SUMMARY

In the hearts of two victims of sudden unexpected death (one age 20 years and the other 11 years) there was abnormally delayed persistence of the pattern of fetal dispersion of the A-V (atrioventricular) node and His bundle within the central fibrous body. This pattern is characterized by a spayed or excessively fragmented histological appearance of these structures viewed in cross-section. Some of the fronds of A-V nodal tissue formed loops connecting one portion of the node to another. Other fragments of nodal tissue appeared isolated within the central fibrous body, occasionally connecting directly to the crest of the interventricular septum. A number of the A-V nodal fragments were undergoing resorptive degeneration. Directly adjacent to the A-V node of the 11-year-old subject there was an island of cartilage within the central fibrous body. Since these anatomically separated fragments of A-V nodal tissue were so numerous and varied widely in size and thickness, in length, in histological organization, and in their apparent state of preservation probably extant during life, it is suggested that they form potential routes for abnormal conduction or impulse formation within the A-V junctional region and that some of these electrophysiological disturbances might be quickly lethal.

SIR ARTHUR KEITH was one of the first to observe that the His bundle of the human fetus is a comparatively enormous structure, whether considered relative to the heart size at that age or to the size of the normal adult His bundle. Some years ago the late Robert P. Grant emphasized that postnatal morphogenesis of the human heart was an important part of its normal development. More recently it has been suggested that the morphogenesis of the normal adult human His bundle always includes postnatal molding and shaping of the structure. While some believe that the process includes cell death, others do not accept this interpretation. Regardless of how the large and irregularly shaped His bundle of the human fetus transforms into the smoother slender His bundle of the adult, there is little question that this difference exists. If the transformation does involve cell death or resorptive degeneration of cells in the A-V (atrioventricular) node and His bundle, similar to the normal occurrence of cell death in other forms of morphogenesis, then there is clearly the possibility of transient periods of electrical instability in the performance of these crucially important components of the cardiac conduction system.

While normal morphogenesis of the human A-V node and His bundle is usually completed in the first year or so of life, the process may sometimes be delayed for reasons which are unknown. If this delayed maturation is eventually successful, then the associated electrophysiological disturbances which may accompany it would ‘spontaneously’ end. On the other hand, during the period of postulated electrical instability of the heart, it is possible that some arrhythmia, with or without an associated abnormality of conduction, could on one occasion be abruptly fatal. Such a possibility is supported by the fact that persistent fetal dispersion (or delayed resorption) of the human A-V node and His bundle has been especially observed in victims of sudden unexpected death. This report will present the post-mortem findings in the hearts of two victims of sudden unexpected death and illustrate an abnormally delayed persistence of the fetal organization of their A-V nodes and His bundles.

Case Reports

Case 1

A twenty-year-old electrician lived with his parents and had always enjoyed good health. One evening he went to see his girl friend and arrived back home just before midnight. He seemed perfectly normal then and helped his mother to get in the cattle which were wandering. After retiring to bed a short time later, he read a book for a while as was his habit. At 4:20 a.m. his father, who was sleeping in the adjacent room, heard him gasping, rushed into the bedroom and found him struggling for breath. The father called the doctor and then gave artificial respiration. However, the son died within a few moments, before the doctor arrived.

Initial postmortem examination, including toxicological studies, was essentially normal except that the lungs were congested and edematous. Careful gross examination of the heart was entirely normal, and there was no microscopic evidence of myocarditis or other myocardial disease. Because the terminal event may have been caused by an arrhythmia or heart block, we conducted a special examination of the sinus node, A-V node, and His bundle with its proximal branches. The methods for such examinations have been described in previous reports of this series on the subject of sudden death.

The sinus node artery was focally narrowed by both concentric and eccentric fibromuscular dysplasia, and there were several foci of abnormal fat accumulation in the crista
Figure 1. Sinus node (SN in A) and its central artery (B) are shown from Case 1. The walls of the artery are eccentrically thickened. Fat at the epicardial margin of sinus node (top of A) is normal, but fat within the substance of the crista terminalis (RA in A) is abnormal. Magnifications here and in subsequent photomicrographs are indicated with reference bars. All specimens were prepared with the Goldner trichrome stain unless otherwise indicated.

Figure 2. The extent of fragmentation of the A-V node just as it is forming the His bundle of Case 1 is illustrated in these four photomicrographs, made from sections about 50 microns apart from each other. The fragment of A-V nodal tissue indicated with an open arrow in A can be seen in the other three pictures as it forms a continuing loop which reconnects with the main body of the A-V node (arrow in D). A vertically disposed linear fragment of A-V nodal tissue indicated with arrows in C is now discontinuous but lies in a general line parallel to the endocardium of the left ventricle (LV) and may once have connected the interatrial septum directly with the interventricular septum. Variations in size and shape of one large fragment of A-V nodal tissue (curved arrow in D) can be compared in the four sections. CFB is central fibrous body.
terminalis of the right atrium (fig. 1), but the substance of the sinus node itself was essentially normal. The A-V node was rather small but normally located. However, in the region of the A-V node and His bundle there were three significant findings: 1) abnormal dispersion of the A-V node within the central fibrous body, with some of these fragments undergoing resorptive degeneration (figs. 2-5); 2) a long left subendocardial course for the undivided His bundle (fig. 6); 3) a predominance of transitional cells (which are typical of the A-V node) far into the His bundle itself, where the normally predominant Purkinje cells appeared only at the most distal portion of the His bundle and were there mixed with a moderate degree of fibrosis (fig. 7).

Case 2

An eleven-year-old boy went out to play on a grassy green near his home in a housing estate. He was joined by six other boys and they played football with a plastic ball. He seemed quite well and was running about tackling. The game ended
when three of the boys had to leave. The boy’s brother went home for a drink and two of the other boys walked over to the far side of the green and lay down. This boy stayed by himself and three minutes later his two friends saw him lying on the grass. They thought he was just resting but when his brother returned a few seconds later, he could see that something was wrong. His brother called for help and one of the boys examined him and found only a weak pulse. There was some blood around his mouth with grass sticking to it. Then the boy’s mother arrived and after she had examined him she ran for a neighbor. The neighbor thought the boy was dead. He was carried to a doctor’s house nearby and then taken by ambulance to a hospital where his death was confirmed.

Almost exactly one month previously this same boy fell off his bicycle in the park. He could not remember why, but he was able to walk home with help. His parents took him to a hospital where he was detained because he seemed a little confused. There was a puffy bruise and three small abrasions on the left side of his forehead. He had no headache or dizziness. A skull X-ray revealed no fracture and as no other abnormality was found, he was discharged apparently in good health three days after admission.

At necropsy there were no abnormalities other than in the heart. There was in particular nothing to suggest that a physical injury during the football game could have killed him. On gross examination of the heart the thicknesses of the left ventricle were somewhat asymmetrical, the anterior wall measuring 11 mm, the septum 13 mm, the posterior wall 6 mm, and the lateral wall 7 mm; however, the histological appearance of the myocardium was entirely normal. Because we have previously found histological abnormalities of the cardiac conduction system in verified examples of asymmetrical hypertrophy of the heart, and because both the terminal event as well as the fall from the bicycle one month before sounded suspiciously like episodes of cardiac syncope, special examination of the sinus node, A-V node, and His bundle was performed.

Except for a small unexplained scar near its posterior margin (fig. 8), the sinus node was normal. As in the previous case, the A-V node had numerous fronds and fragmented strands protruding into the central fibrous body to resemble the situation normally present in the human fetus. Some of these dispersed fragments of A-V node connected directly to the crest of the interventricular septum (fig. 9). Others were undergoing resorptive degeneration (figs. 10–12). In one area of resorptive degeneration of parts of the A-V node, the central fibrous body directly adjacent was transformed into cartilage (figs. 13–15).
Discussion

What it is that insures normal electrical stability of the human heart is surely a complex matter. Fortunately, most examples of electrical instability are either totally innocuous or at the most troublesome by producing annoying symptoms. On the other hand, any form of cardiac electrical instability is potentially dangerous and most believe that otherwise unexplained sudden and unexpected deaths probably represent quickly lethal arrhythmias or conduction disturbances. In both the present cases the terminal circumstances were compatible with such an explanation of sudden death, and in the second case there had even been a preceding suspicious event one month previously. Furthermore, there were similar abnormalities of the A-V node and His bundle in both hearts, characterized by wide dispersion of fronds and fragments of these crucially important tissues into the subjacent central fibrous body. This histological pattern is normally seen in the human fetus and newborn but not in older age groups.

Any attempt to make a functional interpretation from finding a splayed or frayed or eccentrically located A-V node or His bundle is hampered by the lack of factual information as to what the cardiac rhythm and A-V conduction actually was in the terminal period. This handicap is virtually inescapable when one studies sudden unexpected death, since by definition nearly all such victims were considered normal and therefore were not subjects of medical attention. Furthermore, the timing of observations relative to concurrent events must be carefully interpreted. For example, one observer described presence of a weak pulse in Case 2 but his observation (if correct) was made some minutes after the disastrous sequence of events began.

Much is known today about the normal and abnormal...
electrophysiological behavior of the A-V junctional region, and on that basis some reasonable guesses can be made about possible functional significance of the histological abnormalities in our two cases. Most now believe that there are two or more functional pathways through the A-V node, and these have been variously considered slow and fast or otherwise electrophysiologically different routes. In the normal adult human A-V nodal region there are certain fibers which appear to bypass the bulk of the A-V node and may thereby provide two different routes for conduction. However, what the present two cases and certain previous ones illustrate is a multitude of potentially separate routes for A-V conduction. Not only are the strands anatomically separated but the intervening space is occupied by collagen, which is generally considered a poor conductor and must therefore serve as a form of insulation for these separate conduits. Since these separate anatomical pathways vary in size or thickness, and in length, and in histological organization, and in their apparent state of preservation probably extant during life, it may be reasonably assumed that their ability to conduct will also vary, particularly in comparison to the normal A-V node. Furthermore, some of these fronds form actual loops which leave one portion of the A-V node and rejoin another, while others appear to form blind pockets. Isolated clumps of A-V nodal cells also exist totally detached from the A-V node but clearly attached to the crest of the interventricular septum.

Longitudinal dissociation of conduction in the A-V junctional region is now considered to be an important mechanism for certain supraventricular tachycardias based on re-entry of the normal cardiac impulse. However, most of these are not fatal, particularly when they occur in individuals with otherwise normal hearts. Rare instances of such arrhythmia may terminate fatally, perhaps because of unduly rapid or disorganized re-entry. In addition, with an anatomical substrate which could permit multiple re-entrant loops to form there may be an increased likelihood of fatal disorganization of the cardiac rhythm. Furthermore, an unfortunately timed premature beat might originate in one of these isolated strands and arrive in the ventricular myocardium during its vulnerable period, leading to a ventricular arrhythmia. This might especially occur with those A-V

Figure 10. This section of A-V node of Case 2 is about 2 mm from that in figure 9. Fetal dispersion of A-V nodal fragments within the central fibrous body is demonstrated. Arrow in B marks the A-V node artery which has a minor degree of narrowing. IAS is interatrial septum. The area outlined with the rectangle in B is shown in more detail in figure 11B.
nodal fragments directly connecting to the crest of the interventricular septum, either from the A-V node or detached from the node itself. There are still other speculative possibilities for the generation of a lethal electrical instability of the heart, but the essential fact is that these histological abnormalities involve exactly that portion of the conduction system which must function properly for normal life to continue.

In Case 2 there were two other unusual histological features of the A-V junctional tissues, the functional significance of which is uncertain. First, the His bundle was eccentrically located lying just beneath the left ventricular endocardium. This location occurs in just over 10% of human hearts and may or may not be functionally significant. Second, the transitional cells which are normally predominant in A-V node were observed much further into the His bundle than is normally the case. If we knew more about the electrophysiological properties of transitional cells compared, for example, to Purkinje cells, then this apparent "nodalization" of the His bundle might be important. At any rate, one does not normally see so many of these nodal cells so far into the His bundle.

Almost nothing is known of the normal regulation of morphogenesis for the human A-V node and His bundle. However, it may logically be suspected that the fibroblasts of the central fibrous body, perhaps by a genetically programmed process, participate in the postnatal molding and shaping of the human A-V node and His bundle. If this suspicion is correct, then the appearance of cartilage within the central fibrous body may indicate a distinct and important abnormality within those control processes as they operate within the human heart.

It is well known that some animals other than man normally have not only cartilage but actual bone within the central fibrous body, but cartilaginous transformation of the central fibrous body has only once been reported in the human heart. In the Doberman pinscher dog both cartilage and newly formed bone have been observed, and were furthermore associated with sudden unexpected death. In these dogs there were numerous focal narrowings of small arteries in the A-V junctional region and it was postulated that the metamorphosis of normal collagen to abnormal cartilage and bone within the central fibrous body may in part have been the consequence of focal ischemia. This postulation was supported by experimental evidence from several different mammalian species in which metaplasia of myocardial connective tissue to cartilage appeared where degeneration or scarring was present. In the second case reported here there was a minor degree of narrowing of the A-V node artery (figs. 10 and 11) but probably not enough to have produced focal ischemia. This raises the more intriguing possibility that the cartilaginous transformation

**Figure 11.** These photomicrographs are higher magnifications of the section in figure 10 and show the A-V node artery in A and a fragment of nodal tissue undergoing resorption in B.

**Figure 12.** Another example of resorptive degeneration of an A-V nodal fragment in Case 2 is shown here at two magnifications. This section is about 15 microns from that in figure 11.
Figure 13. Directly adjacent to the A-V node of Case 2 there was an island of cartilage, which is not normally found in the central fibrous body of the human heart. B and C are serially increased magnifications of the area outlined in A. A complete loop of A-V nodal cells coursing in the central fibrous body is marked with an asterisk in A, and is similar to that shown in figure 9A of a section about 30 microns from this one.

represents a fundamental fault in the control of these fibroblasts in the central fibrous body, another expression of which may be the delayed completion of the normal molding and shaping of the A-V node and His bundle. Since cartilaginous metamorphosis within the human heart is rather rare, however, and abnormal persistence of the fetal pattern

Figure 14. The island of cartilage within the central fibrous body of Case 2 is outlined with three arrows in A and the area enclosed with the rectangle is enlarged in B. With the Verhoeff-Van Gieson elastic stain here the cartilage appears lighter than the central fibrous body.

Figure 15. Normal appearance of the collagen within the central fibrous body of Case 2 is compared with the abnormally located cartilage, which is forming elastin fibers. Both panels are prepared with Verhoeff-Van Gieson elastic stain.
for the A-V node and His bundle seems by comparison to be more common, these may be unrelated abnormalities in the behavior of fibroblasts within the central fibrous body.

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