The Development of Outflow Tract Obstruction of the Left Ventricle in Idiopathic Myocardial Hypertrophy

By EMILIO TAFUR, M.D., WARREN G. GUNTHEROTH, M.D., DAVID BAUM, M.D., AND JOHN R. BLACKMON, M.D.

THE syndrome of outflow tract obstruction of the left ventricle due to contraction of hypertrophied myocardium was first described by Brock in 1957 [1] in patients with left ventricular hypertrophy resulting from long-standing systemic hypertension. Since this original report, considerable clinical, hemodynamic, angiocardiographic, surgical, and postmortem evidence has accumulated to indicate that idiopathic myocardial hypertrophy may produce muscular subaortic stenosis, and that it is the most frequent cause of the syndrome.[2-17] The term obstructive cardiomyopathy has been proposed by Goodwin et al.[3] Other terms that have been used include: functional obstruction of the left ventricle,[1] pseudoaortic stenosis,[2] idiopathic hypertrophic subaortic stenosis,[4] asymmetric myocardial hypertrophy,[5, 6] and familial muscular subaortic stenosis.[7, 8]

Braunwald and Aygen[9] have recently described a group of patients with idiopathic myocardial hypertrophy in whom the clinical, electrocardiographic, roentgenographic, hemodynamic, and angiocardiographic findings were similar to the findings in patients with idiopathic hypertrophic subaortic stenosis with the exception that no hemodynamic evidence of obstruction to blood flow was present. These investigators have suggested that the same basic process may exist in the patients with idiopathic myocardial hypertrophy without obstruction to blood flow and in patients with idiopathic hypertrophic subaortic stenosis, and that the presence or absence of a pressure gradient in some of the patients with idiopathic left ventricular hypertrophy is dependent upon the precise localization and severity of the muscular hypertrophy.

It is the purpose of this report to present the clinical and hemodynamic findings in a patient with myocardial hypertrophy of unexplained etiology who exhibited no hemodynamic evidence of obstruction of the left ventricular outflow tract when first studied. In contrast, a large pressure gradient across the outflow tract of the left ventricle was found when he was restudied 2 years later. Hemodynamic evidence of the development of a pressure gradient during the resting state in idiopathic myocardial hypertrophy has not been reported previously.

Case Report

D. B., an 11-year-old white boy, was admitted to the University of Washington Hospital for the first time on April 24, 1961. Seven months prior to admission he was first informed of the presence of a heart murmur. He had been in excellent health until 19 months before admission when he experienced two episodes of severe "shortness of breath" when running; the first episode was accompanied by "neck pain" and both were relieved by 1 to 2 minutes of rest. Following this, he noted easy fatigability and dyspnea on severe exertion. Five months prior to admission he had transient swelling of the ankles, which recurred several weeks later in milder form.

Physical examination revealed a robust boy in no discomfort. Blood pressure was 100/60 mm. Hg. The peripheral arterial pulses and the jugular venous pulses were normal. The cardiac impulse had a heaving character and was maximal at the fifth left intercostal space at the anterior axillary line. No thrills were felt. There were normal splitting of the second sound at the base and a prominent third heart sound at the apex.

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A grade-III/VI rough systolic murmur, crescendo-decrescendo in type, was heard at the apex, in the axilla, and along the left sternal border. It was maximal at the third left intercostal space (fig. 1). The remainder of the physical examination was within normal limits.

The electrocardiogram showed right axis deviation, a wide QRS-T angle in the frontal and horizontal planes, QT prolongation, and an unusual pattern of ventricular activation (figs. 1 and 2).

The chest roentgenogram (fig. 3, left) revealed moderate cardiomegaly due to left ventricular enlargement. There was a "double contour" of the right border of the cardiac silhouette suggestive of left atrial enlargement. The pulmonary vascularity was normal.

The laboratory data were as follows: the hematocrit value was 41 per cent, the white blood-cell count 9,500 mm.^{3} with 56 per cent segmented forms, 36 per cent lymphocytes, 6 per cent monocytes, and 2 per cent eosinophils. The erythrocyte sedimentation rate was 10 mm. per hour (Wintrobe method). The urine specific gravity was 1,027, pH 5.5; a trace of proteinuria was found on one occasion. The centrifuged urinary sediment showed 15 to 20 red blood cells per high-power field in one specimen and 7 to 9 red blood cells in another. A 12-hour urinary Addis count showed 67,000,000 red blood cells and 975,000 white blood cells. Antistreptolysin-O titer was 166 Todd units and the C-reactive protein was nonreactive. A serum protein electrophoresis was normal and LE preparations were negative on three occasions. Serum glutamic oxaloacetic transaminase was 20 units.

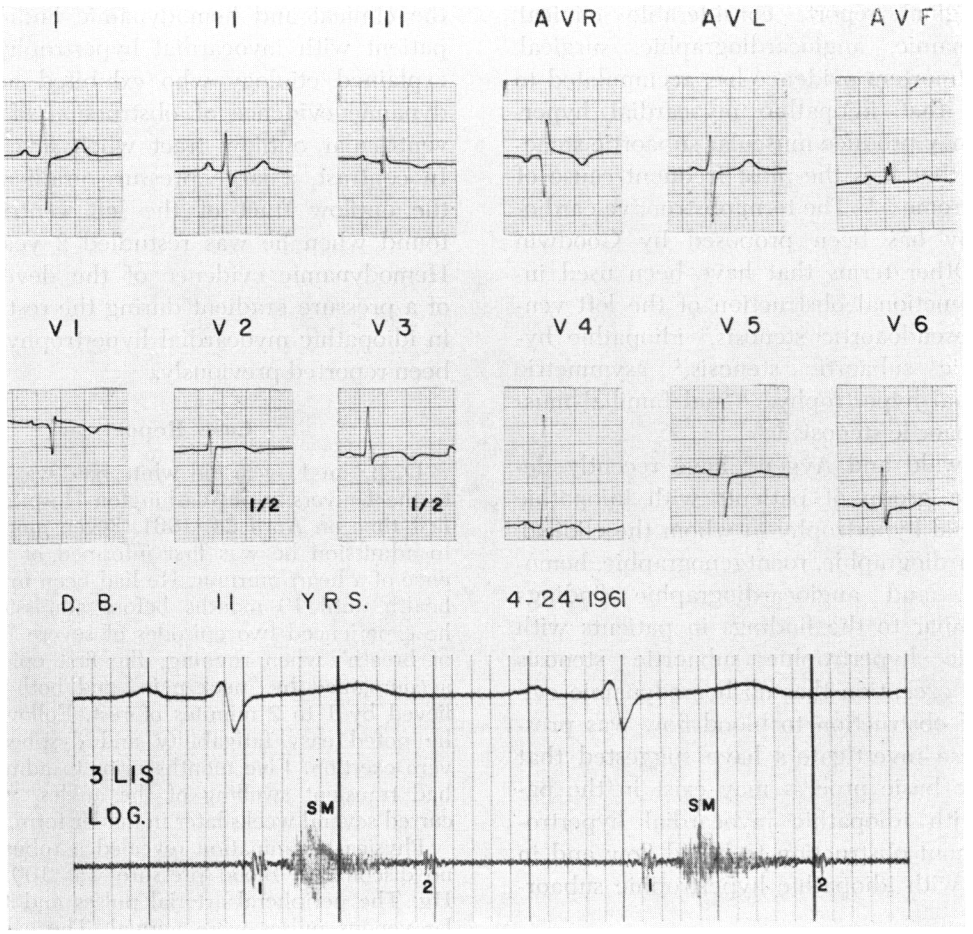

Figure 1

Electrocardiogram showing right axis deviation, abnormal ventricular activation (note Qr complexes in V_1), and a wide QRS-T angle in the frontal and horizontal planes. Phonocardiogram recorded at the third left interspace. There is a diamond-shaped systolic murmur commencing 0.06 second after the onset of the first heart sound.

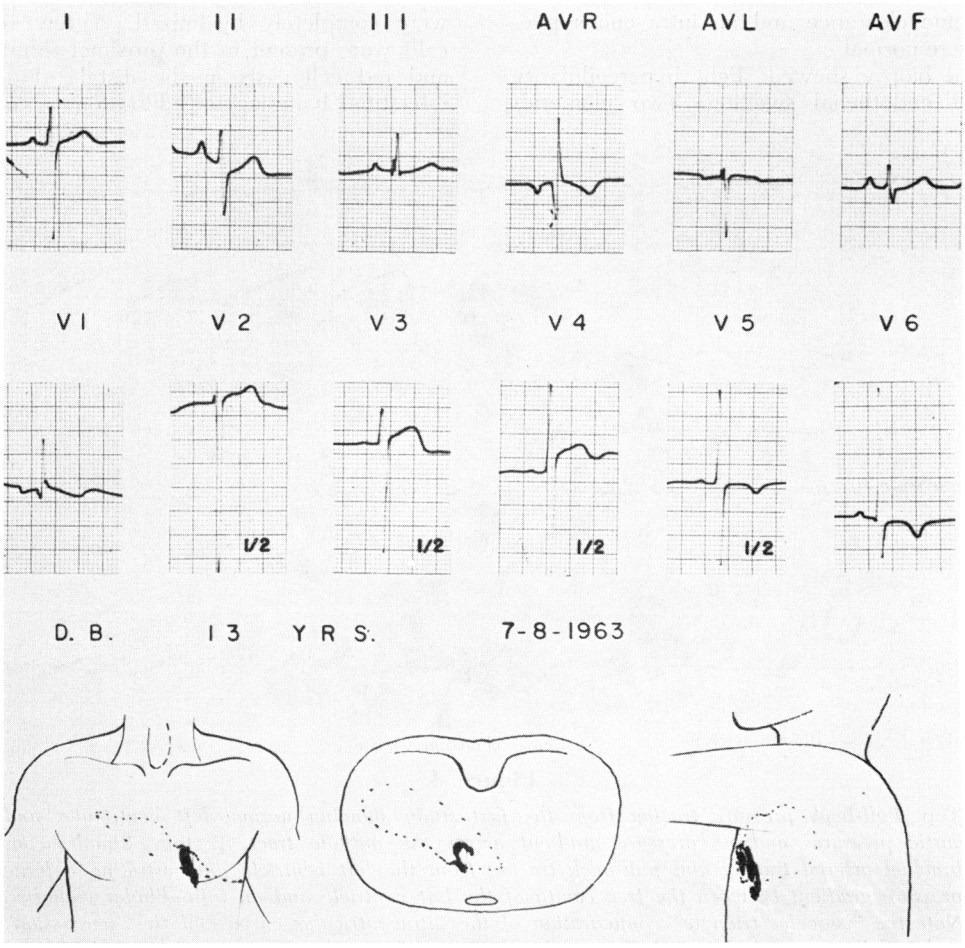

Figure 2

Electrocardiogram 2 years after that in figure 1, showing emergence of left ventricular hypertrophy, T-wave inversion in the left chest leads, and further deviation of the maximum QRS axis to the right. Vectorcardiogram showing a rightward, superior, and posterior orientation of the maximum QRS vector loop. Voltages are greater than normal.

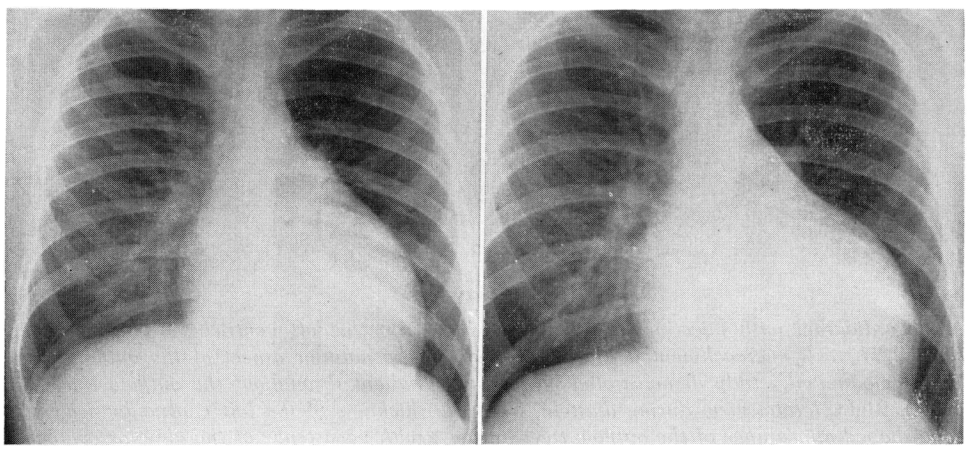

Figure 3

Roentgenograms showing changes in cardiac size over a 2-year period.

A creatinine clearance and an intravenous pyelogram were normal.

A renal biopsy showed slight hypercellularity and mild endothelial swelling. Two glomeruli were completely hyalinized. A few red blood cells were present in the proximal tubular lumen and red cell casts in the distal tubules. Focal interstitial lymphocytic infiltration was slight but

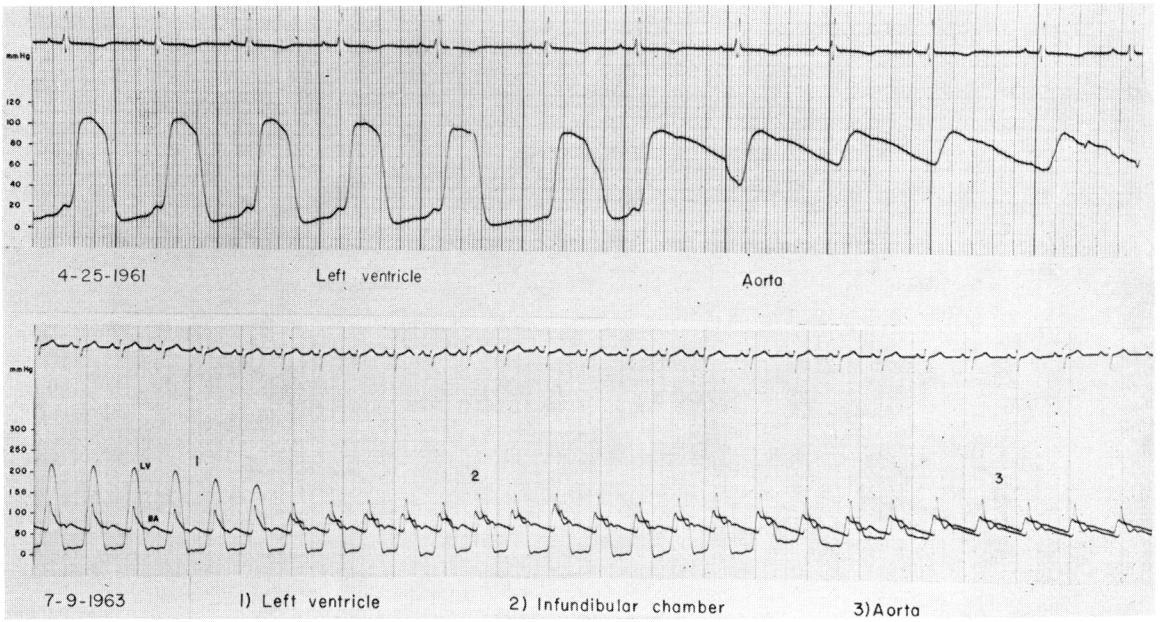

Figure 4

Top. *Pull-back pressure tracing from the first study showing normal left ventricular and aortic pressures and no pressure gradient across the outflow tract.* Bottom. *Simultaneous brachial arterial tracing and pull-back tracing from the left ventricle demonstrating a large pressure gradient between the free cavity of the left ventricle and an infundibular chamber. Note the "isosceles triangle" configuration of the intraventricular curve and the "percussion" and "tidal" waves of the brachial arterial tracing (see fig. 6).*

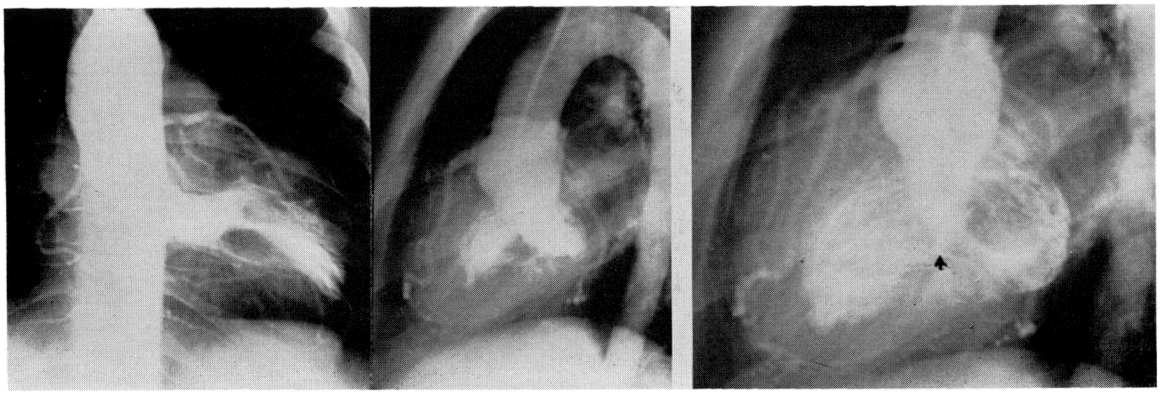

Figure 5

Angiocardiogram with injection of contrast medium into the left ventricle. Left and center, *systole. There is encroachment of the septal wall on the anterior aspect of the outflow tract. The hemodynamic study demonstrated no pressure gradient throughout the outflow tract (see fig. 4).* Right, *lateral view during diastole. Note the thickness of the left ventricular wall, the cone-shaped appearance of the outflow tract* (arrow) *with persistence of the anterior encroachment of the septal wall. The posterior part of the cone is produced by the open aortic leaflet of the mitral valve.*

definite. These findings were interpreted as consistent with glomerulonephritis.

Right heart catheterization demonstrated normal pressures without evidence of shunting. The pulmonary artery wedge pressure was 12 mm. Hg. Retrograde left heart catheterization revealed a left ventricular end-diastolic pressure of 14 mm. Hg with normal aortic pressures. There was no evidence of a gradient across the left ventricular outflow tract during the resting state (table 1, fig. 4). An angiocardiogram (fig. 5) with left ventricular injection showed a relatively small left ventricular cavity with a thick wall and no evidence of mitral regurgitation. The outflow tract appeared narrowed by septal hypertrophy, producing an inverted cone in systole. This appearance was accentuated in diastole by the normal anterior excursion of the aortic leaflet of the mitral valve. Thus, there was encroachment from the septal side of the outflow tract in both systole and diastole.

The diagnosis of cardiomyopathy of undetermined etiology was made. It was felt that the glomerulonephritis was unrelated. The patient was discharged and followed in the outpatient department.

The patient was readmitted to the hospital on July 7, 1963 (27 months after the first admission). In the interval since the previous admission, he had continued to have microscopic hematuria but had appeared to improve gradually as far as his exercise tolerance was concerned. He denied exertional limitation. Physical examination revealed brisk peripheral pulses,

Table 1

Hemodynamic Data

Date	Left ventricular pressure		Aortic pressure		Mean systolic gradient (mm. Hg)	Eff. orif. Size (cm.²)*
	Systolic	End-diastolic	Pulsatile	Mean		
4/25/61	106	14	100/66	85	0	—
7/ 9/63	215	15	110/70	88	82	0.41

* Orifice equations may be applied to "short tubes" up to 2 cm. in length. The use of Gorlin's hydraulic formula in this connection serves primarily as a means of signifying the degree of obstruction and is not intended as an accurate estimation of size of the outflow tract.[18]

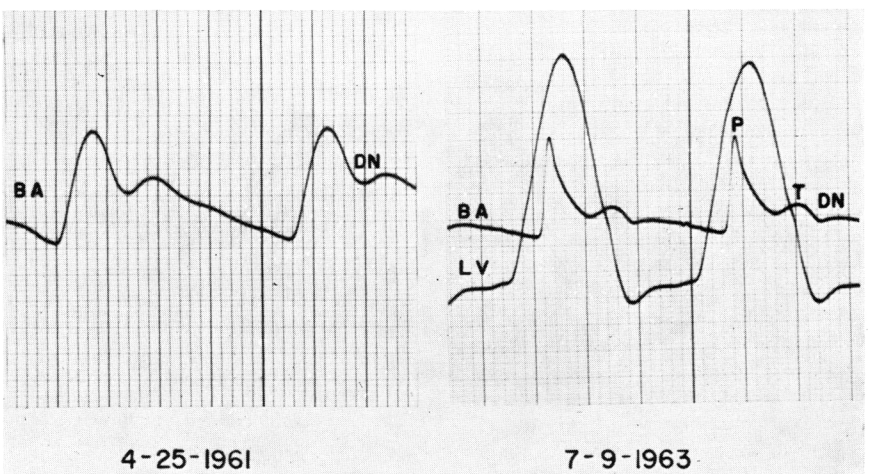

Figure 6

Left. *Normal brachial arterial pressure recorded on the first hemodynamic study on April 25, 1961. The corrected systolic ejection time is 0.27 second.* $\frac{\text{Systolic ejection time}}{\sqrt{R-R}} =$ *Corrected SET.* Right. *Simultaneous left ventricular and brachial arterial pressure tracings recorded on July 9, 1963. Note the presence of the "percussion" (P) and "tidal" (T) waves in the brachial tracing. The corrected systolic ejection time has increased to 0.406 second. Vertical lines in the tracings are 0.04 second apart.*

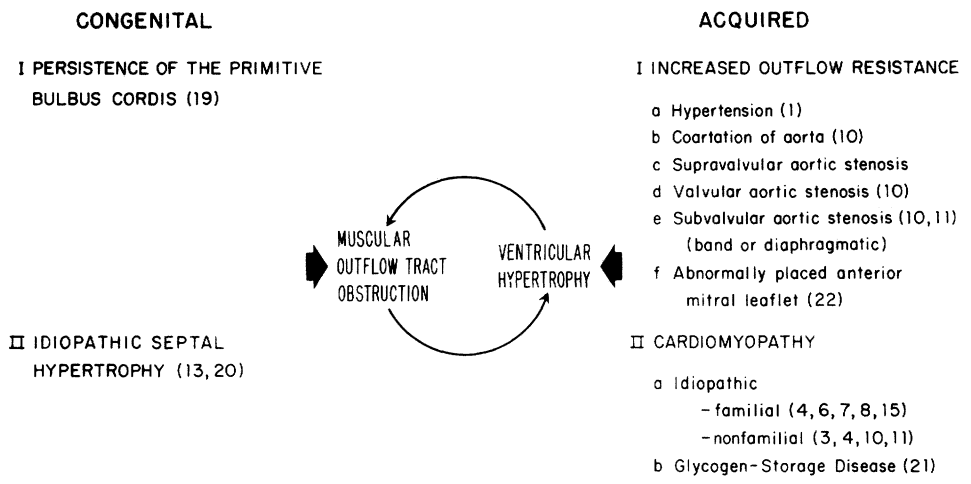

Figure 7

Left. *Congenital abnormalities which may initiate the circle with muscular subaortic stenosis.* Right. *Reported causes of left ventricular hypertrophy resulting in "acquired" muscular obstruction of the outflow tract. In this schema, the term "acquired" refers to the development of muscular subaortic stenosis secondary to left ventricular hypertrophy.*

moderate increase in intensity of the murmur, and clinical and radiologic evidence of further cardiac enlargement (fig. 3). The electrocardiogram (fig. 2) showed greater right axis deviation, widening of the QRS-T angle, and emergence of left ventricular hypertrophy with T-wave inversion over the anterolateral precordium.

Positive laboratory data were a trace of proteinuria and 20 red blood cells and 5 white blood cells per high-power field in the centrifuged urinary sediment. The remainder of the physical examination and laboratory data were normal.

On the basis of the clinical impression that muscular subaortic obstruction had developed, a second hemodynamic study was carried out. Right heart catheterization was normal. A brachial artery tracing (fig. 4 and 6) revealed a sharp upstroke, a mid-systolic trough, and a second smaller positive wave ("percussion" and "tidal" waves of Brachfeld and Gorlin).[10] At retrograde left heart catheterization there was a ventriculo-aortic mean ejection gradient of 82 mm. Hg. An infundibular chamber was found on withdrawal from the left ventricle to the aorta. The left ventricular end-diastolic pressure was 15 mm. Hg (table 1, fig. 4).

It was thought that the gradually increasing hypertrophy of the cardiac muscle had resulted in severe obstruction to left ventricular outflow. Surgical correction was advised but not accepted. Thirty-seven days after discharge the patient complained several times of chest pain and he collapsed and died. No postmortem examination was performed.

Discussion

Although the initial description by Brock[1] inferred that obstruction to outflow from the left ventricle was secondary to muscular hypertrophy caused by hypertension, there have been no reports of left heart hemodynamics before and after the development of obstruction. Our patient had left ventricular hypertrophy with obvious angiocardiographic evidence of septal hypertrophy. There was no intraventricular pressure gradient at rest on the first catheterization. Two years later, however, he had a resting mean systolic ejection gradient of 82 mm. Hg.

Why *all* individuals with advanced left ventricular hypertrophy do not develop obstruction to aortic flow is an intriguing question. Probably in those patients with idiopathic hypertrophic subaortic stenosis there is a unique anatomy that initiates a vicious cycle of hypertrophy and obstruction (fig. 7). Unless there are sequential studies, it is difficult to be certain which of these two abnormalities was first. However, the coexistence of congenital muscular subaortic stenosis and infundibular pulmonary stenosis in the stillborn and newborn patients described by Neufeld et al.[20] and Menges et al.[13] sug-

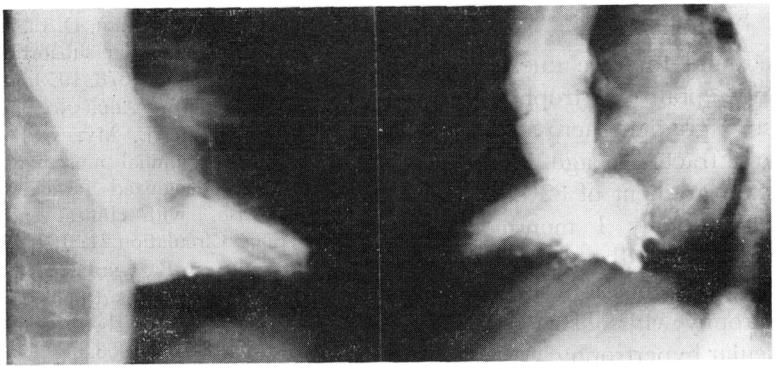

Figure 8

Posteroanterior and lateral angiocardiograms of a 5-year-old girl with anomalous insertion of the anterior leaflet of the mitral valve on the septal wall. The "cone" in this patient is present in systole as contrasted to the diastolic "cone" in figure 5 of the first patient. The encroachment on the anterior aspect of the outflow tract is muscular, and is comparable to the persistent encroachment in figure 5. The left atrium in this girl is opacified by mitral regurgitation, a consequence of the abnormal mitral valve.

gests that muscular obstruction of the ventricular outflow tract may initiate the cycle in some cases. The latter authors believe that in these patients, the asymmetric distribution of the muscle suggests that the gross thickening of the septum may be a primary developmental abnormality, resulting from the incorporation into the interventricular septum of an abnormal amount of muscle during the second gestational month. On the other side of the spectrum are those patients in whom the cycle would begin with ventricular hypertrophy. The occurrence of muscular subaortic stenosis in idiopathic myocardial hypertrophy,[2-17] in glycogen-storage disease,[21] as well as in concentric left ventricular hypertrophy secondary to increased outflow resistance of varied etiology,[1, 10, 11, 22] is now well recognized (fig. 7). We have followed a child who was found to have a heart murmur at 7 months of age. At age 5, this patient had a peak ejection gradient of over 50 mm. Hg across the outflow tract of the left ventricle, and the obstruction was due to an anomalous insertion of the septal leaflet of the mitral valve and muscular septal hypertrophy (fig. 8). It is apparent that this patient's cycle of hypertrophy and obstruction began with the fixed obstruction produced by the abnormal mitral leaflet and was worsened by the secondary muscular septal hypertrophy. In our first patient there was left ventricular hypertrophy involving the septum before there was a measurable ejection gradient. The development of a large gradient 2 years later suggests that the progression and localization of the muscular hypertrophy led to obstruction of blood flow.

The frequent occurrence of electrocardiographic abnormalities has led some investigators to suggest that congenital conduction abnormalities resulting in abnormal sequence of contraction may play a role in the dynamic obstruction of hypertrophic subaortic stenosis. However, there is no uniform electrical abnormality associated with this lesion[23] and electrocardiograms with normal ventricular conduction are found.[24] The patient here reported showed an electrocardiographic conduction abnormality, even before hemodynamic obstruction had developed, suggesting that the conduction abnormality was not causally related to the dynamic outflow tract obstruction of the left ventricle.

We believe that our first patient is an example of "acquired" muscular subaortic stenosis in idiopathic myocardial hypertrophy. We cannot be certain, however, if the ventricular myocardial hypertrophy was congenital.

Summary

A patient was found to have unexplained left ventricular and septal hypertrophy at age 11, but no pressure gradient across the left ventricular outflow tract. At age 13, there was a mean ejection gradient of 82 mm. Hg. The patient died suddenly 1 month later. This patient demonstrates the development of muscular subaortic stenosis in idiopathic myocardial hypertrophy with obstruction due to increasing muscular hypertrophy.

A second patient with left ventricular hypertrophy secondary to a fixed left ventricular outflow tract obstruction produced by an anomalous insertion of a mitral valve leaflet developed additional obstruction due to septal hypertrophy.

We believe that the cases presented establish that "muscular subaortic stenosis" may be the result of ventricular hypertrophy of different etiologies. A schema is presented to assist classification of muscular subaortic stenosis.

Acknowledgment

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"Some General Remarks"

By Richard Bright—1827

From the observations which I have made, I have been led to believe that there may be several forms of disease to which the kidney becomes liable in the progress of dropsical affection: I have even thought that the organic derangements will authorise the establishment of three varieties of diseased structure, generally attended by a decidedly albuminous character of the urine.—In the *first*, a state of degeneracy seems to exist, which from its appearance might be regarded as marking little more than simple debility of the organ. In this case the kidney loses its usual firmness, becomes of a yellow mottled appearance externally; and when a section is made, nearly the same yellow colour slightly tinged with gray is seen to pervade the whole of the cortical part, and the tubular portions are of a lighter colour than natural. The size of the kidney is not materially altered, nor is there any obvious morbid deposit to be discovered. . . .

The *second* form of diseased kidney is one in which the whole cortical part is converted into a granulated texture. . . . This in its earliest stage produces externally, when the tunic is taken off, only an increase of the natural fine mottled appearance given by the healthy structure of the kidney; or under particular circumstances, gives the appearance of fine grains of sand sprinkled more abundantly on some parts than others. On making a longitudinal section, a slight appearance of the same kind is discovered internally, and the kidney is generally rather deficient in its natural firmness. . . . When this disease has gone on for a very considerable time, the granulated texture begins to show itself externally, in frequent slight uneven projections on the surface of the kidney; so that the morbid state is readily perceived even before the tunic is removed. The kidney is generally rather larger than natural. . . .

The *third* form of disease is where the kidney is quite rough and scabrous to the touch externally, and is seen to rise in numerous projections not much exceeding a large pin's head, yellow, red, and purplish. The form of the kidney is often inclined to be lobulated, the feel is hard, and on making an incision the texture is found approaching to semicartilaginous firmness. . . . It appears in short like a contraction of every part of the organ, with less interstitial deposit than in the last variety. . . .

Although I hazard a conjecture as to the existence of these three different forms of disease, I am by no means confident of the correctness of this view.—*Original Papers of Richard Bright on Renal Disease.* Edited by A. ARNOLD OSMAN. London, Oxford University Press, 1937, pp. 67-70.

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