Familial Atrioventricular Heart Block
An Autosomal Dominant Trait

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SUMMARY
A family of 28 individuals spanning four generations was investigated because of a finding of complete heart block in five members and the existence of a low degree of atrioventricular (A-V) heart block in a sixth member. The disorder was characterized by 1) adult onset in all, 2) complete A-V heart block in five and first degree A-V heart block in one, 3) sinus bradycardia in three, 4) atrial fibrillation in five, 5) abnormal QRS complex in five, 6) ventricular tachycardia in three, 7) left ventricular enlargement in all, and 8) mitral insufficiency in five. Proximal location of the A-V heart block was suggested by the fact that atropine caused acceleration of the ventricular rate and by the presence of a His bundle potential preceding the QRS complexes. Involvement of the distal conducting system was indicated by the widened QRS complex and a prolonged H-V interval. Pathologic examination in one case showed extensive sinus node fibrosis and interruption of the A-V node-His bundle connection. This disorder is probably due to an autosomal dominant trait.

Additional Indexing Words:
- Ventricular tachycardia
- Cardiomyopathy
- Carotid sinus massage
- Edrophonium hydrochloride
- Atroventricular conducting system
- Sinus node
- His bundle electrograms

In the adult, we recognize two common forms of chronic atrioventricular (A-V) heart block. The first type is the so-called congenital A-V block which is due to a developmental defect in the region of the A-V node-His bundle complex. Although many of these conduction disturbances are apparent at birth, there is a growing awareness that some may appear later in life. High degrees of A-V block are associated with a pacemaker within the His bundle driving the ventricles. This particular location accounts for many of the clinical and electrophysiologic features. The second type recognized, the so-called acquired A-V block, is due to a degenerative process involving the right and left bundle branches. This commonly develops after the fifth decade of life and when complete block supervenes, the ventricles are driven from an idioventricular site.

We recently had the opportunity of examining a family spanning four generations, in which at least five members had A-V heart block. These patients had some clinical features suggestive of block occurring distal to the common His bundle; however, results of electrophysiologic studies and pathologic examination showed the problem to be localized proximal to that structure.

Materials and Methods
The family covered four generations and included 28 individuals (fig. 1). With the obvious exception of those deceased prior to the study, all family members were examined clinically and had an ECG and chest X-ray performed. Detailed records, including electrocardiograms, of the three adult members who had died were available for study. Direct examination of records from the dead six-year-old girl and 13-year-old boy, second generation, was not possible as they had died over 50 years ago; the available histories regarding them did not permit any firm conclusions. Three individuals of the second generation, and the one from the third generation, who had A-V conduction disturbances underwent A-V conduction studies. In all four cases, the response of the A-V conduction to autonomic maneuvers such as exercise, amyl nitrite inhalation, isoproterenol bolus (1-3 µg i.v.), carotid sinus massage, edrophonium hydrochloride (10 mg i.v.), and atropine (1.2-2.4 mg i.v.) was assessed. Two of these patients also underwent His bundle electrogram studies using standard recording and stimulating techniques. The nature of these investigations was carefully explained to the patients and informed verbal and written consent was obtained.

Results
Clinical Features
The major clinical and electrocardiographic data are summarized in table 1.
Family Pedigree

Figure 1 is a diagrammatic representation of the family tree. The original carrier of the trait was not examined by us since she had died several years ago, but available data indicated that she had A-V heart block, cardiomegaly, and a heart murmur. She died suddenly at age 69 years; the cause of death was not documented. The girl, denoted by the question mark, had died many years ago at the age of six years; apparently, she fell down a flight of stairs and was dead when found. The circumstances surrounding this death suggest that A-V block may have been responsible for her death. The man, denoted by the half-filled symbol, had early signs suggestive of this disorder in the form of sinus bradycardia, first degree A-V block, and mild cardiomegaly.

Cardiomegaly

Cardiomegaly was a common feature in these patients. Figure 2, taken from H.N., is representative and shows moderate left ventricular enlargement. Despite the common occurrence of cardiomegaly observed in these patients, only one had symptoms or signs of heart failure. Apart from chronic bradycardia and mild mitral insufficiency, there were no findings such as hypertension or any form of left ventricular outflow tract obstruction that might account for the cardiomegaly.

Evolution of the Electrocardiographic Abnormality

The patients in this study demonstrated difficulties with impulse formation and A-V conduction. Although the precise evolution of this problem is not

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Status</th>
<th>Degree A-V heart block</th>
<th>SB</th>
<th>A fib</th>
<th>Abnormal QRS</th>
<th>VT</th>
<th>LVE</th>
<th>M insuf</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.N.</td>
<td>69</td>
<td>F</td>
<td>Dead</td>
<td>Third</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>J.N.</td>
<td>62</td>
<td>M</td>
<td>Dead</td>
<td>Third</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M.N.*</td>
<td>60</td>
<td>M</td>
<td>Alive</td>
<td>Third</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>H.N.</td>
<td>53</td>
<td>M</td>
<td>Alive</td>
<td>Third</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>J.N.</td>
<td>51</td>
<td>M</td>
<td>Dead</td>
<td>Third</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>G.N.</td>
<td>42</td>
<td>M</td>
<td>Alive</td>
<td>First</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Because of the presence of two individuals with the same initials — M.N. — an * will identify this patient.

Abbreviations: A-V = atrioventricular; SB = sinus bradycardia; A fib = atrial fibrillation; VT = ventricular tachycardia; LVE = left ventricular enlargement; M insuf = mitral insufficiency.

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known, it ultimately led to sinus bradycardia, atrial fibrillation, A-V block, and an abnormal QRS.

In one individual (H.N.), the progressive evolution could be followed (fig. 3). At the age of 46 years (top panels, 2-10-65), he had sinus bradycardia and first degree A-V block. Tracings taken immediately following exercise showed an increase in the sinus rate and second degree A-V block with a Wenckebach pattern. One year later (middle panel, 5-19-66), the tracing showed the development of complete A-V block. The atria were still driven by a slow sinus mechanism. Six years later, at the age of 53 (bottom panel, 12-10-71), a tracing showed persistence of complete A-V block, but atrial fibrillation was now present. Of additional interest is the absence of an anteriorly directed QRS force in leads V₁, V₂ and V₃, as well as QRS duration prolongation to 0.11 sec.

A more advanced form of the electrocardiographic disorder is shown in figure 4. This individual (M.N.*) is 60 years of age and had atrial fibrillation and complete A-V heart block. The QRS complex is widened to 0.14 sec and shows very poorly developed, anteriorly directed forces in the precordial leads. Despite the abnormal QRS morphologies, none of these patients had any clinical evidence suggestive of coronary artery disease. The pathologic examination of I.N. showed that the coronary arterial tree was free of significant obstructive disease despite the presence of a similar QRS abnormality.

Character of A-V Heart Block

The age at which heart block was detected, coupled with the abnormal QRS complex, suggests that the block was distal to the common His bundle. However, the response of the pacemaker to autonomic maneuvers, as well as the His bundle electrogram recordings, established the fact that the block was proximal to the His bundle and that the ventricles were driven by a pacemaker in the His bundle (table 2). Those in the second generation with complete heart block showed slowing of their ventricular rate by carotid sinus massage or edrophonium hydrochloride (10 mg i.v.). Figure 5, taken from I.N., shows complete A-V block and atrial fibrillation. The ventricular rate was slowed by edrophonium hydrochloride. Similarly, atropine accelerated the ventricular rate in

*Because of two patients with the initials M.N., an * will be used to identify this patient.

Figure 2
Case H.N., chest X-ray. There is moderate left ventricular enlargement.

Figure 3
Case H.N. Top panels were taken at age 46 (2-10-65). Under resting conditions, it shows sinus bradycardia and first degree A-V heart block. The tracings taken post-exercise show second degree block with 3:2 Wenckebach conduction. Fifteen months later (middle panel–5-19-66), third degree A-V heart block has developed. Sinus bradycardia at 55 beats/min persisted. Five-and-a-half years later (bottom panel–12-10-71), complete A-V heart block persists. Atrial fibrillation, along with some widening in QRS, and loss of anteriorly directed forces had developed.

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those who were in complete heart block (fig. 6). In two cases, His bundle electrograms confirmed that the block in A-V conduction was proximal to the His bundle. Despite the wide and abnormal QRS morphology, the ventricles were driven from a His bundle pacemaker (fig. 7). His-ventricular (H-V) conduction time was prolonged to 60 msec in both patients.

A summary of the major features of the A-V block is shown in Table 3. The heart block was proximal to the common His bundle and the ventricles were driven at a rate between 40 and 50 beats/min by a His bundle pacemaker. These patients had an abnormal QRS complex and prolonged H-V intervals. Vagal and vagolytic influences decreased and increased the His bundle rate while sympathetic influences increased the His bundle discharge frequency.

Ventricular Tachycardia

At least three members had documented episodes of ventricular tachycardia (VT). The criteria for VT included: 1) QRS morphology radically different from the one propagated from the His bundle, 2) A-V dissociation, 3) a ventricular rate several-fold faster than the pre-existing A-V junctional rate in all three cases, and 4) absent His potentials in two cases.

Figure 8 shows the rhythm disturbance of one patient (M.N.*). This shows ventricular flutter at a rate of 240 beats/min. Ventricular tachycardia was the direct cause of death in two patients. There may have been a relationship between the slow intrinsic heart rate and the tendency to develop VT. Figure 9 shows M.N.* several months following implantation of a permanent demand pacemaker (R-inhibited type). The external chest wall stimulation is used to turn off the internal pacemaker. When the heart is driven at a rate of 70 beats/min by the internal pacemaker no ventricular ectopic beating is seen. As soon as the internal pacemaker is turned off, an A-V junctional rhythm of 50 beats/min resumes. Frequent short runs of ventricular ectopic beating are seen at this time.

Pathology

Figure 10 summarizes the pathological findings of the heart and its specialized conducting network in patient I.N. The total heart weight was increased to 550 grams, the coronary arteries were free of any significant obstructive disease, and there were no signs of any recognizable form of cardiac muscle disease. The outstanding finding was that of marked replacement of the sinus node cells by fibrous tissue. The proximal portion of the A-V node was easily identified and showed moderate fibrosis. A small amount of

Table 2

Response of Rhythm to Autonomic Maneuvers

<table>
<thead>
<tr>
<th>Case</th>
<th>Rhythm</th>
<th>CSM</th>
<th>Atropine</th>
<th>Exercise</th>
<th>Amyl nitrite inhalation</th>
<th>Isoprotrenol 1-3 MCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.N.</td>
<td>A fib</td>
<td>Slow</td>
<td>Accelerate</td>
<td>Accelerate</td>
<td>Accelerate</td>
<td>Accelerate</td>
</tr>
<tr>
<td></td>
<td>C AVB</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
</tr>
<tr>
<td>I.N.</td>
<td>C AVB</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
</tr>
<tr>
<td>H.N.</td>
<td>C AVB</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
<td>v rate</td>
</tr>
<tr>
<td>G.N.</td>
<td>Sinus bradycardia</td>
<td>Lengthen P-R</td>
<td>Mild inc</td>
<td>Mild inc</td>
<td>Mild inc</td>
<td>Mild inc</td>
</tr>
<tr>
<td></td>
<td>P-R prolongation</td>
<td>Second degree</td>
<td>sinus rate</td>
<td>sinus rate</td>
<td>sinus rate</td>
<td>sinus rate</td>
</tr>
<tr>
<td></td>
<td>Sinus slowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A fib = atrial fibrillation; C AVB = complete A-V block; v rate = ventricular rate; CSM = carotid sinus massage; inc = increase.

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fibrosis was seen in the His bundle in the region of the membranous septum. The sinus and A-V node arteries were widely patent, but their walls showed an increase in mucopolysaccharide material. The anastomosis between the His bundle and bundle branches was normal, as were the proximal portions of the bundle branches. A convincing connection between the A-V node and His bundle could not be established. It is, however, possible that because of a technical error the necessary tissue block was not obtained.

Discussion

The inheritance pattern of the A-V block was probably due to an autosomal dominant trait with incomplete penetration. A sex-linked recessive trait, doubled in the mother (M.N.), is a possibility which further study may clarify. Karyotype of one patient (M.N.∗) disclosed no chromosomal abnormalities. Apart from the cardiac characteristics mentioned, there were no other phenotypic features which the affected family members had in common.

The age at which onset of heart block may be ex-

pected to occur is uncertain. The affected members were in their fifth, sixth, or seventh decade of life when they died or when their disorder was first documented. The lack of obvious involvement in members of the third and fourth generation, except for G.N., may simply reflect the fact that they had not yet reached the age at which this disease presents itself. This, of course, would increase enormously the reservoir of persons with this trait.

At the time of this writing, we are aware of seventeen families with A-V heart block. 3, 8-23 In most of these, sufficient data exists to support the concept of an autosomal dominant mode of inheritance. Sarachek and Leonard, 3 after an extensive review of most of the available literature divided the cases of familial heart block into a congenital form and an adult-onset form. From the existing evidence, they suggest that the congenital familial A-V block is due to the type of A-V node-His bundle lesion responsible for nonfamilial congenital A-V block. 2, 24 In contrast, they suggest the idea that the adult-onset type is due to disease involving both bundle branches. It is becoming increasingly clear that so-called nonfamilial congenital A-V block may embrace a considerable range of A-V junctional pathology. 25, 26 In many of the 17 families reported, conclusive electrophysiologic or pathologic data are lacking to allow precise localization of the block. Many of the cases that had features of so-called congenital A-V block also had features of bundle branch disease. Conversely, some families with members who have bundle branch block also had block proximal to the His bundle. The family we studied provides fairly conclusive evidence that the A-V block was proximal to the His bundle and that bun-

Table 3

<table>
<thead>
<tr>
<th>Heart Block Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal QRS complex.</td>
</tr>
<tr>
<td>His bundle pacemaker.</td>
</tr>
<tr>
<td>Vagal and vagolytic maneuvers decrease and increase the</td>
</tr>
<tr>
<td>His bundle rate.</td>
</tr>
<tr>
<td>Sympathomimetic maneuvers increase the His bundle rate.</td>
</tr>
</tbody>
</table>

Figure 5

Case I.N., lead 3. Atrial fibrillation with complete A-V heart block. The ventricular rate is slowed by edrophonium hydrochloride 10 mg i.v. (middle panel).

Figure 6

Case H.N., lead 2. Atrial fibrillation with complete A-V heart block. Sixty seconds after atropine 2.4 mg i.v. (bottom panel), the ventricular rate increased from 46 to 80 beats/min.
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dle branch disease was coexistent. It is entirely possible that with proper study or sufficient periods of observation many or all of the familial A-V block cases will have a common electrocardiographic and pathologic localization. It is important to note, as Sarachek has done, that sinus bradycardia may be a familial disorder or it may coexist with familial A-V block. The family we studied prominently manifested evidence of sinus node dysfunction. One wonders whether careful follow-up of families with primary sinus bradycardia will disclose the development of A-V block.

The most obvious explanation of complete heart block in an adult with a wide QRS complex driving the ventricles is existence of a block distal to the bundle of His. Obviously, this was not the case with the family we studied. The presence of an abnormal QRS complex and long H-V interval might be explained in several ways. First, the conduction disease may have directly affected the bundle branches. Second, part of the QRS prolongation and poorly developed anteriorly directed precordial forces might have reflected the presence of left ventricular hypertrophy (LVH). Third, the LVH, whether a primary or secondary event, may have caused stretching of the Purkinje fibers of the left ventricle which produced bundle branch conduction disturbances.

The development of atrial fibrillation in these cases is probably related to the fact that the sinus node had been replaced by fibrous tissue. This produces sinus bradycardia which ultimately may lead to atrial fibrillation. The precise relationship between a slow sinus mechanism and atrial fibrillation is unclear, but this type of association is very commonly seen in the so-called sick sinus syndrome.

Ventricular tachycardia is not a rare complication of heart block, but its occurrence in at least three of these patients was certainly more frequent than one might expect in six ordinary cases of chronic A-V block. There were small scattered zones of fibrous tissue throughout the myocardium of case I.N., but this did not appear particularly unique for a man his age. It is possible that the ventricular chamber enlargement coupled with the stretched Purkinje fibers are important factors in the production of VT in these patients.

**Figure 7**
Top panel) Case M.N. Simultaneous tracing of lead V1, bipolar atrial electrogram (BAE) and His bundle electrogram (HBE). Bottom panel) Case I.N. Simultaneous recording of lead V1 and HBE. In both cases, there is complete A-V heart block and the atria are fibrillating. The ventricles are driven by a His bundle pacemaker with H-V intervals of 60 msec.

**Figure 8**
Case M.N. 12-lead ECG during an episode of ventricular flutter (11-4-71).
The relationship of the cardiomegaly and mitral insufficiency to the A-V block remains unresolved. It is tempting to consider the possibility that family members were suffering from a cardiomyopathy as well as a disease of the specialized conducting network of the heart. The lack of any significant congestive heart failure would perhaps argue against the presumption of cardiomyopathy. Other reports dealing with familial A-V block have also grappled with this problem. It certainly is possible that long-standing bradycardia might lead to left ventricular enlargement and some mitral insufficiency.

We have presented a family of 28 persons in whom five individuals had A-V heart block. These patients had sinus node dysfunction which was manifested by sinus bradycardia, atrial fibrillation, and sinus node fibrosis. The A-V heart block was associated with an abnormal QRS complex, and results of electrophysiologic studies localized the block to a level proximal to the His bundle.

A sixth member has an early form of the disease. The most likely mode of inheritance in these individuals is an autosomal dominant trait with incomplete penetration. A sex-linked recessive trait, doubled in the mother, is a possibility which further study may clarify. The relationship of the cardiomegaly to this condition is not clear, but it probably reflects long-standing bradycardia. The ventricular chamber enlargement and the resultant stretch on the Purkinje fibers may be an important determinant in the production of the ventricular arrhythmias seen in some of these individuals.

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