Familial Muscular Subaortic Stenosis

An Unrecognized Form of "Idiopathic Heart Disease," with Clinical and Autopsy Observations

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SUBAORTIC stenosis has been regarded as a rare condition, usually caused by an easily demonstrable fibrous ridge attached to the left ventricular myocardium below the aortic valve. Our recent experience, however, suggests another form of subvalvular stenosis that is caused by muscular hypertrophy, occurs with multiple cases in an affected family, requires special attention in differential diagnosis, and is not operable.

Recently, variant types of aortic stenosis have been encountered in the laboratory and at the operating table.[1-5] Preoperative tests may show a significant systolic pressure gradient between the left ventricular outflow tract and the aorta, which is considered an indication for surgical relief of the obstruction, whether valvular or subvalvular in location. Subsequent operation occasionally reveals an atypical obstruction[6, 7] apparently caused by muscular hypertrophy, which cannot be repaired.

Our interest in subaortic stenosis was aroused by a patient in whom a clinical diagnosis of aortic stenosis was made, but at operation no aortic or subaortic stenosis could be demonstrated. The patient died postoperatively of acute tubular necrosis, and at autopsy a "functional" muscular obstruction of the left ventricular outflow tract was found.

Because of a strong history of heart disease and sudden death in the patient's family, a survey was made of the remaining members. Several months later an uncle of the patient who had been examined in the survey dropped dead in his home, and at autopsy the findings in the heart were identical. Then a third patient was studied, unrelated to the first 2, but with similar clinical findings and a strong family history of heart disease. About 6 weeks later this patient also died suddenly at home. Autopsy revealed the same cardiac changes. The clinical and autopsy observations are presented in this report, along with the family pedigrees suggesting familial heart disease with Mendelian dominant inheritance.

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Case Reports

Family A

Patient 1A

A 29-year-old white man was first seen at age 18 years by his local physician in 1947, after being rejected from military service because of a heart murmur. He had no complaints at that time and there was no past history of rheumatic fever or of other heart disease. Examination showed slight cardiac enlargement, an aortic systolic murmur, and a blood pressure of 124/60. In 1957, 10 years later, he was hospitalized because of palpitation and a rapid heart rate of 4 years' duration. The blood pressure then was 140/70. There was slight cardiomegaly and a grade-III systolic murmur at the apex and along the left sternal border. The chest roentgenogram showed left ventricular enlargement, and the electrocardiogram demonstrated high voltage over the left chest leads. He was treated with digitalis and quinidine with some relief of the palpitation.

He was admitted to the Presbyterian Hospital Unit of the University of Pittsburgh Medical Center at the age of 29, complaining again of palpitation and dyspnea on effort for 4½ years. There were 3 or 4 syncopal attacks in the 2 years preceding admission. He was constantly fatigued and noted swelling of his ankles on occasion. The family history revealed one brother who had died suddenly at age 29 (patient 3A) of "rheumatic"

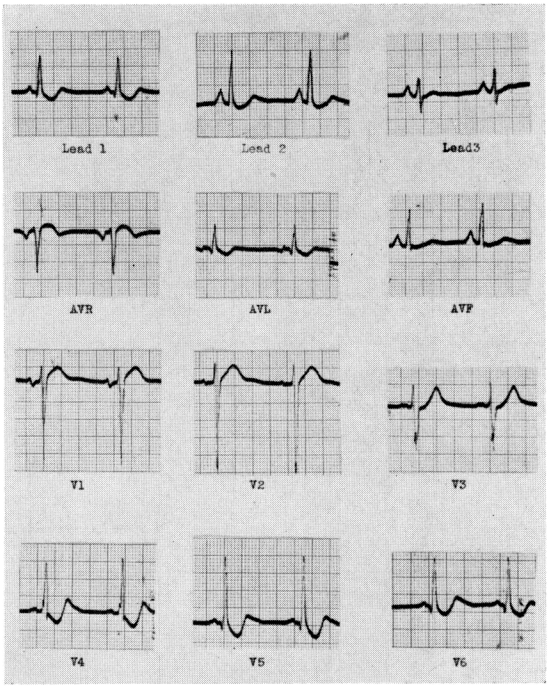

Figure 1

Electrocardiogram of patient 1A.

heart disease, a nephew, (patient 4A) who had surgical exploration in another hospital for pulmonic stenosis, and his father who died of heart disease in 1953.

The blood pressure was 150/70, and the heart rate was regular at 96 per minute. There were no signs of congestive heart failure and no cyanosis. A vigorous apical pulsation was palpable in the fifth and sixth left intercostal spaces, 2 cm. to the left of the midclavicular line, and a systolic thrill was felt at the apex and lower left sternal border. A harsh, musical, grade-IV systolic murmur was heard loudest at the apex and along the lower left sternal border, but transmitted clearly to the neck, axillae, and posteriorly. The aortic and pulmonic second sounds were of normal intensity. There was an apical presystolic and protodiastolic gallop not affected by deep inspiration. The peripheral arterial pulses were all of equal intensity and appeared widened in amplitude with a definite pulsus bisferiens.

The laboratory data, including urinalysis, hemogram, blood sugar, blood urea nitrogen, electrolytes, proteins, and prothrombin concentration were normal. The serum cholesterol was 290 mg. per cent and the protein-bound iodine was 4.4 gamma per cent. The antistreptolysin O titer was normal and C-reactive protein was negative. The electrocardiogram demonstrated left ventricular

Table 1

Right and Left Heart Catheterization

Position	Family A Patient 1 Pressures mm. Hg Systolic/Diastolic (mean)	Family B Patient 1
Left atrium	(12)	(14)
Left ventricle	226/12	134/12-14
Aorta, arch	131/71 (90)	84/52 (66)
Right atrium	(1)	(4)
Right ventricle	32/1	24/4-6
Pulmonary artery	26/5 (13)	24/13 (17)
Surface area $M.^2$	1.6	1.5
O_2 consumption ml./min.	225	221
Cardiac index L./min./$M.^2$	2.3	3.16
Aortic valve area $cm.^3$	0.5	0.8

preponderance (fig. 1) and the chest x-ray film (fig. 2) showed a normal-sized heart with a contour suggesting left ventricular enlargement. On fluoroscopy, the left ventricle alone appeared enlarged. The aortic and pulmonary artery pulsations were normal. There was no poststenotic dilatation of the aorta and no calcification of the aortic valve. A combined heart catheterization was performed, including a standard right heart catheterization and percutaneous left atrial puncture (table 1). Simultaneous left ventricular and left brachial artery tracings demonstrated "severe aortic stenosis" with a calculated valve orifice[8] of 0.5 $cm.^2$ (fig. 3).

On May 5, 1958, the patient underwent open-heart surgery with total cardiac bypass and cardiac arrest with potassium citrate. The ascending aorta was opened with a longitudinal incision and the aortic valve was found to be perfectly normal. The surgeon passed his finger down into the outflow tract of the left ventricle and found no evidence of subvalvular stenosis. Exploration of the right ventricle revealed a markedly hypertrophied ventricular septum and a small right ventricular chamber. After restoration of cardiac activity, direct recordings again demonstrated a systolic pressure gradient between the left ventricular outflow tract and the aorta. The immediate postoperative course was complicated by high fever, blood loss, hypotension, and finally acute renal damage, resulting from sustained hypotension or from incompatible blood. He died 8 days postoperatively of uremia.

Autopsy Findings. The principal anatomic findings were subaortic stenosis of a muscular hypertrophy type and acute tubular necrosis. Other

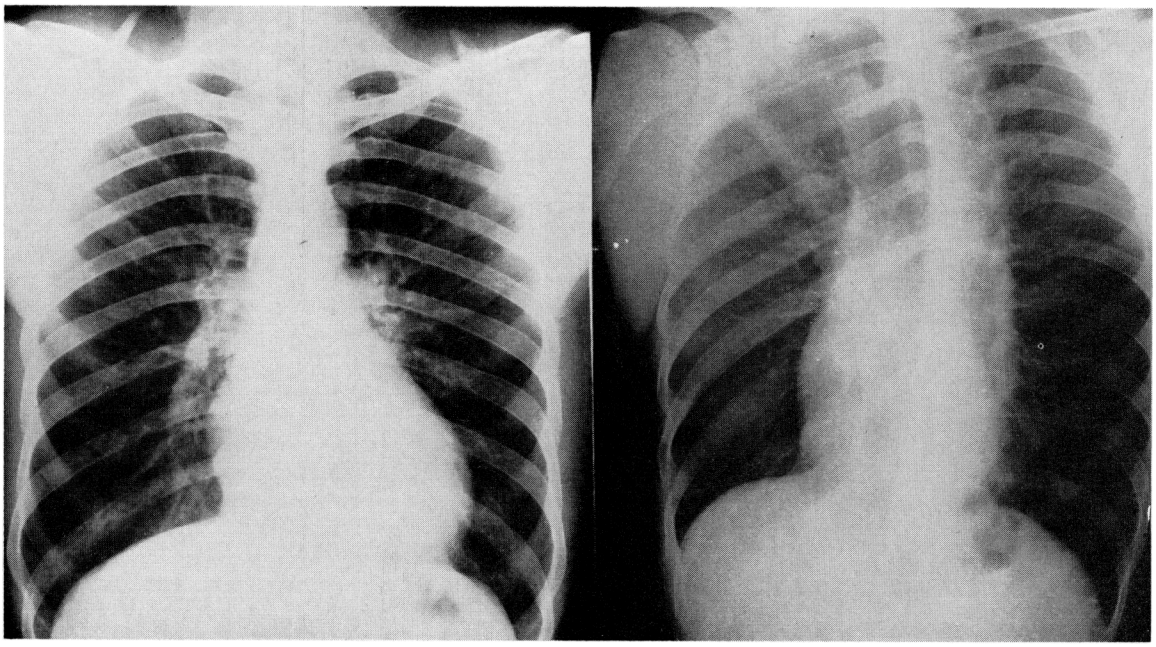

Figure 2

Posteroanterior and left anterior oblique roentgenograms of patient 1A.

pertinent findings were bronchopneumonia, a postoperative hematoma of the anterior mediastinum, bilateral hemothorax, and infarcts of the spleen and right kidney.

The heart was globular and large, weighing 560 Gm. The aortic valve was normal. A finger was easily inserted through the valve but approximately 2.5 cm. from the valve it met some resistance, but not complete obstruction, from a prominent muscle mass in the area of the interventricular septum. A similar muscle mass was felt protruding into the outflow tract of the right ventricle, again in the area of the septum. When the heart was opened, striking hypertrophy of the myocardium of the entire left ventricle was demonstrated. The septal muscle bulged into the left and right ventricles (figs. 4 and 5). The hypertrophy was especially prominent on the left side of the heart, and as the heart was closed and viewed from above, the obstruction of the left ventricular cavity could be seen at a level 2.5 cm. below the base of the aortic valve. Below this level the cavity of the left ventricle was greatly narrowed. Above the obstruction the outflow tract was dilated to form a small chamber, extending up to the valve. The endocardium over the upper portion of the hypertrophied muscle mass was thick, opaque, and gray-white, but it did not form a fibrous ridge or shelf and did not contribute to the obstruction of the outflow tract. The aortic and mitral valves were normal, except that the aortic valve was small, measuring 5.0 cm. in circumference. The mitral valve measured 7.5 cm. in circumference. The left ventricular wall measured 2.3 cm. in average thickness and the interventricular septum measured 3 cm. in thickness. The tricuspid and pulmonic valves appeared normal. The tricuspid valve measured 10.5 cm. in circumference, the pulmonic 5.5 cm. There was slight patchy thickening of the endocardium of the right ventricle. The coronary arteries were patent and smooth throughout.

Microscopic examination of the heart (fig. 6) showed moderate enlargement of the individual fibers. In a few areas the muscle fibers had a bright pink, smudged appearance which was regarded as a terminal change, probably related to the ischemia at operation. There were patchy areas of interstitial fibrosis and occasional small areas of replacement fibrosis. Sections of the left ventricle in the subaortic region showed irregular thickening and increased fibrous tissue in the endocardium and the underlying myocardium (fig. 7). The fibrosis did not extend deeply into the myocardium and there were no vascular changes in this region. Masson's trichrome stains showed an increase in collagen. No increase in elastic fibers was demonstrated by Verhoeff elastic tissue stains.

Patient 2A

Patient 2A was the 54-year-old paternal uncle of patient 1A. He was examined in August 1958 during a survey of the family. He had noted

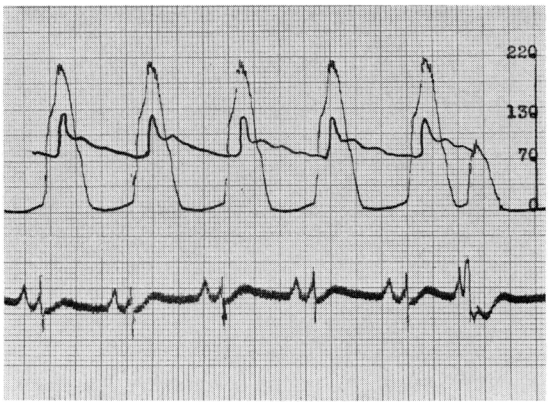

Figure 3

Superimposed, simultaneous pressure tracings obtained in the left ventricle and left brachial artery in patient 1A.

dyspnea on exertion and frequent palpitation of several years' duration. Several months previously he had also experienced a syncopal attack while at work as a lumberjack. He denied orthopnea, chest pain, paroxysmal nocturnal dyspnea, and edema. He had never been told he had high blood pressure. During hospitalization for operative repair of a perforated peptic ulcer in 1951 no cardiovascular complaints were elicited. Physical examination then demonstrated no cardiac enlargement, the blood pressure was 134/76, and there was a systolic murmur at the apex. In August 1958, the blood pressure was 130/80 and the heart was regular at 84 per minute. There were no signs of congestion nor cyanosis. The heart was enlarged 2 cm. beyond the midclavicular line in the sixth left intercostal space. There was a vigorous apical thrust and a harsh, grade-III systolic murmur was heard over the precordium, loudest at the apex and along the lower left sternal border, well transmitted to the aortic area and neck. The aortic and pulmonic second sounds were of equal intensity. The pulses were thought to be normal to palpation. The electrocardiogram demonstrated high voltage over the left precordial leads, but no evidence of strain. Hospitalization was advised for special diagnostic tests, but was refused. His condition did not change until December 24, 1958, when he suddenly dropped dead.

Autopsy Findings. No arterial or venous anomalies were found. Externally the heart exactly resembled that of patient 1A. It also weighed 560 Gm. When the finger was inserted through the aortic valve, the valve appeared normal but considerable resistance was encountered in the outflow tract approximately 1.5 cm. below the valve. The finger was pushed through this narrowed area with considerable difficulty, although no fibrous bands or valves were encountered. The resistance was obviously caused entirely by muscular hypertrophy of the ventricular wall. A prominent muscle mass was encountered below the pulmonic valve but there was no obstruction.

When the heart was opened, the upper portion of the muscle mass and the obstruction were encountered 1.5 cm. from the base of the aortic valve (fig. 8). The outflow tract was somewhat dilated above this level and below it the cavity was almost completely obliterated. The myocardium of the left ventricle averaged 2.0 cm. in thickness, and the interventricular septum measured 2.5 cm. in thickness. The valve circumferences were as follows: tricuspid 12 cm., pulmonic 7 cm., mitral 10 cm., and aortic 6.5 cm. The coronary arteries contained a few small atheromata but there was no stenosis. The other findings were similar to the first case. Microscopic examination showed only slight endocardial thickening with no involvement of the myocardium. Again the individual muscle fibers were hypertrophied. There were no vascular changes.

Patient 3A

Patient 3A was a brother of patient 1A. His local physician first saw him in 1936 at age 16 years because of pneumonia. A systolic murmur was noted then but there were no cardiovascular symptoms. In November 1947 he was hospitalized with infectious hepatitis. He had shortness of breath on exertion and a nonproductive cough, but orthopnea, paroxysmal nocturnal dyspnea, and edema were not mentioned. His past history had revealed rejection from the military service because of a heart murmur. Examination gave no evidence of cardiac enlargement and no murmurs were described. The blood pressure was 140/80. Chest x-ray was reported to show a prominent left ventricle. A diagnosis of rheumatic heart disease was considered even though there was no antecedent rheumatic history, cardiomegaly, or murmur. He was rehospitalized in November 1948 with a gunshot wound of the left arm and subsequent amputation. Examination revealed the blood pressure to be 120/64. No cardiomegaly or murmurs were described at that time and there was no report of a chest x-ray or electrocardiogram. Several months later, 2 or 3 syncopal attacks occurred, and the patient dropped dead on the street. No autopsy was performed.

Patient 4A

Patient 4A, a 12-year-old boy, is the son of patient 3A. At the age of 9 months, he was admitted to a hospital with dyspnea and fever. Physical findings were compatible with bilateral bronchopneumonia. No cardiomegaly or heart murmur was

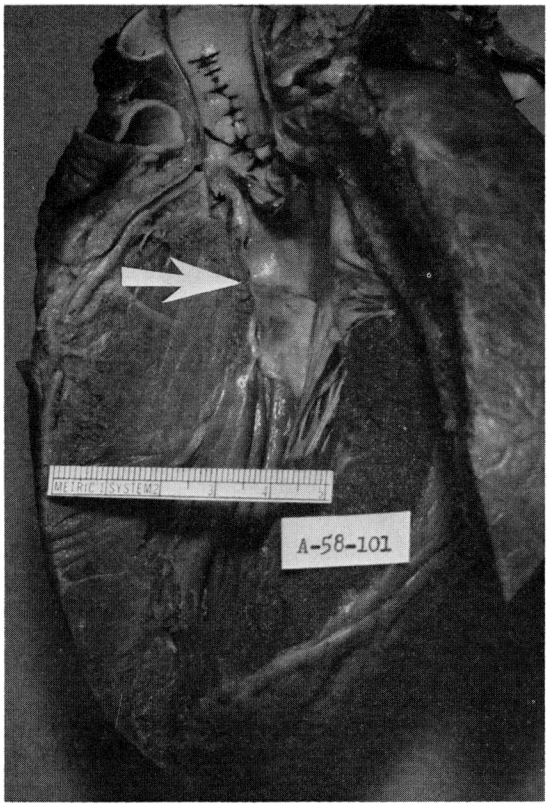

Figure 4

Photograph of the left side of the heart from patient 1A showing location of the subaortic stenosis (arrow).

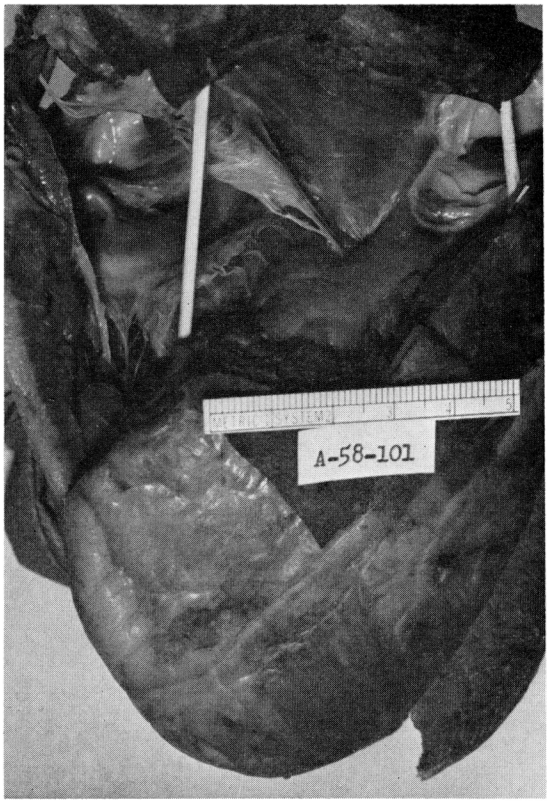

Figure 5

Photograph of the right side of the heart from patient 1A showing the prominent muscle mass in the right outflow tract.

described. The x-ray revealed bilateral bronchopneumonia and a normal heart size. Two years later, in 1948, he was admitted for treatment of cervical adenitis. Again, no cardiac enlargement or murmur was noted. In 1951 the patient was seen by the local physician with complaints of frequent respiratory infections and physical underdevelopment. At this time the blood pressure was 108/70, a systolic murmur was heard at the apex, and the electrocardiogram revealed right ventricular preponderance. The physician considered the diagnosis of an interventricular septal defect. In 1954, at the age of 8 years, the patient was rehospitalized with acute bronchitis. Examination revealed slight cardiomegaly and a grade-III, harsh, systolic murmur along the lower left sternal border and apex. X-ray films revealed ventricular enlargement. Again, the diagnosis of interventricular septal defect was made. In 1956 surgery was performed at another hospital for pulmonic stenosis, but it was not found. He has been followed since at Children's Hospital at this Medical Center, where the chief complaint has been intolerance of exercise. Examination revealed cardiomegaly, a systolic thrill, and a grade-III to IV systolic murmur along the left sternal border that was poorly transmitted to the neck. Chest x-rays and the electrocardiogram suggested biventricular enlargement. A right heart catheterization was performed in June 1958 with normal findings.

Patient 5A

Patient 5A, a 10-year-old boy, a nephew of patient 1A, is asymptomatic. Examination during a survey of the family in August 1958 revealed the apex impulse to be 1 to 2 cm. beyond the left midclavicular line with a forceful apical thrust. There was a grade-III systolic murmur loudest at the apex and lower left sternal border transmitted to the aortic area and neck. Pulses were thought to be normal. The electrocardiogram was normal. The chest x-rays and fluoroscopy were suggestive of left ventricular enlargement. The brachial artery pulse tracing was normal.

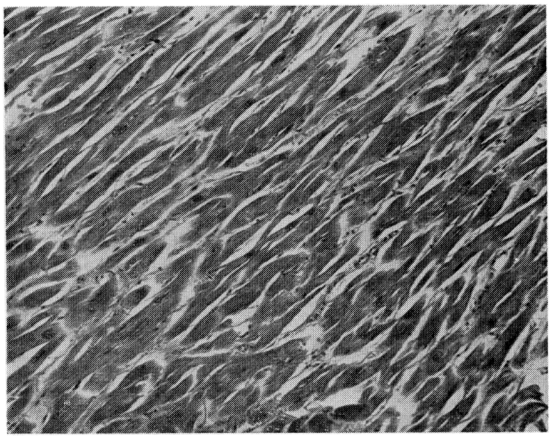

Figure 6

Photomicrograph of heart from patient 1A showing hypertrophy of individual fibers and moderate interstitial edema. Hematoxylin and eosin × 140.

Patient 6A

Patient 6A is a 24-year-old brother of patients 1A and 3A. He is asymptomatic. Examination did not reveal cardiomegaly. There was a grade-II systolic murmur at the apex and lower left sternal border. There were no congestive signs or cyanosis. Arterial pulses were all normal. The electrocardiogram was normal.

In addition to these 6 patients, patient 7A, a paternal uncle of patient 1A, suddenly dropped dead while standing at work 25 years ago. He was approximately 25 years old at the time and was not known to have had any cardiovascular symptoms. An autopsy was not performed. Patient 8A, a first cousin of patient 1A, was admitted to another hospital in July 1946 with the diagnosis of rheumatic heart disease, acute congestive heart failure, and lobar pneumonia. He died 48 hours after admission. There was no well-substantiated antecedent rheumatic history. No autopsy was performed. His father, patient 9A, had been admitted to another hospital in 1945 complaining of palpitation, tachycardia, and ankle edema. He was found to have cardiomegaly, an apical systolic murmur, and enlargement of both liver and spleen. He was thought to have had rheumatic heart disease and subacute bacterial endocarditis. He subsequently died of this illness.

The father of patient 1A died at age 58 years of coronary artery disease, which is well documented by hospital records, but no autopsy was performed. The mother is 60 years of age and living without cardiac complaint. Her physical examination and electrocardiogram were negative. The paternal grandfather died at age of 60 years of pneumonia. Of the 2 surviving uncles, one is living and well at the age of 62 years and the other is suffering from coronary artery disease and congestive heart failure at the age of 70 years. Another uncle died quite suddenly at the age of 64 years, but no information is available regarding the nature of his death.

Family B

Patient 1B

Patient 1B was a 34-year-old white housewife, admitted to Allegheny General Hospital December 29, 1958, with a chief complaint of syncope and chest pain. She had been well until January 1949, when an apical systolic heart murmur was heard during hospitalization elsewhere for an ectopic pregnancy. The blood pressure was then 94/64. Routine laboratory work was negative and the chest x-ray was described as normal. She had no cardiovascular complaints at that time. She remained well until July 1954, when she had a syncopal attack followed by chest pain, which required rehospitalization. Her only other complaint was dyspnea on exertion. Examination revealed an enlarged heart, 1 to 2 cm. outside the left midclavicular line in the sixth intercostal space and a grade-III systolic murmur at the apex and along the lower left sternal border. Routine laboratory data were not remarkable. The chest x-ray is reported as suggestive of "mitral heart disease." An electrocardiogram demonstrated deep S waves over the right precordial leads but little else to suggest left ventricular hypertrophy. She was treated with digitalis without relief. In October 1956, and again in January 1957, she fainted, each time awakening with chest pain. Since she was 8½ months' pregnant on the latter occasion, she was rehospitalized. Examination of the cardiovascular system revealed a grade-III apical systolic murmur and a blood pressure of 100/60. The routine laboratory data were negative. She was treated with digitalis and bed rest and had a successful delivery.

She was first seen at Allegheny General Hospital in December 1958. On the day of admission, she had been playing with her 2-year-old son, when she suddenly fainted. On awakening, she noted pain in the precordial area radiating to her right arm, which gradually subsided. She also complained of shortness of breath with moderate exertion, and fatigability.

Her father had died of alcoholism and heart disease at the age of 47 years. Her mother, age 58 years, was living and well. Her brother had died at age 14 years, supposedly of an enlarged thymus, but no autopsy was performed. One sister had had rheumatic fever and 4 sisters were living and well. At the time of her admission to Allegheny General Hospital, her daughter was also in the hospital

with a diagnosis of rheumatic myocarditis. One son, aged 7 years, reportedly had a clinical diagnosis of interventricular septal defect.

The patient's blood pressure was 92/58, heart rate 86 and regular, and respirations 20. Arterial pulses were all of equal intensity. The heart was enlarged 2 cm. beyond the left midclavicular line in the sixth intercostal space. There was a grade-III systolic murmur loudest at the apex and along the lower left sternal border, transmitted to the neck. The aortic and pulmonic second sounds were of equal intensity. The electrocardiogram demonstrated left ventricular preponderance (fig. 9), and the chest x-rays and fluoroscopy were suggestive of left ventricular enlargement (fig. 10). Combined left and right heart catheterization via percutaneous left and right atrial puncture demonstrated a 50-mm. systolic gradient across the left ventricular outflow tract (fig. 11) with a calculated aortic valve area[8] of 0.8 cm.^{2} (table 1). Despite repeated attempts, the catheter did not pass from the left ventricle to the aorta. In view of the severity of the patient's clinical course and the catheterization findings, an operation was tentatively planned approximately 6 weeks after the catheterization. Because of the family history and our previous experience with family A, however, further diagnostic tests were also planned, including cinecardioangiography, in an attempt to localize the obstruction. Approximately 1 month after discharge the patient suddenly dropped dead at home.

Autopsy Findings. There were no anomalies of the arteries or veins and there were no emboli in the pulmonary arteries. The heart weighed 420 Gm. and was globular, with prominence of the left ventricle. As in the 2 previous cases, the left ventricular cavity was almost obliterated by the greatly hypertrophied muscle mass extending into the outflow tract, and as in the second case, considerable resistance was encountered when the finger was forced into the left ventricle. The obstruction to the outflow tract occurred 1.0 cm. below the base of the aortic valve. The left ventricular wall measured 2.2 cm. in thickness. A prominent muscle mass extended into the right ventricle but without obstruction of the outflow tract. The valves were entirely normal. There was minimal atheromatous involvement of the intimal surface of the coronary arteries, but there was no stenosis or obstruction. In all other respects this heart resembled the 2 previously described. Microscopic examination showed only slight endocardial thickening over the subaortic region and moderate hypertrophy of the individual muscle fibers.

Patient 2B

Patient 2B is the 11-year-old daughter of patient 1B. She was admitted to Allegheny General Hospital in December 1958 complaining of a severe sore throat. Several days prior to admission she had noted soreness of her throat and headache, and was found to have a temperature of 104 F. She also complained of aches in her leg and pain in the right elbow but denied swelling of any joint.

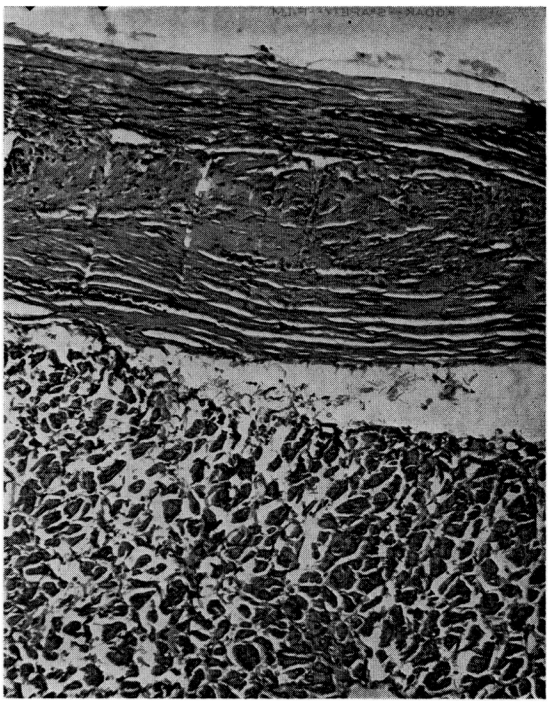

Figure 7

Photomicrograph of heart from patient 1A showing area of subendocardial fibrosis. Hematoxylin and eosin × 140.

The past history, including the neonatal period, was not remarkable except for the usual childhood diseases. One year prior to admission a complete physical examination was said to have been normal.

The heart rate was 80 and regular and the respirations were 20. The physical findings revealed enlarged and inflamed tonsils, but no exudate was seen. The pharynx was injected and there was moderate anterior cervical adenopathy. The lungs were clear to percussion and auscultation. The heart was not enlarged, but there was a grade-III systolic murmur located at the apex and lower left sternal border. The aortic and pulmonic second sounds were normal and the arterial pulses were equal in the arms and legs. The routine laboratory examinations were normal. Numerous determinations of C-reactive protein were negative and the antistreptolysin O titer ranged between 50 and 125

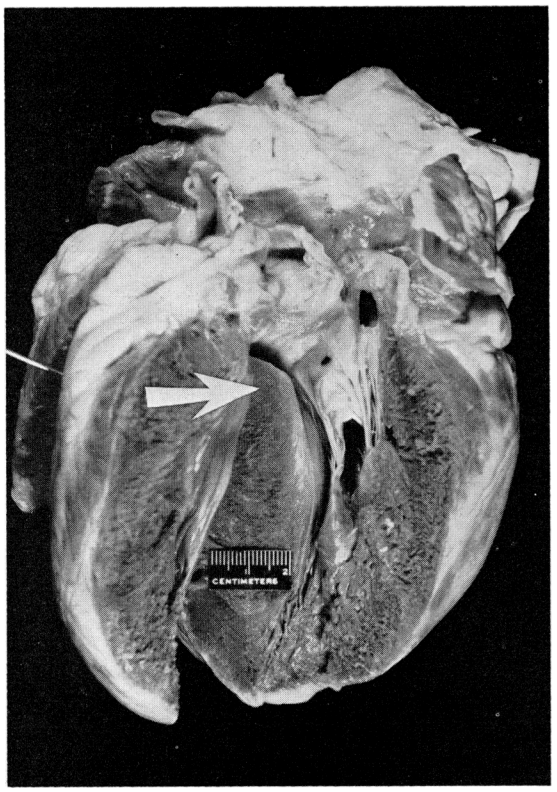

Figure 8

Photograph of heart from patient 2A showing a cut through the interventricular septum and the point of subaortic stenosis (arrow).

Todd units. Several nose and throat cultures did not reveal beta hemolytic streptococci. The chest x-ray films and fluoroscopy demonstrated slight widening of the heart, probably due to left ventricular enlargement. There was no poststenotic dilatation of the aorta. The electrocardiogram, on admission, was not remarkable except for large P waves suggesting atrial enlargement. Subsequently left ventricular hypertrophy developed progressively during a 1-month period. The child was treated with complete bed rest, large doses of adrenal cortical steroids, and salt restriction. There was, however, no improvement either clinically or electrocardiographically. Right heart catheterization was normal with the exception of a pulmonary capillary wedge pressure of 21 mm. Hg. The contour of the wedge tracing does not suggest mitral insufficiency. A left heart catheterization was proposed but the patient's father refused permission. At present, she is at a local rehabilitation center.

Patient 3B

Patient 3B was a brother of patient 1B. In August 1941 he was 14 years of age and in apparently good health when he suddenly dropped dead while skipping rope in his backyard. No autopsy was performed and the cause of death was undetermined.

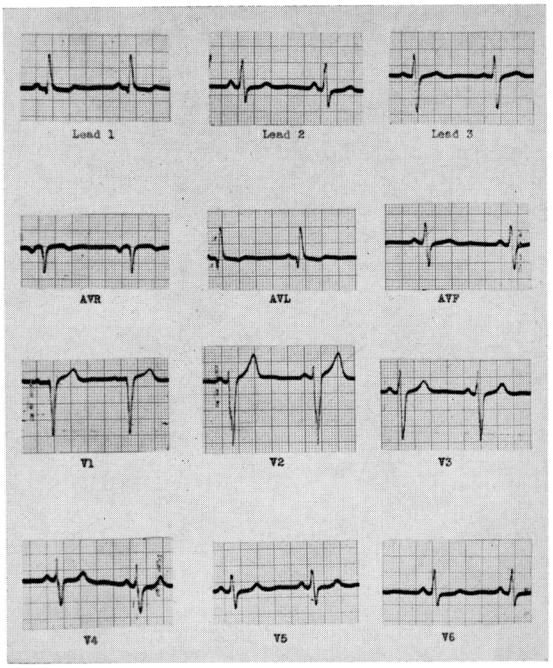

Figure 9

Electrocardiogram of patient 1B.

Patient 4B

Patient 4B, age 23 years, is a sister of patients 1B, 3B, and 5B, and is asymptomatic. Positive physical findings were limited to a grade-II apical and lower left sternal border systolic murmur. The aortic and pulmonic second sounds were of equal intensity. There was no evidence of cardiomegaly or congestive signs. The electrocardiogram was normal and fluoroscopy was not remarkable.

Patient 5B

Patient 5B, age 30 years, is a sister of patients 1B, 3B, and 4B. She has noted shortness of breath with moderate activity and mild substernal distress with exertion for approximately 2 years. She denied syncope but noted lightheadedness with rapid changes in position. She had no antecedent history of rheumatic fever. She has 3 children who are asymptomatic at ages 11, 9, and 7½ years. Her blood pressure was 100/60, heart rate 80 and regular, and respirations 18. Positive physical findings included mild cardiomegaly, the apex impulse being 1 cm. beyond the left midclavicular line in the sixth intercostal space. There was a grade-II systolic murmur along the lower left sternal border

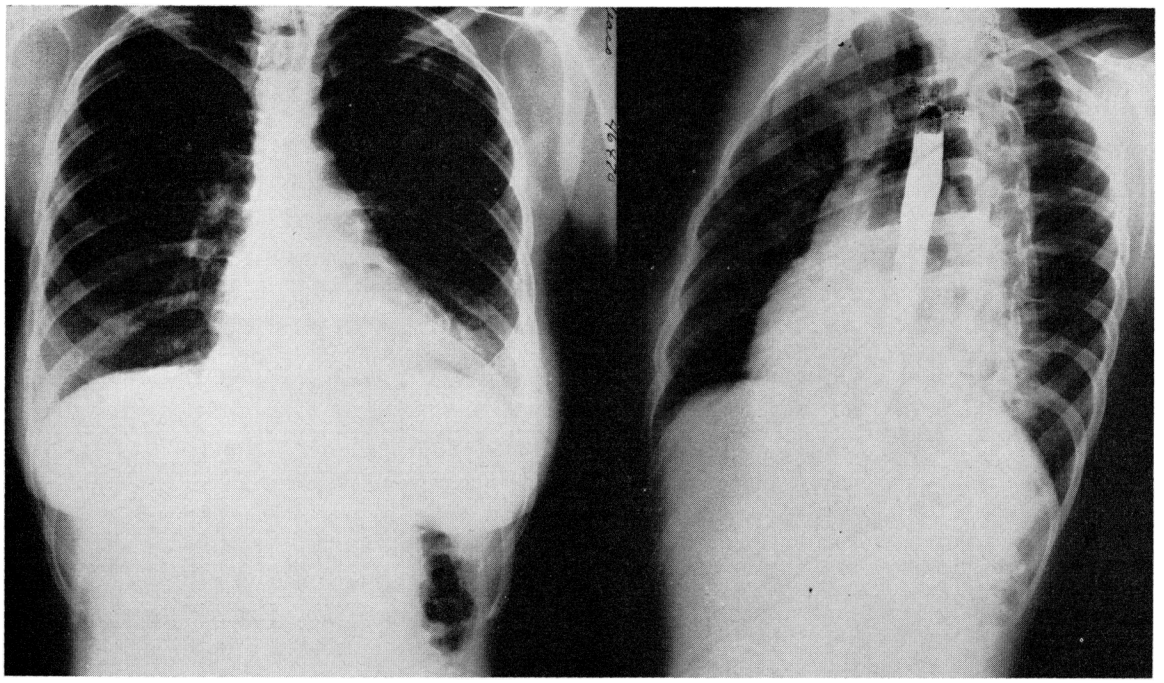

Figure 10

Posteroanterior and left anterior oblique roentgenograms of patient 1B.

and at the apex. The aortic and pulmonic second sounds were normal. The arterial pulses were all of equal intensity. Fluoroscopy revealed the heart to be slightly widened because of left ventricular enlargement. The electrocardiogram demonstrates left ventricular preponderance.

Patient 6B

Patient 6B is the 7½-year-old son of patient 5B. He is asymptomatic. Positive physical findings were limited to a grade-II apical systolic murmur, and slight left ventricular enlargement on fluoroscopy. The electrocardiogram was normal.

The paternal ancestry of patients 1B, 3B, 4B, and 5B has been investigated. The paternal grandfather lived to the age of 65 and died of some type of heart disease. No further history is available. The father died at age 47 of heart disease that had been present almost all of his life. He spent 3 years in a nursing institution following a stroke at the age of 44. A son of his by a previous marriage suddenly dropped dead at the age of 23 (Patient 7B). Another daughter, 24 years of age, has noted shortness of breath on exertion and ease of fatigue. She gives a vague history of rheumatic fever. Her blood pressure was 100/55, heart rate 84 and regular, and respirations 18. The heart was slightly enlarged to the left. There was a grade-III apical systolic murmur that radiated to the axilla. The aortic and pulmonic second sounds were normal. The chest x-ray revealed left atrial and left ventricular enlargement, and the electrocardiogram showed left ventricular preponderance. A retrograde aortic left ventricular catheterization demonstrated no systolic pressure gradient across the left ventricular outflow tract, and rheumatic mitral insufficiency is thought to be present.

A paternal uncle of patient 1B is living at the age of 60, presumably in good health. He has had 7 children, all males, 1 of whom dropped dead at age 18, and 2 more who are thought to have rheumatic heart disease. Another paternal uncle is living in his sixties and has 3 children in good health. The maternal family history has not shown unusual types of heart disease, and the patient's mother has been examined and found to be free of cardiovascular disease.

Discussion

Etiology and Pathophysiology

The exact etiology of familial functional subaortic stenosis is obscure, but structural details suggest an origin different from other lesions of the aortic valve area. Congenital subaortic stenosis of the membranous type is attributed by most authors to persistence of a portion of the bulbus cordis in the outflow tract of the left ventricle.[9, 10] This results in

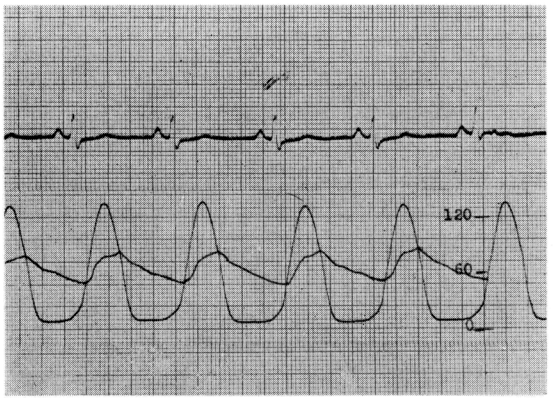

Figure 11

Superimposed, simultaneous pressure tracings obtained in the left ventricle and central aorta in patient 1B.

a membranous obstruction, partially occluding the outflow tract, rather than an extensive area of muscular encroachment.

There are numerous types of myocardial hypertrophy that have been described as clinical entities that can be differentiated either by clinical or pathologic findings. Idiopathic myocardial hypertrophy is characterized by marked cardiomegaly, intractable heart failure, cardiac arrhythmias, tachycardia, and repeated embolic phenomena. Cardiac murmurs or hypertension is not present. At autopsy myocardial hypertrophy and ventricular dilatation are prominent, and subendocardial fibrosis and myocardial degeneration and fibrosis are observed histologically.[11] The signs and symptoms of glycogen-storage disease of the heart become manifest shortly after birth. Initially there is tremendous cardiomegaly with few symptoms. Within months progessive dyspnea and tachycardia develop and sudden death usually occurs within the first year of life. Microscopically, large glycogen deposits in the cardiac and skeletal muscle are predominant.[12] Endocardial fibroelastosis is distinguished by the thickened white endocardium, particularly marked in the left atrium and ventricle. Death at an early age is characteristically preceded by paroxysmal dyspnea, cyanosis, and cardiomegaly.[13] Cardiomegaly has been described in Friedreich's ataxia, more commonly in those with a family history of the disease. Patchy fibrosis and hypertrophy of muscle fibers are the outstanding histologic features.[14] Neurologic features of the disease apparently are present in all those with cardiac enlargement.[15] Several other types of familial cardiomegaly have been described by Evans, Gaunt, and Campbell.[15–17] Tremendous cardiomegaly, arrhythmias, and tachycardias have been characteristic. Patchy fibrosis, hypertrophy, and vacuolization of the muscle fibers have been observed histologically. In none of the above instances has a systolic pressure gradient been recorded across the left ventricular outflow tract, nor in any cases has aortic stenosis, valvular or subvalvular, been suspected clinically.

Some acquired muscular lesions obstructing ventricular outflow have been reported. Engle and co-workers[18] and Brock[19] have described a functional muscular infundibular obstruction of the right ventricular outflow tract that temporarily maintained the systolic pressure gradient following valvotomy in cases of pulmonic valvular stenosis. Morrow et al.[6] reported a case with an analogous, transiently persistent gradient in the subvalvular area of the left ventricle, demonstrated on left heart catheterization 3 weeks after a valvotomy for acquired aortic stenosis. At left heart catheterization 18 months later, this gradient had disappeared. Brock[20] also described the development of a functional left ventricular outflow obstruction in 2 cases, resulting from longstanding hypertensive cardiovascular disease. We have been unable, however, to implicate either valvular disease or systemic hypertension in any of our patients.

Bercu et al.[21] and Morrow et al.[6] have recently described cases similar to our own. Bercu's patient had a severe systolic pressure gradient across the outflow tract of the left ventricle. By means of open-heart surgery with total cardiac bypass, the aortic valves were inspected and found to be normal; and there was no subvalvular membrane. Marked hypertrophy of the musculature of the outflow tract was observed and was presumed to be the cause of the obstruction. The patient subsequently died and at necropsy both ven-

tricles were found to be hypertrophied without apparent cause. Histologic examination was remarkable only for hypertrophy of the individual muscle fibers. An interesting feature of this case is that a brother of the patient underwent transventricular aortic valvotomy for aortic stenosis in 1955 (closed method). He is still living and apparently is clinically improved.

Morrow has had similar experiences with 2 cases in which left heart catheterization had demonstrated subvalvular obstruction warranting surgical relief. At operation, with cardiac bypass and an arrested heart, no obvious obstruction was encountered, either valvular or subvalvular. Again, marked hypertrophy of the musculature of the left ventricular outflow tract was present and presumed to be the cause of the functional obstruction. Later, a functional obstruction of the outflow tract was demonstrated by selective angiocardiography.

In these cases as well as in our own the pathologic physiology can be recognized. The pathologic changes in the heart consist essentially of the tremendous muscular hypertrophy that is particularly marked in the interventricular septum. In the arrested heart at surgery or at autopsy, a finger may be passed with some difficulty from the aorta, past the muscular obstruction, into the left ventricular cavity. Contraction of the muscle during systole in the beating heart causes further obstruction of the outflow tract. The systolic pressure gradient is then due in part to a mechanical muscular component and in part to a functional contracting component. This must be appreciated or the diagnosis could easily be missed, either in the arrested heart at surgery or at autopsy.

No etiologic factor has been apparent. Neither valvular disease nor systemic hypertension can be implicated. The familial incidence of the lesion in our cases strongly implies the likelihood of familial anomaly as the cause; we can only speculate as to its mechanism. The tendency of the musculature of the ventricles to become hypertrophied may be a gradual or an abrupt process, with the terminal stage at any age. A localized hypertrophy in the interventricular septum at the outflow tract may give rise to an obstruction during systolic contraction, which secondarily leads to hypertrophy of the entire left ventricle. A better explanation of the widespread muscular hypertrophy may be found with chemical analysis of the heart muscle. At the present time, the etiology of muscular subaortic stenosis is uncertain, except in those cases secondary to aortic valve disease or systemic hypertension.

Clinical Features

Differential diagnosis of familial functional subaortic stenosis from other varieties of aortic stenosis appears possible. The clinical profile of patients with valvular aortic stenosis, either congenital or acquired, has been well documented by numerous authors.[3, 4, 22, 23] Dyspnea on effort, ease of fatigue, chest pain, and syncope are frequent symptoms of the severe form of this disease. The physical findings include left ventricular enlargement with a vigorous apical thrust, a basal systolic thrill and murmur, and a second aortic heart sound that is either normal or diminished. The typical pulse is described as a small plateau type. The chest x-ray and fluoroscopy usually demonstrate left ventricular enlargement and some degree of dilatation of the ascending aorta. Calcification of the aortic valve is usually present in patients with acquired aortic stenosis over the age of 30 years,[1] and has been reported in congenital valvular and subvalvular stenosis.[24] The electrocardiogram may or may not demonstrate left ventricular preponderance. Pressure recordings show a systolic pressure gradient across the aortic valve area. The cardiac output is usually normal, but in severe aortic stenosis it is fixed and does not rise with exercise.[25] It is the opinion of most authors today that the usual type of congenital subaortic stenosis cannot be distinguished clinically from acquired or congenital valvular stenosis.[3, 7, 24] The presence of an infundibular chamber in subvalvular stenosis may be demonstrated by pressure recordings or on withdrawal of the catheter by cardioangiography.[4, 7]

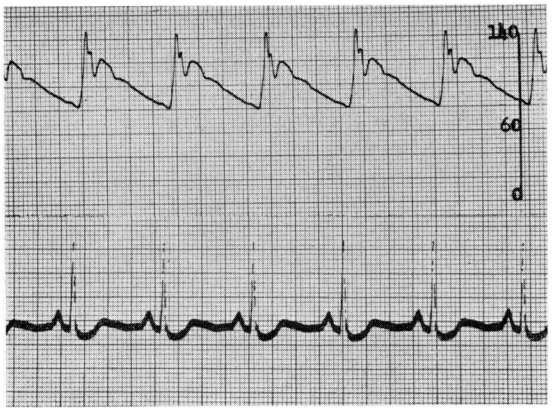

Figure 12

Central aortic pressure tracing in patient 1A demonstrating the widened bisferiens pulse with the rapid systolic upstroke of the initial peak.

It is difficult to distinguish the symptoms of our patients with functional subaortic stenosis from those of acquired aortic valvular stenosis or congenital aortic or subaortic stenosis. Syncope has been the most prevalent complaint among our patients that have been symptomatic, and there has been an alarming incidence of sudden death. However, syncope and sudden death are also common in congenital and acquired aortic stenosis. The physical findings appear to be more helpful. The location of the heart murmur at the apex and in the third and fourth left intercostal spaces adjacent to the sternum has been a constant feature in muscular outflow obstruction, as opposed to the usual basal systolic murmur to the right of the sternum, in valvular stenosis. In no case of muscular subaortic stenosis has the murmur of aortic insufficiency been heard, whereas in congenital valvular and subvalvular stenosis, one third of the patients have an associated murmur of aortic insufficiency.[23] None of our patients had calcification of the aortic valve either on x-ray films or fluoroscopy, and there has been no poststenotic dilatation of the ascending aorta. Pressure recordings during catheter withdrawal may establish the site of the obstruction below the aortic valve; however, they do not distinguish between the usual type of subvalvular stenosis and muscular subaortic stenosis. Angiocardiography has been reported to demonstrate a functional type of outflow obstruction, and perhaps this may permit differentiation.[6]

Another physical sign that may be of diagnostic significance is the widened bisferiens pulse in patient 1A (fig. 12). The initial peak occurs 0.12 second after the R wave and the systolic upstroke duration is 0.07 second. The second peak, occurring 0.24 second after the R wave, is of a much lower pressure. The pulse pressure is 60 mm. of mercury. In severe aortic valvular stenosis, pulsus bisferiens is not uncommon; however, the notch is low on the anacrotic limb and is accompanied by a prolonged systolic upstroke duration and a narrow pulse pressure. The initial peak in patient 1A is most likely due to an ejection of blood early in systole, prior to contraction of the musculature of the left ventricular outflow tract, which causes a functional as well as a mechanical obstruction.

A history implicating other members of the family may be the most significant single clue. Relatives are referred to as having had syncopal attacks, heart murmurs, and sudden death, the latter most frequently in the third decade. Rheumatic valvular disease has been suspected, but in the present reports, a clinical diagnosis of interventricular septal defect has been made in 2 patients who probably have muscular subaortic stenosis.

Familial Aspects of Functional Subaortic Stenosis

The apparent familial incidence of our cases suggests their classification as familial heart disease. Environmental gestational factors as a cause of congenital heart disease have been a source of great interest both in the past and in recent years. In several large series, however, known environmental factors such as rubella and other infections have accounted for only a small percentage of congenital heart disease.[15]

Genetic factors cannot be readily diagnosed. Carleton et al.[26] and Campbell[27] have recently reviewed large series of multiple cases of congenital heart disease occurring in the same families. Although a single gene may not always be the deciding factor, being influenced to some degree by the environment and per-

haps by other genes, they conclude that their material conforms best with a single, recessive, autosomal mode of genetic transmission. Beyond the field of congenital heart disease, there are numerous types of congenital defects based on Mendelian dominant inheritance, i.e., hematologic, neurologic, and connective-tissue disorders. The pedigrees of the family A (fig. 13*A*) and the family B (fig. 13*B*) suggest this type of inheritance. In the absence of consanguinity or of an isolated racial group, which we have excluded to the best of our ability, the appearance of this lesion in 3 generations in large numbers would support this hypothesis. To our knowledge, this is the first series of cases reported that would suggest Mendelian dominant inheritance in familial heart disease.

It should be emphasized that studies on these 2 famlies have only begun. There are many relatives who have not been examined as yet, mainly because of their scattered places of residence. Another important factor will be the long-term follow-up of members of both families with emphasis on further autopsy and catheterization data. We have already seen that the signs and symptoms can appear early or late in life, and the disease can be of either a malignant or a benign nature.

Therapeutic Aspects

Favorable surgical results similar to those in other types of acquired and congenital aortic stenosis cannot be expected in the treatment of this lesion. This opinion is shared by Brock[20] and Morrow,[6] who have also encountered this problem at surgery. Therefore, the criteria for differential diagnosis must be carefully applied to each candidate for operation for aortic stenosis in order to exclude the inoperable muscular type.

Summary

Two families with familial muscular subaortic stenosis have been studied. Hemodynamic data in 2 cases and the operative findings of 1 case are described. Autopsy findings of 3 cases have been presented. Clinical findings indicate at least 3 additional cases in 1 family and 5 in the other.

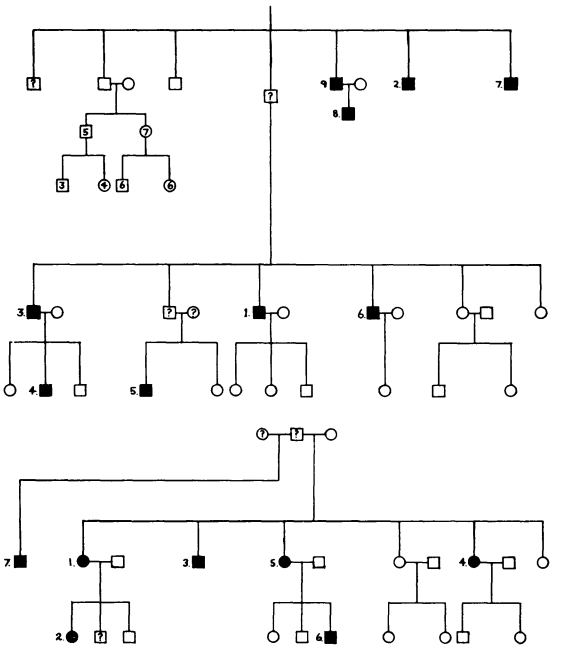

Figure 13

Upper. *Pedigree of family A.* Lower. *Pedigree of family B. The black circles (females) and squares (males) represent involved patients on the basis of (1) clinical, hemodynamic, and autopsy findings, (2) history of heart murmurs and sudden death, or (3) clinical findings. The question marks refer to key persons in the family pedigree, who have not been examined.*

The pedigrees of both families have been discussed. The incidence of this lesion in each family over 3 generations suggests that the defect is related to Mendelian dominant inheritance. To our knowledge, this is the first report of cases of familial heart disease compatible with transmission by a Mendelian dominant gene.

The importance of differential diagnosis of this disease from other types of aortic or subaortic stenosis prior to surgery has been stressed, since no operation has been devised for this lesion. The distinguishing clinical features include the apical and lower left sternal border location of the systolic murmur, the absence of poststenotic dilatation of the ascending aorta, the absence of calcification of the aortic valve, the absence of a murmur of aortic insufficiency, and the strong family history suggesting a familial trait.

Summario in Interlingua

Esseva studiate 2 familias con familial stenosis subaortic muscular. Es presentate le datos hemodynamic in 2 casos. Le constatationes operatori in 1 caso es describite. Le constatationes necroptic de 3 casos es presentate. Constatationes clinic indica al minus 3 casos additional in un del familias e 5 in le altere.

Le arbore genealogic de ambe familias es discutite. Le incidentia de iste lesion in cata un del duo familias in le curso de 3 generationes suggere que le defecto es relationate a hereditate per dominante mendelian. Secundo nostre informationes, isto es le prime reporto de casos de congenite morbo cardiac compatibile con transmission per un gen dominante mendelian.

Le importantia del diagnose differential de iste morbo ab altere typos de stenosis aortic o subaortic ante le intervention chirurgic es sublineate, proque nulle operation ha essite elaborate pro iste lesion. Le distinctive characteristicas clinic include le location del murmure systolic al apice e al margine sternal infero-sinistre, le absentia de dilatation poststenotic del aorta ascendente, le absentia de calcification del valvula aortic, le absentia de un murmure de insufficientia aortic, e le marcate historia familial que suggere un tracto familial.

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Familial Muscular Subaortic Stenosis: An Unrecognized Form of "Idiopathic Heart Disease," with Clinical and Autopsy Observations

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