CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus
XII. Asymmetrical Hypertrophy of the Heart

By Thomas N. James, M.D. and Thomas K. Marshall, M.D.

SUMMARY
Subjects with asymmetrical hypertrophy of the heart are prone to sudden death. Neither the pathogenesis of the eccentric hypertrophy nor the mechanism of sudden death is fully understood. In this report we describe certain postmortem findings in the hearts of 22 subjects who died suddenly, silently and unexpectedly, and in whom the only significant abnormality at autopsy was asymmetrical hypertrophy of the heart. Deep clefts were present in the septum in seven hearts, the small coronary arteries were abnormally narrowed in ten, the sinus node was sclerosed by fibrosis in 12, there was variable narrowing of the atrioventricular (A-V) node artery in many and the His bundle was too thin in three. There were multiple cysts or channels in the central fibrous body and of the adjacent A-V node and His bundle in four hearts. Most of the hearts displayed a fetal dispersion of the A-V node and His bundle throughout the central fibrous body, but this was particularly conspicuous in 13 hearts. These abnormalities in all parts of the conduction system suggest a variety of possible mechanisms by which the heart could become electrically unstable but do not indicate that one single mechanism is at fault in all. They offer some explanation for the reported high incidence of atrial fibrillation in such patients, and why they fare so badly with this arrhythmia. While the pathogenesis of asymmetrical hypertrophy may in some part be attributable to narrowed small coronary arteries or to an abnormal sequence or speed of septal and ventricular activation or to mechanical deficiency caused by deep septal clefts, none of these features was universally present in our series. Both asymmetrical hypertrophy of the heart and the sudden death which so frequently accompanies it probably develop by a variety of pathogenetic mechanisms.

Additional Indexing Words:
Fetal pattern of A-V node and His bundle  Cystic faults of central fibrous body  Atrial fibrillation
Pathological small coronary arteries  Clefts of interventricular septum  Sclerotic sinus node

The observed association of sudden death with asymmetrical hypertrophy of the heart can be examined either retrospectively or prospectively. Teare's original report, in which eight of the nine subjects died suddenly, was a retrospective correlation based on investigation of fatal cases. In prospective clinical studies the incidence of sudden death is somewhat less but remains impressively high. For example, in a recent multicenter cooperative investigation it was found that sudden death was the most common form of demise, occurring in 26 of 49 fatal cases. Some have suggested that these deaths are most likely due to an electrical instability of the heart. However, neither the exact pathogenesis of asymmetrical hypertrophy of the heart nor the prevalent mechanism of sudden death in so many patients with the disease has yet been explained.

In this report we present our findings in 22 examples of sudden death in which asymmetrical hypertrophy of the heart was found at necropsy. It is a retrospective study based on these two facts: that death was sudden and unexpected, and that asymmetrical hypertrophy of the heart was the only postmortem diagnosis to which the death could be attributed. Our examinations included forensic pathological assessment of the possibility of violence or of poisoning, a complete routine autopsy, and whatever clinical information could be obtained from surviving family members or neighbors or witnesses of the death. We also conducted special studies of the sinus node, atrioventricular (A-V) node, His bundle

From the Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama and the Institute of Pathology, Queen's University, Belfast, Northern Ireland.

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Address for reprints: Thomas N. James, M.D., Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama 35294.
and its proximal branches, and of the histological appearance of the small (1 mm diameter or less) coronary arteries. The latter investigation included particularly the small arteries of the interventricular septum and the nutrient arteries of the sinus node and the A-V junctional region.

Case Reports

These descriptions will be limited to the pertinent clinical and pathological findings in each case. In none of the hearts was there significant disease of the cardiac valves or of the large coronary arteries, and there were no examples of atrial or ventricular septal defects. Diseases in organs other than the heart were either absent or of minor degree and not considered contributory to death. In every heart there was asymmetrical hypertrophy, a typical example of which is illustrated in figure 1. The histological appearance of fibers in the hypertrophied regions (figs. 1–3) were as described by Teare and others. The sequence of presentation follows the actual accession of cases over an 11 year period during which over 12,000 autopsies were performed.

Case 1. A sixteen-year-old girl with no known health problems was seen as she fell from her bicycle while enroute to work one morning and died.

The heart weighed 390 grams and there was asymmetrical hypertrophy involving the interventricular septum and adjacent anterior and posterior walls of the left ventricle. Maximal thickness of the septum was 25 mm. There were numerous deep clefts in the septal myocardium.

Many small coronary arteries were narrowed, both within and outside the areas of septal fibrosis. An excess number of nodal fragments and branching of the node were seen in the central fibrous body adjacent to the A-V node. This A-V nodal histological pattern resembles the human fetal heart rather than the normal adult. The central fibrous body contained cystic faults (fig. 4). The sinus node was normal.

Case 2. One evening a 59-year-old woman was a passenger in the back seat of a car when she was seen to collapse without a sound. She was rushed to a doctor’s house and then to a hospital but was dead.

The heart weighed 434 grams. Both anterior wall and adjacent interventricular septum were asymmetrical hypertrophied, the former measuring 20 mm and the latter 12 mm. There were many narrowed small coronary arteries. The septal myocardium contained several deep clefts. The sinus node and A-V node were each small, their respective volumes being less than half that normally expected in the adult heart. The histological appearance and location of the A-V node and His bundle were normal. At its

Figure 1

The typical gross and microscopic appearances of hearts in this study are illustrated. The photograph is from case 6 and the photomicrograph from case 3. RV and LV refer to the two ventricles. Magnification is indicated by the reference bar. Unless otherwise indicated, all histological stains shown are the Goldner trichrome.

Figure 2

Two examples of the disarrayed hypertrophy and of narrowing of multiple small coronary arteries are shown here from case 3. Magnification is the same in both.
The heart was enormous, weighing 760 grams. All cardiac valves, including the mitral, were thin-walled and pliable. All cardiac chambers were hypertrophied at least moderately, but the anteroseptal region was disproportionately hypertrophied, measuring 27 mm in thickness compared to 16 mm for the posterior and lateral walls of the left ventricle and 6 mm for the right ventricle.

The right bundle branch had extensive focal fat. The A-V node was as extensively partitioned throughout the central fibrous body as the normal human fetal A-V node. The A-V node artery was moderately narrowed proximal to its entry into the node. The anterior two thirds of the sinus node was completely replaced by dense fibrosis, while the posterior third was essentially normal although of small volume.

Case 5. Three years before his death this 23-year-old man had influenza and was examined by a physician who diagnosed a murmur due to a ventricular septal defect; further studies were advised but the man did not have them. He was then considered in good health until one Sunday when he came to the kitchen for a cup of tea, at which time he suddenly slumped to the floor and died in a matter of minutes. He uttered no sound and did not appear dyspneic or cyanotic.

The heart weighed 580 grams and was asymmetrically hypertrophied with the anterior wall measuring 30 mm in thickness and the septum 20 mm. There was no septal defect.

The anterior portion of the His bundle was abnormally subdivided by fibrosis. Numerous cysts or chambers were present in the central fibrous body and portions of the A-V node. One branch of the A-V node artery was markedly narrowed, as was a single branch of the sinus node artery. The sinus node was otherwise normal.

Case 6. This 71-year-old man was found dead in bed at 1:30 p.m. by his sister. He had been well the previous evening at 11 p.m. For about four years he complained of intermittent dyspnea but had not seen a physician.

The heart was markedly enlarged, weighing 690 grams and exhibiting excess thickening of the anteroseptal region where the free wall measured 32 mm (fig. 1).

Moderate fibrosis was present in the His bundle and A-V node with fatty replacement of other foci in the node. The A-V node artery was markedly narrowed within the A-V node. Dense focal fibrosis was present throughout the sinus node and at its junctions with the adjacent right atrium (fig. 5).

Case 7. A 39-year-old man went to bed in good health one night. The next morning at 7:30 a.m. his wife awakened to hear him breathing heavily and unable to speak. Within a few minutes he was dead. Two of his brothers also had died suddenly, each at the age of 25. Both were autopsied and in the one no cause of death was found. The other brother had been sitting in the kitchen talking with his girl friend when he suddenly placed his hand over his heart and fell forward dead. His autopsy revealed localized hypertrophy of the heart wall with patchy fibrosis in the involved segment. A maternal uncle was also said to have died at a fairly early age.

The heart weighed 510 grams with the anteroseptal region being 28 mm thick and the other walls of the left ventricle 12 mm.

There was reticulated fibrosis of the anterior portion of the His bundle, but the remainder of the His bundle was extensively splintered and divided throughout the adjacent central fibrous body, resembling the normal fetal appearance (figs. 6 and 7). The A-V node was smaller than
normal and contained focal fibrosis. The sinus node artery was slightly narrowed and the sinus node was abnormally fibrotic (fig. 8).

Case 8. A 15-year-old boy walked into his school one morning and was seen to hold his hand to his head. A minute or two later as he entered his classroom he again clutched his head and then his stomach and collapsed. Except for a few convulsive grunts before he died, he made no sound. For the preceding five years he had been diagnosed and treated as being epileptic but the exact basis for this diagnosis is uncertain. Once a month on the average he would have a spell in which he became glassy-eyed and quietly collapsed; he would then lie still until he came around in a few minutes, after which he was sometimes but not always amnesic for a short time. The last such attack was five days prior to death. His father died suddenly two years previously of undetermined cause. His living brother, aged 14, was diagnosed as having mitral incompetence and left ventricular hypertrophy.

At necropsy the heart weighed 475 grams and the anterior portion of the ventricular septum was 21 mm thick, the adjacent anterior wall of left ventricle 16 mm and other sections of the wall 14 mm or less. A number of small coronary arteries in the septum were narrowed.

Both the His bundle (figs. 9 and 10) and the central fibrous body adjacent to the A-V node contained numerous empty channels or cysts. The A-V node artery was 50% narrowed. The sinus node was normal.

Case 9. A 72-year-old woman was standing in the living room of her sister’s house when she suddenly collapsed and died without a sound. Although deaf since childhood, she had been considered in recent good health. The heart weighed 440 grams and showed eccentric anteroseptal hypertrophy, where the maximal thickness was 20 mm; the posterior portion of the septum measured 7 mm while the lateral and posterior walls of the left ventricle were 10 mm. Scattered small coronary arteries in the septum were narrowed by mural fibrosis.

There was focal fibrosis of varying density throughout the His bundle. Near its midpoint the His bundle had focal fat.
Case 11. Just after school this 14-year-old boy became involved in an argument and then a fight with three other boys his age. In the exchange of blows he was struck in the chest by a fist, immediately threw up his arms and collapsed backwards onto the ground unconscious. The other boys quickly summoned a teacher who applied resuscitative measures but to no avail. Three years before, this same boy had been seen at a hospital for a murmur but was told it was of no significance. All considered him to be normal and healthy and he enjoyed playing football regularly.

Asymmetrical hypertrophy of heart, which weighed 444 grams, was predominantly in the septum which measured 30 mm in thickness. The septum bulged beneath the aortic valve and the overlying endocardium was considerably thickened.

Most of the left half of the His bundle was undergoing resorption and being replaced by young fibroblasts, as is characteristic of the postnatal period in normal human cardiac development.6-9 There was some reticulated fibrosis in other portions of the His bundle and its proximal branches. The sinus node was closer to the endocardium of the right atrium than usual but was otherwise normal.

Case 12. A seventeen-year-old boy was found dead about 30 minutes after he had left a church meeting. He had been healthy and had had no recent medical attention.

The heart weighed 450 grams with predominantly anteroseptal hypertrophy. The maximal thickness there was 22 mm while the walls of the left ventricle elsewhere averaged 13 mm.

The dividing portion of the His bundle was of generous size, but the undivided segment was unusually small in diameter. The A-V node was irregular in shape and showed focal fibrosis. The A-V node artery was markedly narrowed. The sinus node was normal.

Case 13. A 23-year-old woman went for a walk one evening with two neighbor children. While sitting in a swing in a park she suddenly collapsed and died without uttering a sound. A brother had collapsed and died suddenly at the age of 10, and at postmortem examination was said to have had an enlarged heart.

At her postmortem examination the heart weighed 425 grams and showed asymmetrical anteroseptal hypertrophy, the maximal thickness measuring 20 mm; other portions of the left ventricular wall varied from 7 to 11 mm in thickness. Many of the small coronary arteries in the septum were narrowed by fibrosis.

The sinus node was located deeply in the crista terminals near the endocardium but was histologically normal. The A-V node artery was narrowed 50% by intimal hyperplasia but the node itself appeared normal. The His bundle was abnormally small in diameter (fig. 13).

Case 14. A 77-year-old man was found dead in bed early one morning. He had seemed well the previous evening and had no complaints during a drive with a friend. All considered him a healthy man and he had sought no recent medical attention.

Asymmetrical hypertrophy of the heart (520 grams) involved primarily the upper anterior septum which was 20 mm thick; other walls of the left ventricle measured 10 to 13 mm except the anterior wall which was 15. There were a number of clefts penetrating the septum from both endocardial surfaces. Extensive patchy septal fibrosis was present. The small coronary arteries appeared normal.

The right bundle branch was abnormally fibrotic in its septal course, while the left branch was fibrotic near its origin from the His bundle. Scattered fibrosis was seen in

Throughout its left half. Just posterior to that point nearly three quarters of the His bundle was replaced by fat. Near the junction with A-V node there were many nodal and His bundle strands weaving throughout the central fibrous body in a pattern resembling the state in the human fetal heart.

Some of these included Mahaim type connections directly to the crest of the ventricular septum (fig. 4). The sinus node had focal fat and fibrosis in its anterior third, was densely fibrotic in its middle third and only minimally fibrotic in its posterior third. The sinus node artery was thickened.

Case 10. An eleven-year-old girl was standing in the lunch line at school when she suddenly collapsed without a sound. A teacher attempted resuscitation without success. The girl had made no complaints to those around her and had always been thought to be healthy.

At necropsy the heart weighed 250 grams and was asymptomatically hypertrophied. The left ventricular wall measured 19 mm thick anteriorly near the septum, 13 mm laterally, and 11 mm posteriorly; the septum was 11 mm thick posteriorly.

The His bundle was rather short, quickly dividing into right and left branches. There was extensive scattering of the A-V nodal and His bundle cells throughout the central fibrous body in the typical fetal pattern (figs. 11 and 12). The A-V node itself was small. The sinus node was also small in size, with a few abnormal foci of fat at its junction with the right atrium.
the His bundle and the A-V node. The A-V node artery was markedly narrowed proximal to its entry into the node. There was extensive fatty fibrosis surrounding the sinus node, virtually severing its connections with the right atrium. The substance of the sinus node itself was densely fibrotic.

Case 15. A four-year-old girl appeared to be in her usual health while walking up a hill with her aunt. Suddenly she complained of feeling tired and almost immediately collapsed onto the ground. Her aunt lifted her up and ran to a hospital which was only 200 yards away, but the girl was found to be dead. The child had been having cyanotic attacks since the age of 6 months and was known to have a harsh aortic systolic murmur and evidence of left ventricular hypertrophy on her electrocardiogram. However, she had been well recently.

The heart weighed 175 grams, being moderately enlarged for this age. Hypertrophy of the left ventricle was asymmetrical with the anterior wall measuring 10 mm, septum 19 mm, posterior wall 11 mm and lateral wall 8 mm in thickness.

There were extensive divisions of the His bundle and A-V node coursing within the central fibrous body in a fetal pattern not normally present at the age of 4 years. The A-V node artery was only slightly narrowed but the sinus node artery was 50% narrowed within the node itself.

Case 16. A 48-year-old woman and her husband went to visit her sister, where she went to bed in apparent good health. About 1 a.m. the husband was awakened by her getting out of bed, shortly after which he heard a thud. He got out of bed to investigate and found his wife dead on the floor in the bathroom. She had made no complaint.

The heart was asymmetrically hypertrophied and weighed 470 grams. The anterior left ventricular wall was 15 mm, the septum 19 mm, the posterior wall 11 mm and the lateral wall 13 mm in thickness. Many small coronary arteries were abnormally narrowed within the septum. Numerous clefts were present in the septum.

Within the right bundle branch there was an abnormal group of vein-like channels similar to those of case 8 (figs. 9 and 10). The His bundle and A-V node were normal. The sinus node was densely sclerosed by collagen and virtually destroyed (fig. 14). The sinus node artery was moderately narrowed.
**ASYMMETRICAL HYPERTROPHY OF THE HEART**

**Figure 7**

Histological appearance of the normal human fetal A-V node in A can be compared to that of the A-V node from case 7 in B. In both there is the same widespread dispersion of nodal tissue throughout the central fibrous body, but in the fetus the collagen of the central fibrous body has not matured to its compact adult acellular consistency.

**Case 17.** A 30-year-old woman was chatting with her husband shortly after tea one afternoon. He left the room and when he returned ten minutes later she was dead. She had never been noticed to have peculiar heart beats or fainting attacks.

At postmortem examination the heart weighed 500 grams and was asymptomatically hypertrophied with the lower two thirds of the septum being 20 mm thick, the adjacent anterior wall 15 mm and other sections being 13 mm.

The His bundle was fibrotic to a moderate degree and exhibited a few focal hemorrhages. The A-V node artery was markedly narrowed (fig. 15). There was focal fatty degeneration in the anterior third of the sinus node but the remainder of the node was normal.

**Case 18.** A fourteen-year-old schoolgirl was considered in good health when she suddenly collapsed just as she was entering the doorway to the lunchroom. She did not respond to resuscitative measures and was declared dead on arrival at a hospital a short time later. Six years previously she had been found to have a murmur of mitral incompetence. One year previously (her most recent examination) the electrocardiogram showed inverted T waves as well as left ventricular hypertrophy. She had no orthopnea or palpitations and was considered well until her death.

The heart weighed 590 grams and the septum visibly bulged into the left ventricular outflow region; at this point the septum was 30 mm thick. The anterior, lateral, and posterior walls of the left ventricle measured 23, 18, and 16 mm in thickness, respectively. There was also some hypertrophy of the right ventricle and of the atria, but the predominance of the left ventricle was clear.

Slight fibrosis of the His bundle was present. Numerous large divisions of the A-V node branched into the adjacent central fibrous body in a fetal pattern. The sinus node artery was slightly thickened but the sinus node appeared normal.

**Case 19.** A 26-year-old woman was walking from her home to a shop when she was seen to slump over a wall by the roadside. A passing motorist stopped to assist her when she fell to the ground and was found to be dead. Seven months previously she had collapsed on the roadway while running for a bus but recovered and was said to have no abnormality at a hospital examination. Between then and her death she had a number of attacks of lightheadedness and fainted several times while rushing around. A doctor who examined her for this one month before her death found nothing abnormal.

At postmortem examination the heart weighed 250 grams. There was asymmetrical thickening of the wall of the left ventricle, being 17 mm anteriorly, 16 mm in the septum, 10 mm posteriorly and 11 mm laterally. There were a number of septal clefts connected to both endocardial surfaces; their
indentation in some places gave a lobulated appearance to the septal surface.

Although the A-V node and sinus node appeared normal in size, location and histological organization, the His bundle was abnormally small in diameter (fig. 13).

Case 20. A 47-year-old woman was getting ready to go to church. When her husband returned to the bedroom, having been gone about 15 minutes to shave, he found her collapsed on the bedroom floor. She tried to speak but could not. Efforts to revive her were unsuccessful and she died within a few minutes.

The heart weighed 500 grams and was asymmetrically hypertrophied, the left ventricular thicknesses being 14, 19, 12 and 10 mm for the anterior wall, septum, posterior wall and lateral wall, respectively. Although the membranous septum was intact, it was unusually large (10 mm diameter). There were many thickened small coronary arteries in the septum.

Focal fibrosis and fat were present in the His bundle and A-V node, but the node was fragmented throughout the central fibrous body in a fetal pattern. The fragments were undergoing resorption in some areas but not in others. There were dense scars of collagen and large foci of fat at the junction of the sinus node with the right atrium.

Case 21. A 17-year-old boy was running to catch the last bus home near midnight when he staggered and fell on his face. Two women talking in a nearby doorway came to his aid; one felt a pulse which then disappeared. When the police arrived five minutes later he seemed dead. However, an ambulance arrived about the same time and resuscitation was continued enroute to a hospital, where ventricular fibrillation was seen in an electrocardiogram. This was reverted to a more stable rhythm by countershock but then quickly lapsed back to ventricular tachycardia. Over the next few hours a stable cardiac rhythm could not be maintained despite repeated efforts and a terminal bout of ventricular fibrillation failed to respond at all.

Fifteen months previously he was running across a street and also had collapsed. Passersby applied external cardiac massage until a cardiac ambulance arrived in nine minutes. At that time he was also found to have ventricular fibrillation, which was reverted to sinus rhythm by three countershocks. During his convalescence in a hospital the electrocardiogram revealed left ventricular hypertrophy. Cardiac catheterization was performed and said to have shown no outflow tract obstruction in the left ventricle. The discharge diagnosis was ventricular fibrillation of unknown etiology. Over the intervening months he was seen at regular intervals as an outpatient. During that period he gradually developed an ejection systolic murmur at the left sternal border and increasing evidence of “ischemia” in the electrocardiogram. It was then decided that he must have a cardiomyopathy. The last examination had been two months prior to death.

At postmortem examination the heart weighed 520 grams and exhibited asymmetrical anteroseptal hypertrophy of the

Figure 9
Numerous spaces or channels in the His bundle of case 8 are shown here at two magnifications. Of the three asterisks marking the spaces in A the two to the left are enlarged in B.

Figure 10
Other spaces in the His bundle of case 8 are shown here about 1 mm away from those in figure 9.
ASYMMETRICAL HYPERTROPHY OF THE HEART

Fetal dispersion of the His bundle is illustrated with two sections from the heart of case 10. The His bundle is seen near its nodal junction in A and is just veering into the central fibrous body, while B is 160 microns further anterior. As in the normal fetal heart, most of the tenuous fascicles of the His bundle are in its left half. These are normally eliminated during the first year of postnatal life.

left ventricle. The anterior wall was 20 mm thick, the adjacent septum 23 mm, the posterior wall 13 mm and the lateral wall 13 mm. There were many narrowed small coronary arteries in the septum (fig. 3).

A minor degree of fibrosis was seen in the His bundle. The A-V node was normal but its artery was markedly narrowed (fig. 15). The sinus node was normal although its nutrient artery was considerably smaller in caliber than usual (but of normal histological structure).

Case 22. A 13-year-old boy was last seen by his parents in mid-afternoon when he was watching television. Shortly after they left the house, he went to play with a friend but the friend was not home. When the friend returned home about 15 minutes later, his mother told him of the call and he went to the boy’s home where he found the boy lying dead on the front lawn near a football. A soft systolic murmur had been known for several years but an electrocardiogram was said to be normal and the boy was considered in good health. A brother had suddenly dropped dead at the age of nine years; he had had a mitral systolic murmur for at least three years but was considered to be in good health. At postmortem examination there was asymmetrical hypertrophy of the brother’s heart.

In the present subject the heart weighed 530 grams at postmortem examination, and there was also asymmetrical hypertrophy of the left ventricle. The anterior wall measured 12 mm in thickness, the adjacent septum 17 mm, the posterior wall 10 mm and the lateral wall 11 mm. There were a large number of clefts in the septum, extending inward from both endocardial surfaces in all directions (figs. 16 and 17); each was lined by endocardium and ended in a blind pocket, not being connected to either veins or arteries. There was degeneration in the tunica media of many small coronary arteries in the septum but no significant narrowing of their lumens.

The A-V node was filled with cysts or channels, which were associated with wide dispersion of A-V nodal fragments in the central fibrous body into a fetal pattern (figs. 18 and 19). The sinus node and its artery appeared normal. Focal fibrosis was present in the right bundle branch, but even more impressive was an extensive honeycombing of both the right and left bundle branches as well as the His bundle itself by empty channels (figs. 20-22).

Summary of Findings

Mode of Death. Death was witnessed in 16 of these 22 subjects. In every case it was virtually instantaneous and silent. One child did complain of being tired just before collapsing, and two adult victims tried to speak but were unable, but in all 13 others there was not even an effort to utter a word. Most
strenuous despite difficulty deaths occurred during rest rather than exertion and during the waking hours. In case 21 there was documented ventricular fibrillation and great difficulty in restoring an effective cardiac rhythm despite strenuous medical efforts. This same young man had experienced ventricular fibrillation and collapse from which he had been successfully resuscitated 15 months previously.

Familial History. Four of the 22 subjects had other family members with either probable or proven asymmetrical hypertrophy of the heart. Two brothers of case 7 had each died suddenly at the age of 25 years; both were autopsied and in one the heart was asymetrically hypertrophied. A brother of case 8 is alive but has mitral incompetence and left ventricular hypertrophy; the father had died suddenly of unknown cause. A brother of case 13 suddenly collapsed while running and died without warning; autopsy disclosed an enlarged heart. A brother of case 22 was known to have a mitral systolic murmur when he suddenly died at the age of 9; at autopsy there was asymmetrical hypertrophy of the heart.

Clefts in the Septum. In seven of the 22 hearts there were deep clefts into the interventricular septum entering from either or both endocardial surfaces. In cases 1, 3 and 22 (figs. 16 and 17) these were particularly numerous and exceptionally deep, coursing both in a transverse and vertical plane within the septum. They did not communicate with either arteries or veins. None crossed all the way from one ventricle to the other.

Small Coronary Arteries. Significant narrowing of multiple small arteries in the septum was present in ten hearts (figs. 1–3), and lesser abnormalities were found in some of the other hearts. This is a difficult matter to quantify, even with postmortem arteriography or several similar proposed approaches to the question; however, arteriography was not attempted in this series. It is our judgment that more arteries were more narrowed than normal in the ten hearts,
and that the narrowing could have accounted for some focal ischemia and fibrosis. The foci of narrowing were more often in sections of myocardium rather than in fibrotic areas, although some occurred in the latter as well.

**Sinus Node.** Abnormal fibrosis was present in the sinus node of 12 of the 22 hearts (figs. 5, 8 and 14). This was about as often associated with or independent of any narrowing of the sinus node artery or its branches. In all of these examples there was sufficient histological abnormality to question normal stable performance by the sinus node, and in some the scirrhous destruction was so extensive as to suggest that the sinus node could not perform normally at all.

**Fetal Pattern of A-V Node and His Bundle.** Most of the hearts exhibited more fragmentation or divisions of the body of the A-V node or His bundle than is usual, but in 13 of the 22 this was particularly conspicuous (figs. 4, 6, 7, 11, 12, 18 and 19). This extent of superfluous tissue is characteristic of the human fetal heart but normally disappears or becomes greatly diminished during early postnatal life.8, 9

At the other extreme there was focal fibrosis or fatty replacement of A-V node or His bundle in some hearts as indicated, and the A-V node artery was variably narrowed in many of these (fig. 15). In three hearts the diameter of the His bundle was abnormally small in cross-section (fig. 13).

**Central Fibrous Body.** There were multiple cysts or channels within the central fibrous body of four hearts, and in all four of them there were comparable abnormal spaces within the substance of the A-V node and His bundle (figs. 4, 9, 10 and 18–22). Two of these (cases 1 and 22) also had multiple clefts in the interventricular septum, but the other two (cases 8 and 9) did not.

**Discussion**

There are four aspects of asymmetrical hypertrophy of the heart which we wish to discuss based on our findings and in the light of observations by others: the pathogenesis and clinical significance of atrial fibrillation, the deep clefts seen in the interventricular septum of some of the hearts, mechanisms of sudden death, and the pathogenesis of asymmetrical cardiac hypertrophy.

**Atrial Fibrillation**

At least three of Teare's nine cases were known to have had atrial fibrillation and each had complained of palpitations.1 However, subsequent studies by others indicated that this arrhythmia was rare until the matter was specifically investigated by Glancy and his colleagues.10 Their study established that atrial fibrillation was not rare, being observed in 16 of 167 patients, that it was unrelated to the severity of left ventricular outflow obstruction, that in most patients sinus rhythm could only be restored transiently, but that the onset of atrial fibrillation was often associated with obvious clinical deterioration. Why atrial fibrillation should develop in these patients was not explained.

In 12 of our 22 cases the sinus node was histologically abnormal. Impairment or loss of its pacemaking control of the heart may be an important contributory factor in the development of atrial fibrillation. The fact that sinus rhythm is difficult to restore and retain (reference10 and our case 21) supports the likelihood that the sinus node functions abnormally in these patients. Since many patients with asymmetrical hypertrophy of the heart undergo special hemodynamic and electrophysiological studies, it should not be difficult to study function of the sinus node carefully in them.

Braunwald and his colleagues11–12 have discussed four physiological mechanisms by which atrial fibrillation could lead to the observed rapid clinical deterioration. 1) Loss of atrial systolic contribution to ventricular filling. 2) Rapid ventricular rate in untreated patients, with diminished time for diastolic

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*Figure 15*

Two examples of narrowing of the A-V node artery are shown in A (case 17) and B (case 21). A has more endothelial proliferation while B shows predominantly subintimal fibrosis, but the net effect in both was a narrowed lumen. The stain in A is Verhoeff-Van Gieson.
filling in stiff hearts and thereby net loss of cardiac output. 3) Positive inotropic effect of short cardiac cycles just after long ones during the irregular rhythm, causing increased outflow tract obstruction; this would be compounded by the reflex sympathetic effect of intermittently lowered cardiac output and aortic hypotension. 4) Inability of these patients to increase stroke output which should normally occur during long cardiac cycles, which also are present during irregular cardiac rhythms.

To these hemodynamic consequences of atrial fibrillation may be added two electrophysiological considerations. First, during atrial fibrillation the excitatory input to the A-V node is constantly variable and the A-V nodal activation front would be changing. If one then assumes there is normally longitudinal dissociation in the His bundle,\textsuperscript{13-18} then the sequence of ventricular activation would also be changing, a condition which would be expected to impair performance of an asymmetrically hypertrophied heart. Moreover, in many of the hearts in our series there was structural abnormality in the A-V node and His bundle of such a nature as to make altered activation sequences even more likely during atrial fibrillation. Second, the rapidly changing cardiac cycle lengths during atrial fibrillation might readily exceed the refractory period of portions of the His bundle or its branches even with little or no change in the activation front within the A-V node, again leading to variation in the sequence of ventricular activation. How atrial fibrillation may also be responsible for sudden death will be considered later.

**Septal Clefts**

Teare noted large clefts between muscle bundles in two of his hearts, in one of which they communicated...
with both ventricular chambers. We found no example of complete trans-septal continuity, but there were septal clefts in seven of our 22 hearts. As Teare indicated, these are endothelial lined channels but give no evidence of being Thebesian or arteriocameral vessels. They do not appear to be the consequence of muscular tears or separation during life, nor post-mortem artifacts.

It is unclear what these septal clefts represent or what their functional significance may be. They may serve as slippage planes for a muscle-bound heart. Because they course in a variety of directions, they must have a mechanical influence on the sequence and the efficiency of septal contraction. Recent echocardiographic studies have suggested that the septum in these patients moves little if at all, but it would be useful to know if there is any evidence of fractionation of movement or paradoxical motion of segments of the septum. The mechanical impairment may influence not only the septum but also the ventricular walls attached to it, and even the performance of the mitral valve apparatus. Shifting of a portion of the septum via these cleavage planes could account for the left ventricular-aortic offset which Burchell has described. Finally, it would not seem possible for electrical activation to cross these abundant clefts, making derangement or impairment of septal electrical activation still an additional burden.

**Sudden Death**

A number of possible mechanisms of sudden death are suggested by the variety of pathological changes found in the sinus node, A-V node and His bundle of these patients. In previous reports of this series we have discussed how a narrowed A-V node artery might be responsible for sudden death, and in other

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*Histological appearance of the clefts of case 22 is illustrated. These photomicrographs are from two different areas in a section 8 microns from the one in figure 16B.*
examples how diseases of the sinus node\textsuperscript{20-23} or of the His bundle\textsuperscript{22-25} could be quickly lethal. All of these have as a final common pathway the production of fatal cardiac electrical instability of one form or another. In the present discussion we wish to concentrate on three topics: atrial fibrillation, the fetal pattern of the A-V node and His bundle, and the significance of eccentrically distributed increased myocardial mass.

That the onset of atrial fibrillation rapidly leads to clinical deterioration of patients with asymmetrical hypertrophy of the heart has been clearly demonstrated by Glancy et al.\textsuperscript{10} Theirs were cases under direct observation, and one can only conjecture about the fate of patients who developed atrial fibrillation at home or otherwise not under medical supervision. However, based on the severity and speed of observed clinical deterioration, and on the extent and prevalence of histopathological abnormalities in the sinus node of our own cases, one would expect that paroxysmal atrial fibrillation must be more frequent in patients with asymmetrical hypertrophy of the heart than has been or perhaps can be documented. In some of these the speed of clinical deterioration may terminate in sudden death.

Atrial fibrillation may more directly have lethal consequences under special circumstances. Patients with the Wolff-Parkinson-White syndrome are one example,\textsuperscript{26} and young mammals of several species are another.\textsuperscript{27} In both examples ventricular fibrillation has been observed shortly after the onset of atrial fibrillation and has been attributed to the failure of a normal protective delay usually introduced by relatively slow conduction through the A-V node. One electrocardiographic feature of patients with asymmetrical hypertrophy of the heart is a short P-R interval.\textsuperscript{28-32} In

Figure 18

*Multiple cysts or faults in the central fibrous body of case 22 are associated with a fetal dispersion of A-V nodal fragments. Some of the fragments (open arrow in B) come very near the interventricular septum but these did not connect with it. A is a section 40 microns from that in B.*
our own cases the large number of accessory routes for potential short-circuiting between the atrial and ventricular septa via the central fibrous body are similar to ones which have been described in the Wolff-Parkinson-White syndrome. In many respects this A-V junctional histology resembles the fetal pattern of the human A-V node and His bundle. Thus, the onset of atrial fibrillation in patients with asymmetrical hypertrophy of the heart may in rare instances be followed by ventricular fibrillation.

Ventricular fibrillation is sometimes (rarely) self-terminating, but the likelihood of this in the patients being discussed may be reduced by two factors. Their inordinately large and eccentrically hypertrophied hearts offer the physiological substrate (large myocardial mass) for continued fibrillation; e.g., difficulty in terminating ventricular fibrillation in hypertrophied hearts is well known among cardiovascular surgeons who face the problem during surgery. A second disadvantage is the prevalence of abnormalities of the sinus node in our cases, and the reported difficulty in restoring sinus rhythm during atrial fibrillation in such patients, both suggesting that the fundamental rhythm in such patients is not a stable one.

**Pathogenesis of Asymmetrical Hypertrophy**

Just as it was apparent that no single mechanism could be invoked as the likely explanation of sudden death (although most cases probably terminate with ventricular fibrillation eventually), it seems equally unlikely that hearts become asymmetrical hypertrophied because of a single fault. It is already known that asymmetrical hypertrophy can indeed be secondary to a variety of mechanisms, including demonstrable preceding forms of cardiac disease. Perhaps we should be less surprised that hearts can grow lopsided as they hypertrophy than that it does not happen more often. Eccentric stress of any pump would teleologically be anticipated to produce an eccentric response. The restorative adaptability of the myocardium to prevent this must be controlled by some exceptionally sophisticated system. How this intricate control could become deranged includes many possibilities, such as some forms of valvular disease or focal myocardial abnormalities, but we wish here to consider three possibilities in the light of our own observations: 1) pathology of the small coronary arteries, 2) abnormal A-V conduction tissues, 3) abnormal collagen.
In about half of our cases there were abnormally narrowed small coronary arteries. Teare has commented that the vascular supply of the area of principal hypertrophy appeared to have diminished blood supply.\textsuperscript{1, 30} Friedreich's ataxia is sometimes associated with cardiac enlargement and an increasing number of observers have noted that there may be asymmetrical hypertrophy.\textsuperscript{31-33} Abnormal small coronary arteries do occur in the cardiomyopathy seen with Friedreich's ataxia,\textsuperscript{32, 43} but there may be additionally some abnormality in neural control of myocardial contractility in such patients. Furthermore, while about half of our patients had abnormal small coronary arteries, the others did not. Focal ischemic fibrosis and abnormal compensatory hypertrophy may thus play a role in some cases of asymmetrical hypertrophy of the heart but this cannot be the only cause. How important this role is remains to be determined, although it is difficult to believe that focally abnormal coronary supply could be insignificant.

A variety of abnormalities were observed in the A-V conduction system of most of our patients, including focal fibrosis and narrowing of nutrient arteries, but one which may be of particular importance is the persistence of a fetal pattern in the histological anatomy of the A-V node and His bundle. It has already been indicated that this may be an anatomic substrate for abnormally rapid A-V conduction, bypassing the A-V node via the central fibrous body. This weaving eccentricity of normal tissues may also lead to desynchronization of the usual activation process for either the septum or the free walls of the left ventricle. Abnormal sequence or speed of activation of the interventricular septum and ventricles deserves further consideration as a possible factor in the pathogenesis.
of asymmetrical hypertrophy of the heart,45-52 and our anatomical findings support this hypothesis. Whether this form of desynchronized septal or other activation need be associated with currently recognized electrocardiographic or vectorcardiographic abnormalities is uncertain, although short P-R intervals are already one frequently described feature. But as with changes in the small coronary arteries, not all of our hearts had a fetal pattern of their A-V node or His bundle so that this cannot be a sole explanation.

Finally, there is reason to suspect a primary abnormality of collagen in these hearts. Dense sclerotic fibrosis of the sinus node was out of keeping with the observed local vascular disease, and similar abnormalities have been noted in patients with scleroderma heart disease.53 The central fibrous body of at least two of our hearts contained cyst-like chambers or channels of an appearance suggesting a fundamental developmental fault similar to that also observed in the Wolff-Parkinson-White syndrome.53, 54 In addition to abnormal influence on fetal and postnatal development of the A-V node and His bundle, these changes in the central fibrous body may be mechanically important because this structure probably serves as a functional fulcrum for normal motion by three neighboring cardiac valves (mitral, aortic and tricuspid).8, 54 If the collagen of the central fibrous body is representative of nearby collagen in the crest of the ventricular septum, then abnormal properties of the septal collagen may prevent its serving as an appropriate framework for myocardial hypertrophy, with an ultimate consequence being disorderly or bizarre septal histology.

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T N James and T K Marshall

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