applied with the battery pack positioned beneath the skin of the abdomen. Respiratory distress developed postoperatively and required long term respiratory assistance. Pneumonitis was treated with antibiotics and nutrition was maintained by intravenous hyperalimentation. Despite these efforts she gradually deteriorated and died on the 26th day.

At necropsy the body weighed 2420 grams and was 40 cm in length. There was edema of the lungs and liver plus pulmonary atelectasis. Acute fibrinous pericarditis covered the heart. The heart weighed 32 grams and was normal in shape and appearance except for the pericarditis. There were in particular no abnormalities of the valves or septa or the major coronary arteries. In order to make serial sections of the conduction system, all but the apical half of the heart

Figure 3

In this schematic drawing of the human A-V node and His bundle, three different planes of sectioning are indicated (intermediate planes are of course also possible). One plane would be in slices as shown in the original drawing to the left; two others would be perpendicular to that and to each other, as shown to the right. The plane used in the present case is shaded.
Figure 4
These and all the following photomicrographs are from case 2 (sister of case 1). At low power magnification (A) the pericarditis in the upper third of the picture covers the sinus node (SN). Myocardium of the right atrium (RA) is seen below. A central portion of the sinus node is seen in B, where apparent gaps exist between the normal interweaving slender fibers of the node; see text for discussion.

Figure 5
Both A-V node (AVN) and His bundle (AVB) are shown in the photomicrograph in A. The area seen at higher magnification in B is outlined above. Note the discontinuity between A-V node and His bundle, and the walling off of the A-V node from atrial septum in A. The density of this collagenous isolation of the A-V node was even more extensive at levels above the plane of this section. The His bundle in B is extensively degenerated.

Figure 6
The two histological processes affecting the His bundle are shown here. Normal resorption occurs as part of the postnatal molding and shaping of the His bundle as seen in the right half of A, while the abnormal caseous degeneration of the more distal portion of the His bundle is shown in B.

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Fig. 7

Normal histological appearance of the central portions of the A-V node is shown in A. In B the general preservation of over-all structure is apparent even in the areas of caseous degeneration; normal cells in the left half of the picture are compared to ones being destroyed in the right half.

resorption of His bundle cells exclusively on its left side (fig. 6). In the distal portion of the His bundle as it began to branch, there was focal infiltration by a few round cells. The most important abnormalities were present in the origin of both the right and left bundle branches, where the entire His bundle was destroyed (figs. 6–9). Although remnants of cells could be recognized, they appeared to have been transformed into caseous ghosts. There was no evidence of amyloid at this site or elsewhere in the heart, and particularly none in the sinus node, a site of special predilection by cardiac amyloid.9 The sites of destruction in the His bundle and proximal portions of both bundle branches were conspicuously devoid of any evidence of inflammation such as recent hemorrhage or leucocyte infiltration. The over-all picture in the major site of disruption was one of orderly death and caseous transformation of previously present cells which may have been in viable continuity in the recent past.

Exactly the same homogeneous degeneration of cells was present for the first few millimeters of the left bundle branch and for about one millimeter of the right bundle branch (figs. 9–11). Beyond that point the right bundle branch was entirely normal. For an additional millimeter or so beyond its complete disruption, the left bundle had isolated foci of degeneration interspersed with normal cells, but further on the left bundle branch was also entirely normal (figs. 12, 13). The distribution of pathological findings for the entire A-V junction is diagrammed in figure 14.

Discussion

One cannot generalize about congenital heart block from postmortem findings since survivors may be preselected in part because their A-V junctional tissues have a structure different from those of patients who die. Newer electrophysiological tech-
Figure 9
Where the His bundle was first dividing, the left bundle branch (LBB) was degenerated, but a few cells of right bundle branch (RBB) were preserved. The degenerated LBB is seen at higher magnification in B.

Figure 10
At a point less than 1 mm distal to the section seen in figure 9, the right bundle branch (RBB) was completely destroyed. This was the predominant situation within the first millimeter of the proximal course of RBB. The outlined area in A is seen at higher magnification in B. After the first millimeter of its proximal course, the RBB was histologically normal.

Techniques will permit more accurate definition of the location of conduction failure as determined by those methods, but more needs to be known about the histological substrate of phenomena such as the His potential before the physiological observations can be confidently related to anatomical findings. Even with these caveats, certain matters concerning the present cases merit discussion. Both infants had complete heart block at or shortly following delivery, and in both the prenatal examinations suggested that the fetuses either did not have heart block at that time or that some faster rhythm was dominant. Neither child had hemodynamic or angiographic evidence of other congenital heart disease, and none was present in the one at necropsy.

Our two cases being siblings, and in the absence of any evidence for a coincidental acquired form of heart block, the familial nature of the problem seems securely established. While complete heart block was diagnosed shortly after birth in both cases, it is possible that relatively normal A-V conduction had been present until at least late in pregnancy and possibly for a short period after delivery. Actually, there is increasing evidence that true familial congenital heart block may not only become first manifest later in childhood but even in adult life.9-12 One theoretical explanation for such delayed appearance of heart block is gradually progressive narrowing disease of the A-V node artery,14 although it has not been shown that such a process has a familial incidence.

In some respects one may look on the region of the His bundle as a locus minoris resistentiae, not for infection but as a matter of survival. The human His bundle is the anatomic interface between two normal sources of arterial supply coming to the region from opposite directions.15 While this could mean that one source should substitute for failure by the other via potential collateral circulation, it is also a fact that the His bundle is near the terminal distribution of the smallest arteries from either source. Second, the His bundle is that site where the inward migrating A-V node normally makes its ultimate connection with cells of the bundle branches which probably develop in situ;16 failure of this junction could evolve in a
number of ways. Third, the His bundle is normally ensheathed in a dense fibrous environment, a situation which introduces two problems. (1) The only route of normal entrance of blood supply is from the proximal or distal end of this fibrous canal, whereas most of the myocardium potentially has collateral supply from virtually all directions. (2) During the postnatal period in man the central fibrous body undergoes an increasing condensation of its collagen which is by contrast remarkably loosely organized during fetal development; during this period there is an associated "molding and shaping" of the normal His bundle. 16, 17 Postnatal processes characterized by such molding and shaping are normal in several components of the heart. 19 Hazards which may accompany faulty shaping and molding in the vicinity of the His bundle include its transection or other damage. What controls the process during this crucial period is unknown, although it may logically be deduced that some form of intercellular recognition between fibroblasts and cells of the His bundle must take place.

There are several ways in which familial congenital heart block may develop. First, there may be some inherited fault in the nutrient blood supply of the region, although the A-V node artery in case 2 was widely patent. Second, the normal postnatal molding and shaping 16, 17 of the His bundle as it adapts to its containment by more dense collagen may go awry. Some of this resorptive degeneration was present on the left side of the His bundle, which is where it usually occurs, but this did not appear to be responsible for the more extensive and more distally located degeneration of the His bundle. Furthermore, familial congenital heart block is known in some examples to appear during intrauterine life, 2 a time when the postnatal molding and shaping activity is conspicuously absent. 17 A third form of developmental failure has been observed in the region of the A-V node and His bundle, wherein a normal size A-V node is present in its usual location but it is composed entirely of small dark cells; these resemble very early embryonic cells which had failed to mature into normal postnatal and adult A-V nodal cells and fibers. 19 There was nothing to suggest such a failure of maturation in the present case, the cells on the contrary appearing appropriately mature.

Figure 11
In its proximal few millimeters the left bundle branch (LBB) was replaced by a mixture of caseous degeneration and dense fibrosis. Details of its histological appearance are seen at two magnifications in A and B.

Figure 12
Distal to the area of maximal destruction in the left bundle branch, first a few normal fibers appeared (dark arrow in B), then the picture became predominantly one of normal bundle branch cells as seen in A. In both A and B the general area of LBB is indicated (open arrows) beneath the left subendocardium.
Since the blood supply did not appear to be abnormal in the present case, the molding and shaping of the His bundle did not seem uncontrolled, and the cells present had appropriately matured, a fourth consideration could be that the cells in the His bundle underwent a form of programmed death based on a genetic fault, one which theoretically could become expressed at any period from fetal life to adulthood. This hypothesis would take recognition of the fact that the cells in question are directly within a region undergoing extensive evolutionary changes shortly following birth, when there is active fibroplasia and formation of very dense collagen on all sides of the His bundle tube. Both for this purpose and because the His bundle is the junction site during embryonic formation of the A-V node and bundle branches, it may logically be expected that some exquisitely sensitive and remarkably effective intercellular recognition mechanism exists within these crucial cells of the His bundle. What such a mechanism may be, and what turns it on or off to cope with its neighbors (A-V node, bundle branches and the central fibrous body fibroblasts) is completely unknown.

In the girl’s heart there was not only interruption of the His bundle but also a complete absence of connection between the A-V node and myocardial cells in the atrial septum. There was thus no available route for normal internodal conduction. The density of collagen which isolated the A-V node would suggest that this was an old process. It is possible that a faster rhythm was originating within the A-V node or proximal His bundle during fetal life, but that failed at about the time of delivery, concomitant with the newer degenerative process which destroyed the distal His bundle. One may consider whether some aspects of normal connection between the A-V node and the rest of the atrium (perhaps an accompanying innervation) is important to the postnatal survival of the His bundle. However, if this were the case, then every example of congenital heart block with lack of connection between the atrial septal myocardium and A-V node should concomitantly exhibit interruption of the His bundle, and this does not appear to be the case.3

Figure 13
Still more distally the left bundle branch became entirely normal (A, open arrows) except for tiny foci of degeneration as indicated with the black arrow in B.

Figure 14
This diagram summarizes the location and nature of abnormalities described for the A-V node and His bundle. A wall of collagen isolated the A-V node. Resorptive degeneration involved the left side of the His bundle as part of the normal postnatal and molding process. Caseous degeneration had destroyed virtually all of the deviating His bundle, much of the proximal left bundle branch, and a smaller initial portion of the right bundle branch.
Although the boy survived and his sister did not, the explanation need not be due to any difference in the nature of their heart block. The second child had problems with infection, malnutrition and ventilation which in aggregate became insurmountable. Neither child responded with significant acceleration after atropine or isoproterenol, indicating that at the time of those tests there was no dormant A-V conduction capable of being stimulated into function. In both children the QRS complexes were abnormal in configuration, although not of excessive width. The fact that the boy's QRS configuration changed shortly after birth could be attributable to progressive destructive changes already occurring in the A-V junctional tissues. Where their rhythm originated can only be conjectured, but the relative narrowness of the QRS complexes would suggest that it was near the bifurcation of the His bundle or in the proximal bundle branches. In case 2 this was most likely from the very proximal right branch, since the proximal left bundle branch was more extensively damaged.

Both children had normal heart rates while in utero, and the sister's heart rate was found to be 100/min during labor. It has already been suggested in the discussion above that their cardiac rhythm could have been of A-V junctional origin even before they were born. The fact that the sister's immediate prenatal heart rate was almost two-thirds of her postnatal sinus rate (100 compared to 160) may be especially significant.

Recent experimental evidence from dogs suggests that the rate of escape A-V junctional rhythms may be of more prognostic importance than is generally thought. In the dog there appear to be two distinct types of A-V junctional escape rhythm. AVJ-1 appears consistently following selective default of the sinus node, and it is normally responsive to both vagal and sympathetic neural stimulation. AVJ-2 appears consistently following selective pharmacological production of complete heart block by perfusion of test substances with a negative dromotropic action via the A-V node artery (e.g. acetylcholine, physostigmine, or sodium pentobarbital). AVJ-2 exhibits no response whatever to either vagal or sympathetic neural stimulation, and is furthermore completely resistant to negative chronotropic effect by acetylcholine. AVJ-2 does not appear to be a stable long-term rhythm while AVJ-1 does. However, the maintenance of normal rate and stability of AVJ-1 is dependent on the presence of normal adrenergic neural tone. In a suitable series of experiments mathematically analyzed for the relationship between the rate of the sinus node and that of the two forms of A-V junctional escape rhythm, there proved to be a highly consistent (P < 0.001) ratio so that sinus rhythm:AVJ-1:AVJ-2 was 9:6:2. In other words, AVJ-1 was normally 66% of control sinus rate, while AVJ-2 was 22%, making the AVJ-2 rate one third of AVJ-1.

The immediate prenatal rhythm of the sister (and perhaps of her brother as well) may thus have been AVJ-1, while their postnatal rhythm was AVJ-2. Instability of the escape rhythm during complete heart block was clinically manifested by syncopal attacks in the boy and by overt cardiac failure with a moribund state in his sister. Whether these two children with heart block may be seen as an experiment of nature subject to any analysis directly comparable to the physiological experiments is uncertain, although the preliminary evidence would suggest the two situations are analogous. The possibility of dependable mathematical predictability concerning forms of human A-V junctional escape rhythms has so many potentially valuable applications that it merits serious further consideration for clinical use.

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