MEDICAL GRAND ROUNDS

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Idiopathic Hypertrophic Subaortic Stenosis

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During the past decade, idiopathic hypertrophic subaortic stenosis (IHSS), a previously unrecognized form of heart disease, has attracted the interest and attentinn of clinical cardiologists, cardiovascular physiologists, radiologists, internests, and surgeons. It is now quite clear that IHSS is not a particularly rare form of heart disease, and it is also recognized that it possesses unique anatomical, physiological, pharmacological and clinical features. The disease entity presents in a broad spectrum of pathophysiological and clinical manifestation. Now it is important to review the features of the disease, and emphasize the changes in therapy and natural history of the disease which have evolved during the past ten years.

The first published description of IHSS was that of Schemincke*(1)*, of Weurzburg, Germany, in 1907, who presented "the gross and pathologic findings of two adult women with diffuse hyperplasia" of a muscular mass constituting the wall of the left ventricular outflow tract. He considered the condition to be congenital in origin, and speculated that the condition might cause left ventricular outflow obstruction. Following this, Bernheim*(2)* described several patients with eccentric hypertrophy of the left ventricle of unknown etiology. This hypertrophy caused the septum to bulge into and obliterate portions of the right ventricular cavity. This clinical entity still bears his name, and probably represents examples of IHSS with right ventricular outflow obstruction. In 1952, Davies*(3)* described a family whose members had heart disease with systolic murmurs and the history of sudden death. The pathological findings in this family were those of IHSS. Following Brock's*(4,5)* clinical report in 1957 and the pathological descriptions of Teare*(6)* in 1958, a large number of papers have appeared describing the clinical entity with it's varied pathophysiology*(7-15)*. Synonyms which have arisen for the disease include hypertrophic obstructive cardiomyopathy, and muscular subaortic stenosis. Before progressing to a detailed analysis of the disease process, it is important to briefly outline the differential diagnosis of left ventricular outflow obstruction. Refer to Table I and Figure I. The most common form of outflow obstruction is that of aortic valvular obstruction, while idiopathic hypertrophic subaortic stenosis is the second most common variety. The discrete subvalvular aortic stenosis is relatively uncommon, especially in adult cardiology, and supravalvular aortic stenosis is very rarely seen in the adult. The findings on cardiac examination, electrocardiogram, chest x-ray, and associated lesions are outlined in brief in Table I, and should be self explanatory.

PATHOLOGY AND PATHOLOGIC ANATOMY

GROSS ANATOMY

The gross anatomical findings in IHSS have been described in detail by a number of observers*(8,9,10,14)*. The universal finding in these patients is a marked increase in heart weight, which usually exceeds 500 gms. in adults. This increase in heart weight is primarily due to hypertrophy of the left ventricle, which enroaches upon the left ventricular cavity, which, on cross section, is slit like. Left ventricular dilitation does not occur, and its presence is incompatible with diagnosis of IHSS, since with dilitation the left ventricular wall and septum do not encroach upon the cavity, and do not obstruct left ventricular emptying. Grossly, there are two types of left ventricular hypertrophy which may be responsible for IHSS. The most common form is that of asymmetric hypertrophy. Teare has described diffuse hypertrophy of the interventricular septum, particularly of its upper portion adjacent to the anterior leaflet of the mitral valve. Several of his specimens had hypertrophy involving the anterior wall of the left ventricle, while the posterior wall was spared. Pare*(14)* described the asymmetric ventricular hypertrophy as a nodular muscle mass in the cephalic portion of the ventricular septum. The hypertrophied septum, and in some instances the hypertrophied anterior wall of the left ventricle, bulges into and impinges upon the lumen of the left ventricular outflow tract. In some hearts, these abnormalities resemble a complete ring of muscular tissue 1 to 3 cm. below the aortic valve*(16)*.

Menges and collaborators*(10)* have shown that if the ratio of the thickness of the septum to that of the free wall of the left ventricle exceeded 1.3, then the possibility of muscular subaortic obstruction during life should be considered. In post mortem examinations the diagnosis may be difficult, simply because the obstruction to the outflow tract is primarily a dynamic process during systole and little obstruction may occur during diastole or in the arrested heart, as seen at post mortem. In addition to the septal hypertrophy, there may be marked hypertrophy of the papillary muscles and trabeculae carnae, and endocardial thickening may be present. Deformity of the mitral valves has been observed in several patients. The mitral valve may be distorted and thickened due to its regurgitation and constant motion against the septum. Bjork and associates*(17)* have described a mal-insertion of the mitral leaflet which they consider to be an etiological factor in the obstruction of the outflow tract. Dinsmore and associates*(18)* consider that the distortion of the mitral leaflet may be due to abnormal traction by chordae tendineae due to the hypertropied septum. These factors may also be contributory to the mitral regurgitation.

The second form of hypertrophy, and less common than the asymmetric type seen in IHSS, is that of a relatively consentric hypertrophy of the entire ventricular wall. Marked impingement on the lumen of the left ventricle is present. These patients may demonstrate the same type of outflow obstruction, but the gradients are usually less than in the asymmetric form of hypertrophy.

In addition to the left ventricular outflow tract, the right ventricular outflow tract may be involved as well. In these cases, there may be hypertrophy of the free wall of the right ventricle. More commonly, the hypertrophied septum bulges into the right ventricular outflow tract.

In summary, there are three anatomic features which characterize muscular subaortic stenosis:

1. Severe hypertrophy and bulging of a portion of the ventricular septum.
2. Thickening of the endocardium and the outflow tract of the left ventricle.
3. Abnormal mitral valve, usually with focal fibrous thickening of the leaflets, particularly the anterior ones, and abnormalities in length of the chordae tendineae.

In addition, the left atrial cavity may also be dilated. The aortic valve is almost always normal(19) in IHSS.

HISTOPATHOLOGY

Teare first pointed out that the muscle fibers in IHSS were abnormal, there seem to be a bizarre arrangement of the muscle fibers which separate large quantities of connective tissue into clefts, in which fibers run at multiple directions. These findings have been confirmed by other investigators. The muscle fibers themself seem to be thickened, although this is not a consistent finding and may be sporadic in the same heart. There is no evidence of inflammatory reaction in the myocardium.

ANGIOGRAPHIC ANATOMY

The anatomical disarrangement can best be seen when large film angiograms are taken in the PA and lateral view, or when cineangiograms are taken in the LAO position. In films exposed during diastole, the outflow tract in IHSS is narrowed by the hypertrophied muscular interventricular septum and appears as an inverted cone. This cone is formed by the hypertrophied septum anteriorly and the open anterior mitral leaflet posteriorly. In films exposed during systole in patients with IHSS, the hypertrophied ventricular septal protrudes into the outflow tract, and the leading edges of the leaflets of the mitral valve are seen held in the outflow tract, creating a curved, shelf like deformity projecting against the septum. This is predominately the anterior mitral leaflet, although on occasion the posterior mitral leaflet may

contribute in part to this obstruction. At catheterization, this area seen on the angiograms can be demonstrated to be the point at which the obstruction occurs(20). Mitral regurgitation can be seen in at least 50% of patients with IHSS. The degree of mitral regurgitation varies from minimum to moderate. It is of interest to note that one patient that had severe mitral regurgitation that underwent surgery for IHSS by Dr. Marrow(21) at the National Institutes of Health, had complete relief of mitral regurgitation after removal of a portion of her septum without any surgery involving her mitral valve.

The concept of pathogenesis of the obstruction in patients with IHSS may be developed as follows. Asymmetric hypertrophy in the ventricular septum is the primary alteration. Narrowing of the anterior portion of the outflow tract occurs due to direct impingement of hypertrophied muscle. The inferior portion of the hypertrophied septum reflects into the diaphragmatic aspects of the ventricular cavity, resulting in a change in the axis of the papillary muscle. This protrusion of the inferior portion of the septal mass also causes obliteration of the left ventricular cavity, resulting in a very low apex to base shortening of the left ventricle. The angulation of the papillary muscles and the lack of apex to base shortening causes abnormal traction on the chordae tendineae, and hence on the mitral valve leaflets during systole. Therefore, the mitral leaflets do not complete their normal excursion in the outflow tract during systole, and thus produce an obstruction against the hypertrophied septum, since both leaflets are pulled forward during systole. The net effect is to produce left ventricular outflow obstruction during systole and mitral regurgitation.

SEX, RACE, AGE, AND GENETIC LINKAGE

IHSS presents in two forms, a familial variety and a sporadic variety. There is a significant difference in the presentation and distribution of patients with the familial form of IHSS when compared with that of the sporadic form of the disease. Of the cases reported in the literature, approximately 30% tend to be familial, while 70% are sporadic. This difference may, in part, be due to the fact that some familial cases may well be placed in the sporadic group because of the lack of family history or follow up. There seems to be little evidence for race predication of the disease, since the distribution is about comparable to the race distribution in our general population(22).

Patients with familial IHSS tend to be younger, with the average age of 27 years at the time of presentation, whereas those with sporadic IHSS average 33 years at presentation. The age of patients discovered with IHSS ranges from six years to seventy four years of age. In the careful genetic studies in the familial form of the disease, the male to female ratio tends to be equal, while in the sporadic variety, only 28% of the patients were female.

The clinical manifestations of the disease seem to be less disabling in patients with the familial variety than in patients with the sporadic variety. This may, in part, be due to the fact that in the course of the familial follow up of the disease many of the patients were detected and studied who were asymptomatic, whereas those patients with the sporadic form tend to present themselves after symptoms become Manifest. Hemodynamic studies reveal less abnormal findings in patients with the familial variety. However, the mortality rate does not seem to vary between the sporadic and familial forms of the disease.

The genetic analysis is best exemplified by the family trees presented in Figure V*(23)*. There is no significant deviation from the expected family members by sex or sibship. The analysis does suggest there is some age dependency from the expression of the trait, since the younger age group in the familial disease tends to be spared. The largest and most thoroughly studied family is that presented by Nasser and his group*(24)*. He studied a negro family with 30 family members and performed cardiac catheterization in 20 of the individuals. He has clearly shown there is no disturbance in the segregation ratio of .5, expected in the case of autosomal dominant inheritance when comparing the affected sexes. Penetrance seems to be complete. The age of onset could not be determined.

They conclude that the disease is autosomal dominant with complete penetrance and varied expressivity, but the expressivity is influenced by age.

HISTORY

Approximately one third of the patients with proven IHSS present with a heart murmur which was detected, but had no symptoms at the time of presentation. In the remainder of the patients that were symptomatic, the predominant symptom which occurred first was that of dyspnea. The following is a summary of presenting symptoms.

FIRST PRESENTING SYMPTOM (23)

Dyspnea	60%
Angina	10%
Syncope	10%
Palpitations	8%
P N D	4%
Acute pulmonary edema	4%
Dizziness	2%

At the time of presentation for evaluation for cardiac catheterization, the symptomatology changed slightly: 69% of the patients present with dyspnea, 39% with angina, 34% with dizziness, 31% with PND, 30% with syncope, 20% with edema, and 17% with palpitations. It is interesting to note the progress of symptoms is that from dyspnea to angina and dizziness. The first symptom is usually that of easy fatigability. However, this is rather non-specific and difficult to analyze, and therefore is not included. The average age of onset of symptoms was around 23 years of age.

The symptoms from IHSS are similar to those, and perhaps indistinguishable from those of other forms of aortic stenosis. There is one striking difference, however, in that the syncopal attacks which occur with IHSS seem to be more benign than with valvular aortic stenosis. The syncopal attacks have been reported to disappear or certainly regress in frequency with IHSS, which is extremely unusual in valvular aortic stenosis. In addition, the syncope is not necessarily associated with hemodynamic evidence of severe obstruction in IHSS. This may be due to the fact that the dynamic obstruction in IHSS changes from time to time. The syncope frequently occurs *after* a bout of difficult effort, rather than during physical exertion as with valvular aortic stenosis(22). The syncope may be orthostatic in nature, which is not surprising, considering the hemodynamic changes which occur in the upright position with IHSS.

PHYSICAL FINDINGS AND PHONOCARDIOGRAPHY

Subaortic obstruction is a dynamic process, for this reason, the stenosis varies in severity from time to time, resulting in varied phonocardiographic and ausculatory findings. Certain maneuvers can increase the vigor of ventricular contraction, which will increase the subaortic obstruction and change the physical findings which can be used for diagnostic aids.

The carotid pulse displays a highly characteristic abnormality*(25)*. There is a very rapid upstroke, faster than the normal upstroke time, which occurs in early systole(See Figure II and III). There then follows a dip and a late flow systolic wave, giving the impulse a bifid appearance. The total ejection time may be slightly longer than normal, but the upstroke time may be shorter than normal. This wave form differs sharply from that seen in fixed, subvalvular or valvular aortic stenosis, which has an extremely slow upstroke time (see Figure II).

The bifid pulse contour is found in approximately 65% of the patients, and correlates very well with the pressure gradient. The pressure gradient averages 66 mm mercury in the patients with the bifid pulse contour, whereas many of the patients with a normal contour have no pressure gradients at rest*(22)*.

The heart size is considered to be enlarged on physical examination in over 2/3 of the patients. However, enlargement is never severe. Most all of the patients have an increased precordial activity, which is primarily left ventricular in nature, and frequently associated with a double, or triple apical impulse (Figure IV).

The apex cardiogram is quite striking in IHSS. There is a triple, apical impulse which may be felt as well as recorded in most cases*(26)*. The first portion of the triple impulse is the A wave, which is taller than usual. The other two components of the triple impulse occur during systole. The first systolic impulse is that of the initial rapid ejection during systole, and the second systolic apical wave reflects the appearance of subaortic obstruction midway in systole. These two waves correspond with the two wave forms reflected by the carotid pulse. Precordial thrills are palpable in approximately one half of the patients, and correlate well with a large pressure gradient.

As a result of subaortic stenosis, a mid-systolic crescendo-decrescendo (diamond shaped) murmur is produced which is best heard and recorded in the lower left sternal border and toward the apex*(27)*. Little or no radiation to the neck occurs. The murmur begins relatively late after the first heart sound, as long as 0.1 sec., reaching a peak midway in the systolic period*(28)*. It tappers rapidly and disappears shortly before the aortic second sound (Figure III). It's timing is generally constant, regardless of the severity of aortic obstruction. Amyl nitrite causes the murmur to intensify considerably. This response to amyl nitrite is similar to the response of the systolic ejection murmur of many other conditions, but it is more intense and serves to distinguish the murmur of IHSS from the systolic "regurgitant" murmurs of ventricular septal defect and mitral insufficiency. The classical and unique feature of the murmur of IHSS is its marked intensification

during the straining period of a valsalva maneuver in contrast to other systolic murmurs which decrease during this phase(29). This is a diagnostic, ausculatory feature of the disease. An additional diagnostic feature is the decrease in carotid or peripheral pulse pressure in a post PVC beat, which may be palpated or recorded with the phonocardiogram(19). A fourth heart sound is quite prominent and reflects the compliance change of the left ventricle in this disease. The findings on physical examination in IHSS are summarized on the following table, and a comparison made with valvular aortic stenosis.

COMPARISON OF PHYSICAL FINDINGS IN IHSS AND VALVULAR A.S.

I. Common characteristics of both divisions

a. L.V. Left
b. Third heart sound
c. Systolic murmur

II. More common with IHSS

a. Double and especially triple apical impulse with the last two components in systole
b. Loud 4th heart sound
c. Prominant A wave in J.V.P.
d. Normally split S_2

III. More common with Valvular A.S.

a. Systolic thrill
b. Single S_2 or paradoxically split S_2

PHYSICAL FINDINGS	*IHSS*	*VALVULAR A.S.*
Locating murmur	L.S.B. or apex No radiation to neck	Basal with radiation to neck
Type of murmur	Holosystolic or ejection	Ejection
Ejection click	Rare	Common
Diastolic murmur	Rare	Common
Arterial pulse	Rapid upstroke, Bisferin's	Delayed upstroke
Pulse pressure	Increased or normal	Decreased or normal
Murmur with valsalva	Increases	Decreases
Post PVC pulse pressure	Decreases or no change	Increases
Post PVC murmur	Increases	Increases

It should be emphasized that not only is the differential diagnosis between valvular aortic stenosis and IHSS, but also must be made between IHSS and mitral regurgitation. Many of these patients are originally diagnosed as having mitral insufficiency on a rheumatic basis. The reasons for this are quite evidence since the arterial pulse is not characteristic of that of valvular aortic stenosis, and the location of the murmur is more typical of that of mitral regurgitation at times than of aortic stenosis. The electrocardiogram shows frequently, left ventricular hypertrophy and left atrial enlargement, adding to the difficulty.

THE ELECTROCARDIOGRAM

The predominant abnormalities in the electrocardiogram in IHSS occur in the QRS complex, and have been virtually documented in all patients with idiopathic hypertrophic subaortic stenosis. Among the more remarkable findings described have been broad Q waves, suggesting myocardial infarction*(11,30,31,32)*, and tall R waves in the precordial leads consistent with left, right, or combined ventricular hypertrophy*(33)*. In the absence of coronary artery disease, the Q wave abnormalities have been interpreted as an effect of septal hypertrophy*(34)*. Their diminution with the passage of time occasionally occurs, and has been interpreted as an effect of late or delayed hypertrophy of the free wall of the ventricle in response to resistance imposed by an impingement of the hypertrophied septum upon the outflow tract area*(33)*. Gorlan*(36)* describes a vector pattern which will often differentiate the patterns of myocardial infarction and IHSS. Analysis of the .02 sec. horizontal plane vector allows discrimination between true myocardial infarction and IHSS. The vector in IHSS is shifted anteriorly and to the right, consistent with septal hypertrophy and increased left to right early septal forces, which can be differentiated from acute anterior myocardial infarction when the vector is shifted posteriorly.

The largest series of electrocardiographic analysis is again that by Frank and Braunwald*(22)*, in 123 patients with IHSS, which is summarized below.

RHYTHM

Normal simus rhythm occurred in 92% of the patients. Eight percent of the patients presented in atrial fibrillation, and 10% of the patients had ectopic beats, 7% were ventricular, and 3% either atrial or nodal beats.

ELECTRICAL AXIS

Electrical axis was normal in 63 of patients, left axis in 30%, right axis in 2%, and indeterminate axis in 5%.

"P" WAVES

The P wave was normal in 50% of the patients, showed left atrial enlargement in 30% of the patients, and right atrial enlargement in 8% of the patients. Left atrial enlargement tended to occur in patients with worse disease.

P - R INTERVAL

The P - R interval was normal in 81% of the patients, and was short or long in 19%. Wolff-Parkinson-White syndrome occurred in 3% of the patients with all three criteria satisfied, and in 9% of the patients with two of the three criteria satisfied.

QRS DURATION

Eighteen percent of the patients manifested abnormalities in intra-ventricular conduction. Two showed patterns characteristic of left bundle branch block; four had patterns of right bundle branch block; and 16 had patterns which were characterized as intra-ventricular conduction defects. Peri-infarction block has been noted to occur occasionally.

Q WAVE ABNORMALITIES

Fifty six percent of the patients exhibited abnormal Q waves, usually occurring in limb leads, but occasionally found in right precordial leads and left precordial leads. The electrocardiographic finding of Q wave abnormalities does not seem to correlate with the severity of the outflow obstruction, age, or degree of disability, but is the most characteristic abnormality.

LEFT VENTRICULAR HYPERTROPHY

Seventy per cent of the patients satisfy the electrocardiographic criteria of left ventricular hypertrophy with S in V_1 plus R in V_5 or V_6 exceeding 35 millivolts. This finding correlates with a higher pressure gradient and a more disabling disease symptomatically.

HEMODYNAMICS

The hemodynamics have now been elucidated quite clearly in hypertrophic subaortic stenosis. There has been a large number of patients that have been studied by catheterization as completely as any disease has been studied. It is clearly appreciated, that this disease char-

acteristically has changing patterns of hemodynamics, which may change from minute to minute in any given patient, and during any one catheterization. This makes the findings quite variable in this disease, but yet they are distinctive.

The characteristic finding is that of a large intraventricular systolic pressure gradient between the body of the left ventricle and an infundibular chamber just above the septum and mitral valve leaflets. Characteristically, there is no gradient between this subvalvular chamber and the aorta.

In IHSS, ejection is rapid in early systole and obstructed in late systole, producing the characteristic early quick rising arterial pulse*(37)*. The left ventricular chamber is small and empties more completely than normal in systole*(38,39)*. In cardiac cycles following post-extra systolic pauses, the obstruction may increase markedly, resulting in an inverse relation of arterial pulse pressure with increasing cycle length*(40)*. In general, obstruction is increased by a wide variety of drugs and physiologic maneuvers which either increase myocardial contractility or decrease left ventricular volume*(41,42)*. There is also some evidence that a lowered arterial diastolic pressure tends to increase the degree of obstruction by a mechanism independent of ventricular volume or myocardial contractility*(42)*.

SYSTEMIC ARTERIAL PRESSURE

Generally the patients are normo-tensive or slightly hypotensive. However, a few patients have been reported that were hypertensive. The arterial pulse pressure is usually normal, ranging between 30 and 50 mm mercury. This is in contrast to the diminished pulse pressure seen in other forms of discrete aortic stenosis.

RIGHT HEART CATHETERIZATION

The right atrial mean pressure is usually normal, but characteristically there is a large "a" wave. This "a" wave may be an indication of mild pulmonary hypertension, but usually is indicative of decreased compliance in the right ventricle*(22)*.

RIGHT VENTRICULAR PRESSURE

The right ventricular end diastolic pressure is frequently elevated, above 6 mm mercury, in many of these patients. This may be secondary to pulmonary hypertension or to right ventricular obstruction, but in the absence of either, then it is secondary to a compliance change in right ventricle. In general, the peak systolic right ventricular pressure corresponds to pulmonary artery pressure. The pulmonary artery pressure averages 28 mm mercury with a range from 13 to 96 mm mercury. The

tendency was for most patients to have upper limits of normal pulmonary artery systolic pressure, but with occasinnal patients having quite markedly elevated pressures. The disability of the patient clinically seemed to follow the pattern of elevated pulmonary artery pressure. It is now well known that right ventricular obstruction may occur from septal hypertrophy in myocardopathies in a similar manner as left ventricular obstruction occurs. In a review of the literature, the following number of cases were reported of right ventricular obstruction (see Table V) *(13,43-48)*.

It is of interest that several of these patients had only right ventricular gradients, with no evidence of left ventricular disease. Provocative testing in the left side was negative in some of these patients, but positive on the right side. These patients that had right ventricular gradients were no more symptomatic than the patients that had left ventricular gradients*(22)*. The combination of the two gradients did not seem to make the patient more severely ill or symptomatic than the single isolated left sided lesion. There apparently are two types of obstruction in the right ventricle. One is a separate isolated chamber in the right ventricle that develops high pressure during systole, and the other seems to be a subvalvular obstruction beneath the pulmonary valve. These right sided gradients are increased by isuprel and decreased by propranolol, and often show post-extra systolic potentiation of the gradient*(49)*. The type of obstruction is frequently only diagnosed by cineangiography.

CARDIAC OUTPUT

The cardiac output in most patients tend to be normal. The cardiac index for the group of patients studied by Frank and Braunwald was 3.5 L/min/M^2 BSA. There is an occasional patient reported that has a high cardiac output, and a few patients have low cardiac outputs, especially when they are in Class 4 category*(22)*.

LEFT HEART CATHETERIZATION

Interventricular pressure gradients that are recorded in patients with IHSS differ in many respects from those observed in patients with various discrete forms of obstruction to left ventricular outflow. It is now generally recognized that the pressure gradient measured in a resting state may bear little relation to the severity of the patient's symptoms.

The left ventricular dynamics are summarized in Table II *(13,22,50-59)*. It can be seen that the gradients from the body of the left ventricle to the aorta varies considerably. These range from 0 to 175 mm mercury with an average of 65 mm mercury. It must be emphasized that these gradients may change with various drugs and physiologic states which may occur in any one given catheterization. The left ventricular end diastolic pressure is almost universally elevated. The average is 19 mm mercury, with ranges from 0 to 55 mm mercury. This elevated left ventricular end diastolic pressure is a manifestation of the marked

hypertrophy and compliance change of the left ventricle in this disease.

The majority of patients with IHSS exhibit a distinct notch in the ascending limb of the left ventricular pressure pulse. This is a characteristic of the disease(51,60,61). The mechanism responsible for the production of this notch has not yet been elucidated. This may bear a relationship to the observation that a large fraction of stroke volume is expelled during the first half of the ejection. This may relate to the slowing of the pressure rise just prior to the occurrence of the dynamic obstructive process.

The obstruction is localized during left heart catheterization by a pull back of the catheter from the body of the left ventricle to just above the anterior leaflet of the mitral valve, where the subvalvular chamber is found (Figure VI). This is about 2-4 cm below the aortic valve. There is an abrupt pressure drop at this point, the systolic pressure being the same as the aortic systolic pressure. The diastolic pressure at this point is the same as the diastolic pressure in the left ventricle. To further define the area of obstruction, many patients have had trans-septal left heart catheterizations with a pull back from the cavity of the left ventricle to the left atrium. There is a continuation of a large pressure gradient between the left ventricle and the brachial artery until the catheter reaches the mitral valve, at which point the pressure abruptly drops to that of the left atrial pressure. This indicates that the obstruction is somewhere in the outflow tract of the left ventricle, rather than being in the obliterated cavity or the inflow tract of the left ventricle.

Stewart, Mason, and Braunwald(62) have shown there is also an impairment of left ventricular filling in IHSS, due to a decreased left ventricular compliance rather than any type of anatomical obstruction in the inflow tract or mitral valve.

The ventricular volume has been analyzed by cineangiography by Rackley(58), who has shown that the diastolic ventricular volume is normal or slightly diminished in IHSS, and that the systolic volume is smaller than normal in almost all cases. This is compatible with the findings at port-mortem examination of patients who had died with IHSS.

LEFT ATRIAL PRESSURES

The left atrial pressures tend to be elevated in most of the patients, corresponding to the rise of left ventricular end diastolic pressure. A characteristic finding in the left atrium is the "a" wave which exceeds the "v" wave. This is a reverse of the usual hemodynamic finding. On fluoroscopy and cineangiography, the large atrial kick can be seen, which is due to the strong atrial contraction from the hypertrophied left atrium.

Mitral regurgitation is a frequent finding in these patients, and a mechanism has been suggested by Dinsmore, Sanders, and Harthorne(18),

seems the most plausible. They feel that the mitral regurgitation is secondary to papillary muscle dysfunction, which occurs as part of the abnormal ventricular contraction. The increased tension produced on the chordae tendineae by the papillary muscle contraction interferes with the normal mechanism of the mitral leaflets, preventing effective closure of the mitral leaflets during systole. Wigle*(63)* has shown very nicely with regurgitant dye studies measured from the left atrium, that the mitral regurgitation is proportional to the amount of left ventricular outflow obstruction. He reduced left ventricular aortic gradient by infusing angiotensin, and concomitantly showed that the amount of mitral regurgitation dramatically decreased.

PHYSIOLOGIC AND PHARMACOLOGIC INTERVENTIONS

PULSE PRESSURE RESPONSE TO PREMATURE CONTRACTIONS (PVC RESPONSE)

In normal individuals, the cardiac cycle following a premature contraction is characterized by a ventricular contraction which is more forceful than the normal ones which preceed the premature ventricular contraction. This more forceful contraction manifests itself in the higher peak systolic left ventricular and arterial pressures, in longer duration of ejection, and a greater arterial pulse pressure in the cycle following the premature beat. The augmented arterial pulse pressure, which characterizes the post-premature beat, is due to the increase in stroke volume, such as aortic stenosis, the post-extra systolic beat is also more forceful than the normal beats, and therefore the arterial pulse pressure is normally increased since more blood is ejected through the same fixed orifice size with the increase in contractile state (Figure VIII).

Patients with IHSS, however, have a paradoxical relationship in that the pulse pressure in the post premature contraction beat either remains the same or decreases (Figure VII). This is probably due to the fact that the augmented contractile force in the left ventricle causes a marked increase in left ventricular outflow obstruction in this dynamic process. This is almost a universal and diagnostic phenomena. Almost all the patients with IHSS exhibit this post PVC response*(64)*.

There is considerable confusion about this PVC response. It must be remembered that the pulse pressure measured in the aorta is decreased in the beat following the PVC and not with the PVC itself. In addition, it must be remembered that the gradient across the outflow obstruction increases in all forms of outflow obstruction, and this is not a helpful finding.

MUSCULAR EXERCISE

The left ventricular aortic gradient is usually increased during exercise. However, in some patients, this occurs immediately following exercise*(23)*. It is not surprising that these patients have poor exercise tolerance since exercise tends to cause a profound sympathetic stimulation in the heart which in itself, causes an increase in contractility, a decrease in heart volume, and an increase in left ventricular outflow obstruction. This finding correlates with the clinical findings in patients often experiencing angina, syncope,or severe dizziness immediately after exercise rather than during the actual period of exertion when venous return is augmented. This is in contrast to fixed type of aortic stenosis where these symptoms are usually associated with the exertinnal episode itself.

INCREASING VENOUS RETURN

It has been shown by Mason et al*(65)* that a change in body position of patients with IHSS may change their LV-aortic gradient significantly. Many patients who have very little or no gradient during the supine catheterization, when placed on a tilt table and tilted to the upright position, will dramatically increase their left ventricular aortic gradient. This is due to a decrease of venous return and a decrease in left ventricular cavity volume with an increase in outflow obstruction. This same manifestation can be elicited by simply leg raising and lowering while supine.

VALSALVA MANEUVER

The valsalva maneuver has been shown to reduce cardiac dimensions and to diminish the inflow of blood into the thorax. In patients without obstruction to ventricular outflow, the maneuver results in an elevation of absolute left ventricular and aortic pressures, but it does not induce a significant pressure gradient. In patients with valvular aortic stenosis, the valsalva maneuver lowers the trans-valvular pressure gradient, due to a reduction in stroke volume. In contrast, however, when patients with IHSS perform a valsalva maneuver, the left ventricular arterial pressure gradient rises in spite of the reduction in stroke volume (Figure IX). This is due to a reduction in the diminsions of the outflow orifice, which occurs when the venous return is suddenly reduced as the intraplueral pressure rises. The valsalva maneuver is one of the provocative tests which is applied to patients with IHSS for diagnostic purposes*(66,67)*. It is especially useful in patients that have no outflow obstruction at rest.

DRUG RESPONSE OF IHSS

DIGITALIS

The response of patients with IHSS to digitalis might be predictable. Since the action of digitalis is to augment myocardial contraction, it might well be speculated that patients with IHSS would increase the amount of outflow obstruction because of the increase in contractility, elicited by digitalis. It has been repeatedly demonstrated that a large and consistent increase in ventricular-arterial pressure gradient occurs after the administration of digitalis, The cardiac output falls or remains unchanged*(23)*.

It is recommended that digitalis not be administered to most patients with IHSS. This policy excludes patients with atrial fibrillation, in whom digitalis may be the only means of reducing the ventricular rate, and in patients with evidence of little or no obstruction to left ventricular outflow, and in patients in the early post-operative period following relief of obstruction. Patients that have been inadvertently placed on digitalis often get marked symptomatic relief upon discontinuance of the drug*(57)*.

SYMPATHOMIMETIC AMINES

The effect of the drug isuprel (Isoproterenol) is similar to that of digitalis, in that it is an intense inotropic agent which results in stimulation of beta adrenergic receptors and as a consequence, results in a marked augmentation of the contractile state of the muscular outflow tract. As a result, isuprel produces a striking increase in the gradient in IHSS. Many patients have been reported with familial IHSS and no resting gradients, but with isuprel may develop very large gradients IFigure X)*(69)*. In fact, this drug is used in provocative testing for the diagnosis of IHSS. Other sympathomimetic amines, which are primarily beta receptor stimulating drugs, have the same effect as isuprel. For this reason, these sympathomimetic drugs are usually contraindicated in the treatment of shock or hypotension in patients with IHSS.

NITROGLYCERIN

The fundamental mechanism of action of nitroglycerin is to cause arteriolar dilitation and as a consequence reduction in left ventricular dimensions throughout the cardiac cycle. This action also increases the left ventricular outflow obstruction which can be shown dramatically in the catheterization laboratory (Figure XII)*(66)*. Nitroglycerin should be prescribed with caution in patients with IHSS for this reason.

BETA ADRENERGIC BLOCKADE

Since those phyiologic and pharmacologic interventions, which result in an increase of contractility or increase in beta stimulatinn or sympathetic discharge, produce an increase in the left ventricular outflow obstruction and are detrimental to patients with IHSS, it seems only logical that blocking of the beta receptors would have a beneficial effect. Propranolol has been shown to dramatically decrease the outflow obstruction in IHSS*(70)*. In fact, it now is the major armamentarium for the pharmacological treatment. The administration of propranolol has been shown to block the effect of muscular exercise and Isuprel on the left ventricular outflow obstruction. This drug will be covered in more detail in the section of medical management.

ALPHA STIMULATING DRUGS

Methoxamine (Vasoxyl) and phenylephrine (Neo-synephrine) are two alpha receptor simulating drugs whose actions are primarily that of increasing arterial tone, which results in an increase in systemic blood pressure. Either of these drugs, when administered to patients with IHSS, consistently decrease the pressure gradient (Figure XIII). This is due to an increase in the systemic pressure which results in an increase in left ventricular dimensions. This results in a decrease in the outflow obstruction*(23)*.

In summary, the actions of many of the drugs used in cardiac patients have a paradoxical or detrimental effect on patients with IHSS. The drugs which are used for treatment of congestive heart failure and cardiogenic hypotension, such as digitalis and isuprel, are contraindicated in patients with IHSS. Nitroglycerin, which classicaly is used to treat angina, also produces an adverse hemodynamic effect. In patients who have become hypotensive the usual catechol amines are contraindicated and in their place must be used drugs such as Neo-synephrine or Vasoxyl.

Tables III and IV explain some of the mechanism involved in the various pharmacologic and physiologic interventions and their effect on the hemodynamics in IHSS.

It can be readily seen from the two tables that there are three operative mechanisms at work in IHSS. Anything which tends to decrease venous return, decrease arterial pressure, or increase contractility, tends to make the obstruction worse. Any factor which tends to increase arterial pressure, increases venous return, or has a negative inotropic effect tends to relieve the obstruction.

OUTFLOW TRACT OBSTRUCTION VS CAVITY OBLITERATION

After the initial description of the disease of IHSS and elucidation of an outflow tract obstruction in the left ventricle, several reports*(59,71,72)* began to appear which were not in agreement with the description of an outflow tract obstruction at the point of the septum and the mitral valve. Reports*(73,74)* began to appear in animal studies in which the catheter was entraped or obstructed against the myocardium or in a "pocket" within the trabeculae. This form of intramyocardial or intracavitory pressure rise is termed "cavity" obliteration".

It now seems quite clear there are two forms of intraventricular pressure differences which may be encountered within the left ventricle of man*(70,75,76,77,78)*. In the muscular type of subaortic stenosis all pressures proximal to the outflow tract obstruction including that just inside the mitral valve (which is the inflow tract pressure), are elevated above the systolic pressure in the outflow tract distal to the stenosis. In the second type, there is an intraventricular pressure difference which results from catheter entrapment. In this instance an elevated ventricular systolic pressure is recorded only by the entraped catheter and all other truely intracavitary pressures are not elevated, including the initial inflow tract pressure. This is not IHSS, but rather an artifact of catheterization.

The finding that in patients with IHSS approximately 80% of the stroke volume is ejected during the first half of left ventricular systole led Hernandez and coworkers*(79)* to consider the possibility that no obstruction of left ventricular outflow occurred in this disease. They postulated that in fact the high pressure may exist only in the trabeculations in the wall of the empty ventricle. Burchell*(80)*, on the basis of angiographic observations, also raised the possibility that a small apical portion of the left ventricle might act as a self obstructive diverticulum. Criley*(71)* proposed the high ventricular pressures in IHSS resulted from sustained contraction in obliterated portions of the left ventricular cavity. He felt that the increased pressure gradients in IHSS patients with post-premature beats and after isuprel were associated with more rapid and complete ventricular emptying, rather than evidence of increased obstruction. He experimentally produced these cavity obliterations or cavity entrapment pressures in animals*(74)* and clearly showed this was a distinct entity. He made a very important contribution in differentiating artifactual pressures produced during catheterization in non-obstructive disease. Criley pointed out that cavity obliteration without obstruction should be strongly considered in the following circumstances.

1. When the ventricle empties rapidly to a small volume.
2. When provacative maneuvers are required to produce a significant gradient, since these maneuvers may produce a large pressure gradient in a normal ventricle without obstruction with catheter entrapment.
3. When there is no angiographic evidence of obstruction.

It now seems quite clear that cavity obliteration, especially as seen in animals and proven to occur in man, is entirely different from that of the disease IHSS. There is no abnormal PVC response in cavity obliteration, and no anatomical evidence of obstruction with either post-mortem studies or angiographic studies. Also, there is no evidence of the abnormally high left ventricular pressure occurring in the inflow tract as well as in the apex. It must be pointed out, that in order to differentiate between these two forms of intraventricular pressure gradients, it is necessary to measure the pressure in the inflow tract of the ventricle. In other words, it is of importance to obtain a pull back pressure from the left ventricle to the left atrium to show that the gradient between the left ventricular cavity and the aorta exists at the inflow tract site, as well as in the cavity of the left ventricle. This differential point has been clearly defin ed by Ross and Wigle*(76,77)*, as shown in Figure XIV.

Since the discription of these two types of intraventricular pressure differences, several reports have appeared which have clearly elucidated the two types. Wigle*(77)* has clearly shown the difference in the inflow pressures in the two types, and in addition, he has reported one patient*(75)* which had both right ventricular outflow obstruction compatible with the IHSS variety and cavity obliteration in the left ventricle.

The importance of differentiating these two conditions cannot be over emphasized. The treatment of the patient with IHSS may be surgical, whereas the cavity obliteration patient would certainly not be subjected to surgical intervention.

NATURAL HISTORY OF THE DISEASE

Long term follow up of patients with IHSS elucidated a number of important features concerning its natural history. First of all, it is clear that the course of the disease is often extremely variable. The symptomatic patients tend to be significantly older than those which are asymptomatic. The patients who are asymptomatic when initially seen tend to remain so, while those who are disabled generally tend to deteriorate, become more disabled, or die. A few of the patients with symptoms spontaneously improve, however it is extremely difficult to predict the course in any given patient. Sudden death is certainly a feature of the disease, and is often seen in any series of patients which are reported. It is of special interest to note that sudden death frequently occurs in patients with the familial form of the disease and very mild or no obstruction at rest.

A group of 126 patients reported from National Heart Institute by Frank and Braunwald*(22)* have been the most thorougly studied in terms of natural history and course of the disease, as shown in Figure XV. These patients have been followed up to twelve years.

CLASS I

Seventy one percent of the patients who presented themselves as Class I patients showed no function change during the follow up period. Fifteen percent of the patients developed clinical deterioration, several of these seem to occur after a bout of arrhythmia. The remainder of the patients who became symptomatic developed symptoms of angina pectoris, syncope, or symptoms of congestive heart failure. Only one patient deteriorated into Class III. The other patients remained in Class II. One patient died suddenly, while three patients were operated upon because of a progressive downhill course.

CLASS II

Of the patients who presented themselves as Class II patients, less than 1/2 of these remained stable, the other half progressively deteriorated. Ten percent of these patients died suddenly. Ten percent of the group also progressively deteriorated, while 20% fluctuated between Class II and Class III. It is important to note that none of these patients improved and became Class I patients after presenting as Class II patients.

CLASS III

Twenty five percent of the patients presented as Class III patients or Class IV patients. *Seven* of these patients were operated upon because of their symptoms. In the unoperated group, four died, two of them in refractory failure, and two died suddenly. Of considerable interest is that about 20% of these patients improved to Class II from their initial presentation as Class III patients.

MORTALITY STATISTICS

Fourteen percent of the patients who were followed at the Heart Institute died during the course of the 12 year follow up study. This constituted 14 patients. Four of these deaths could not be considered to be a direct result of the natural history of IHSS, but died of other causes. Ten deaths were due to the direct consequences of IHSS. Six of these deaths were sudden and in these patients the LV-aortic gradient average was 23 mm mercury during their initial catheterization. In four patients, death followed progressive increasing disability. The average gradient at initial catheterization in these four patients was 56 mm mercury. It is of interest to note that half of the patients had the familial form of the disease, while half the patients had the sporadic form of the disease. This finding suggests that instances

of sudden death were not the result of severe obstruction of left ventricular outflow, and occurred equally in both familial and sporadic forms of the disease (Figure XII). It is likely sudden death resulted from cardiac arrhythmias, although there is no definite concrete data to support this. These findings *do not* support the recommendation of operative treatment for asymptomatic or mildly disabled patients with no hemodynamic obstruction, since the death rate did not correlate with the severity of the obstruction.

INFECTIVE ENDOCARDITIS

Infective endocarditis is a little known complication of IHSS, though it may not be uncommon.

Boiteau and Allenstein*(81)* in 1960 described two cases, one of which had evidence of healed endocarditis on the mitral valve at necropsy. Soulie et al*(51)* in 1962,and Linhart and Taylor*(82)* in 1966 reported two additional cases. Frank and Braunwald*(22)* in 1968 have recorded three other well documented cases. In one of these, the aortic valve was seen at operation to have been the site of the infection. The same authors describe one probable and two possible other cases of endocarditis in patients with this condition.

Vecht and Oakley*(83)* in 1968 described three well documented cases of endocarditis associated with IHSS. The following table shows an analysis of the sites of infection in the reported cases.

AUTHORS	REF.#	TOTAL NO. OF SUBACUTE BACTERIAL ENDOCARDITIS	SITE OF INFECTION KNOWN	UNKNOWN
Boiteau and Allenstein,1961	*(81)*	2	1 mitral	1
Soulie et al, 1962	*(51)*	1		1
Linhart and Taylor, 1966	*(82)*	1		1
Frank and Braunwald, 1968	*(22)*	6	1 aortic valve	5
Vecht and Oakley, 1968	*(83)*	3	1 mitral valve	2
Nagle, 1967	*(84)*	1	1 aortic valve	
	TOTAL	14	2 mitral valve 2 aortic valve	10

TREATMENT - DRUG THERAPY

It is well recognized that the severity of obstruction to left ventricular outflow in patients with IHSS may be variable and is profoundly influenced by the state of myocardial contractility. It has been shown that when the contractility is augmented by digitalis, by the administration of isuprel, or by muscular exercise, the obstruction frequently becomes more severe. It is also well known that the beta receptors are stimulated under some of these conditions, and therefore it seems only logical that drugs which block the activity of the beta receptors would be beneficial in IHSS.

Harrison et al*(85)* studied a group of patients with Nethalide, a beta blocker, which is no longer in use because of its severe toxicity, in a group of ten patients with hypertrophic subaortic stenosis to determine the effects of adrenergic blockade. Nethalide has been shown to block the positive chronotropic and inotropic activity of catachole amines in sympathetic nerve stimulation in animals and the modified circulatory response to exercise in man without any apparent direct sympathomemetic effect. This was the first study with beta blockade in IHSS.

These authors found that there is no striking changes with beta blockade on the resting circulatory dynamics of patients with IHSS. The cardiac output, cardiac index, heart rate, and left ventricular-aortic gradient did not change after treatment with the drug. However, they did find that after treatment with Nethalide the response to isuprel was blocked. There was no increase in gradient, and no increase in heart rate from the isuprel after beta blockade. In addition, Nethalide reduced the augmentation of heart rate and rate of pressure development (dp/dt), in the ventricle after muscular exercise, thus diminishing the obstruction between the left ventricle and aorta during exercise.

Their conclusion was that beta blockade had very little effect on the resting hemodynamics of IHSS, and would be of little value to patients at rest in the supine position. However, the marked increase in augmentation of heart rate and obstruction with exercise in these patients suggested that beta blockade would be advantageous in treatment in the upright ambulatory position.

Cherian and group*(86)* was the first to study the effect of propranolol (Indural), a beta blocking agent which is now in therapeutic usage, in thirteen patients with IHSS. They found that propranolol effectively decreased or abolished the increase in the outflow gradient, resulting from exercise or isuprel infusion during these interventions, but had little effect on resting hemodynamics. Long term studies in thirteen patients showed subjective improvement in ten of these patients. They noted an increase in heart size in these ten patients, and postulated one of the mechanisms of action of beta blockade was to increase the heart volume, which in turn would decrease the outflow obstruction. They also speculted that the improvement in syncope in these patients may be due in fact to a relief of arrhythmias associated with the disease.

Following this report, Scheu et al(87) reported two patients with IHSS who underwent long term treatment with propranolol. Both patients had dramatic improvement with relief of both angina and syncope. The electrocardiograms showed regression from its left ventricular strain pattern. They suggest that morphologic improvement might occur in long range therapy.

Sloman(70) reported five cases of IHSS treated with propranolol. One of these patients had excellent improvement, three had fair improvement, and one developed congestive heart failure which required discontinuation of the drug. The improvement paralleled the reduction in heart rate at rest, and with exercise. He suggested that the patients most likely to benefit from beta blockade were those with symptoms associated with high resting and exercise heart rate, but care should be taken in treatment of patients with mild symptoms of heart failure since the congestive heart failure may be potentiated.

Cohen(88) studied the effects of oral propranolol on the level of exercise required to produce angina in seven patients with IHSS. Marked improvement occurred in exercise performance in six of the patients taking propranolol. The dosage range was between 80 and 480 mg daily. The study very nicely revealed that the increase in exercise tolerance was produced by the decrease in heart rate at any given work load for these patients. He concluded that "the mechanism by which propranolol is efficacious in this disease is probably related to the diminsion of myocardial oxygen requirements resulting from the reduction of wall tension, the velocity of contraction, and heart rate with beta adrenergic receptor blockade.

Rosenblum(90) reported ten patients treated with propranolol and studied hemodynamically. Seven of these ten patients had marked clinical and hemodynamic improvement with long term propranolol therapy.

A conflicting report by Bliss(91) in four patients with IHSS has shown that propranolol therapy strikingly and uniformaly reduced cardiac output, heart rate, and mean systolic ejection rate in all four patients. This occurred both at rest and with supine exercise. He pointed out that the provocative testing with isuprel, post PVC pulse pressure, the Valsalva maneuver, and amyl nitrite inhalation produced the same hemodynamic effect after, as before, propranolol therapy. He concluded that the beneficial effect from propranolol is simply to reduce arrhythmias, rather than to reduce the outflow obstruction.

An observation has been made by Gorlin(92) and others that the coronary vessels seem to be quite large in IHSS. He studied coronary blood flow, oxygen consumption, and lactate and pyruvate balances in a group of five patients, and found these to be within normal limits. He postulated that ischemia does not exist in these patients due to lack of evidence of lactate production, and the presence of

normal AV O_2 oxygen difference across the coronary bed. However, conflicting reports by Brink*(93)* with a simular study in a patient revealed that the oxygen supply and coronary blood flow are not adequate for the demands of the greatly hypertrophied myocardium, and in fact, lactate productinn occurred across the coronary bed. They speculate this may be the etiologic factor in effort intolerance, and in angina pain which occur in this disease. They studied their patient after propranolol and found that the metobolic changes returned toward normal, as the hemodynamics improved.

In summary, propranolol acts to block the beta receptors in the myocardium which in turn decreases the left ventricular outflow obstruction and decreases the heart rate and perhaps decreases myocardial oxygen consumption and arrhythmias. This action plays a more major role during exercise than at rest. Currently, this is the drug treatment of choice in IHSS.

Boyer*(94)* reported two patients with IHSS which were treated with Guanethadine, and who experienced a significant reduction in gradients at rest and exercise with marked symptomatic improvement. He postulates that the patients are improved due to the decreased sympathetic stimulation, and to decrease myocardial catachol amines. One of these patients was hypertensive prior to therapy, This drug may be of value in treating IHSS, but currently it has not been used in a significant number of patients to evaluate its usefullness.

Emphasis must be again placed on the treatment of IHSS patients in cardiovascular collapse. The drugs of choice in treatment of these patients are alpha stimulating agents or peripheral vasoconstrictors. The drugs most commonly used are methoxamine (Vasoxyl), angiotensin, or phenylephrine (Neo-synephrine). These drugs predominantly act on the peripheral vasculature to increase peripheral vascular resistance and increase blood pressure, therefore increasing left heart volume and decreasing left ventricular outflow obstruction. The patients may have a dramatic response to these drugs.

In summary, it must be pointed out that the unique hemodynamic abnormality in patients with hypertrophic subaortic stenosis poses a therapeutic parodox to the physician. A positive inotropic effect, so desirable for patients with other forms of heart disease, is certainly not beneficial, and may even be detrimental to these patients. Obstruction can be diminished, or even abolished, when ventricular diminsions are augmented by means of a pressor amine, such as methoxamine, which has no positive inotropic action. Simularly, the administration of a drug that directly depresses myocardial contractility and increase heart size, is likely also to diminish the severity of obstruction. Indeed, abolition of intraventricular pressure gradient has been observed in several occasions in patients with hypertrophic subaortic stenosis during general aneasthesia. Therefore, beta blocking drugs such as propranolol are the drugs which are the most beneficial to block the augmentation of sympathetic influences that act upon the heart in IHSS.

SURGERY

Since Brock's*(4)* initial description of subaortic stenosis in 1957, followed shortly by Teare's*(6)* report of another case in 1958, many procedures have been devised in an attempt to surgically correct the septal hypertrophy which occurs in this condition. Initially, exploratory operations were very poorly tolerated by these patients, in part due to the fact that very ill patients were all that were selected for surgery. Also, the elucidation of the dynamic process of the disease was not fully appreciated in the early stages of surgery and consequently the mortality rate was quite high. Cleland and group*(95)* reported the first successful surgery on a patient with subaortic stenosis. He removed bits of muscle from the obstructed ventricular septum and postoperatively the patient improved symptomatically. Left bundle branch block was produced by the surgery, and initially the good result was attributed to the left bundle branch block, and as a consequence was thought that the surgery must produce left bundle branch block in order to obtain relief. It was speculated that LBBB would change the contraction of the ventricle in such a manner that the septum would no longer impinge on the outflow tract. Subsequently, Morrow and Brockenbrough*(96)* operated on two patients through the aortic valve doing a ventriculomyotomy. Both of these patients did well, improved symptomatically, and had considerable hemodynamic improvement by catheterization. Only one of these patients developed left bundle branch block, and it was speculated that the muscle-splitting incision itself, not the altered ventricular conduction, produced the gradifying results. Theycompared this surgery, in principle, with the Fredet-Ramstedt operation for pyloric stenosis. Following these good results several other surgeons devised different operative techniques to relieve the muscular obstruction. Kirkland*(97)* reported a technique of direct ventriculotomy for removal of a portion of the left ventricular septum. Lillehei*(98)* devised a transatrial approach for the removal of a portion of the left ventricular septum. Julian*(99)* used an apical left ventriculotomy to give good visualization of the left ventricular septum for his myotomy and myectomy. Cooley*(100)* is currently using a right ventricular approach to remove a large section of the septum from the right ventricular side rather than attacking the left ventricle directly. His results seem to be comparable hemodynamically to the other approaches. It appears to be fairly well agreed now that not only does the muscle of the ventricular septum need to be incised, but a portion of it must be excised in order to give a free outflow tract during systole.

The surgical mortality and the complications are summarized in the following table.

SURGEON	REF.#	NO. OF PATIENTS	NO. OF DEATHS	MORTALITY	AVE. GRADIENTS PREOP	AVE. GRADIENTS POSTOP
Cooley	(100)	26	5	19%	90	29
Trimble	(101)	6	-	---	56	0
Cleland	(102)	12	3	25%	64	28
Morrow	(20)	25	1	4%	102	3
Julian	(99)	5	0	0	91	16
Kirklin	(97)	16	3	18%	85	19

As can be seen from the preceding table, the opeative mortality varies considerably, from 0 to 25%. None of these are large series, and many of the higher mortality figures occurred early in the development of the operative techniques. The operative mortality should now be considerably improved from that which is reported in some of these series. The complications which occur with this type of surgery are frequent. Complete heart block occurs in 5-10% of these patients post-operatively, requiring permanent pacemaker implantations at the time of surgery. A large number develop left bundle branch block, in some series as many as 90% of the patients. This in itself is probably not of much significance unless it progresses on to complete heart block. Ventricular aneurysm has been reported on more than one occasion with follow-up examinations. These aneurysms are actually septal aneurysms, and are usually due to the removal of a large portion of the septum.

The surgical results in these patients are quite striking. Most of these patients that are operated upon are Class III or Class IV patients, and almost all of them return to Class I or Class II following their operations. However, as pointed out in the section on *THE NATURAL HISTORY OF IHSS*, the mortality rate probably does not change with the surgery since the mortality rate is most likely secondary to arrhythmias and the primary muscle disease itself. The post-operative hemodynamic changes are quite dramatic. The change in gradients can be seen from the previous table. Most of these patients prior to surgery have a large ventricular-aortic gradient, which is usually abolished following surgery. Left ventricular end-diastolic pressure falls in some of these patients, but in most of them it is not reduced dramatically. The pulmonary artery and left atrial pressures usually change in correspondence with the decrease in gradient and relief of their symptomatology. It is of interest that most of these patients who have been restudied postoperatively and undergone provocative testing with the Valsalva maneuver, isuprel infusion, or post-PVC response have the same abnormal finding with testing as they did prior to surgery. In other words, the provocative testing can still elicit the same findings that are present in any patient with IHSS, however the gradients are much less even with provocative testing following surgery.

It is of interest the patients that have significant mitral regurgitation are almost totally relieved of their mitral regurgitation following a good operation for their IHSS.

In Morrow's group of patients, none had syncope or congestive heart failure after operation, and none had significant angina to limit their usual physical activities.

At the present time, operative treatment may be considered when a patient with IHSS:

1. Has disabling symptoms.
2. Does not improve significantly with propranolol, when a therapeutic trial of this drug is indicated, and
3. Either has severe obstruction to outflow at rest, or
4. Has severe obstruction provoked by exercise, the Valsalva, or the administration of isuprel, or all three.

Most of these patients actually fall in the category of having 50 mm Hg or more gradient. However, a few patients with small gradients have been operated upon who have essentially intractable angina, which is unrelieved by propranolol. Both categories of patients develop dramatic relief from their symptomatology following surgery. Morrow indicates that the risk of operation in patients with IHSS is low, and that dramatic relief of symptoms can be expected in all cases. The operative method of transaortic myotomy and limited muscular resection can be carried out with little risk even in seriously ill patients.

VARIETIES OF OBSTRUCTION TO LEFT VENTRICULAR EJECTION

	Valvular Aortic Stenosis	Discrete Subvalvular Aortic Stenosis	Idiopathic Hypertrophic Subaortic Stenosis	Supravalvular Aortic Stenosis
Incidence	Most common type; 5-10% of CHD ♂ > ♀ 4:1	Relatively uncommon	May be most common form subvalvular obstruction. ♂>♀ (nonfamilial), ♂=♀ (familial)	Least common
Cardiac Examination	Soft A_2. S_2 may be paradoxically split. S_4 when severe. EC common. SEM at LSB, radiates to neck and apex. EDM of A1 uncommon. Delayed carotid upstroke. Narrow pulse pressure.	A_2 soft or normal. EC uncommon. SEM may be low at LSB. EDM of A1 common.	Triple apical impulse. S_2 paradoxically split. S_4 common. EC rare. SEM at LLSB not transmitted to neck; ↑ with Valsalva. MI common. Rapid carotid upstroke, bisferiens quality. Prominent "a" wave in JVP.	A_2 normal or loud. EC unusual. SEM at high R + LLSB. EDM of A1 rare. BP higher in right than left arm.
Electrocardiogram	LVH LAH relatively uncommon	Same as Valvular AS.	LVH with strain pattern. Deep "septal q waves". Short P-R interval with "delta" wave.	Same as valvular AS.
Chest Roentgenogram	CTR normal. Poststenotic dilation of Ao, common. Calcium in aortic valve.	Poststenotic dilitation Ao, unusual	CTR may be ↑. LAH. Poststenotic dilation rare.	CTR normal.
Complications	SBE AI. Calcification, heart block	Progressive AI. SBE.	Variability of symptoms. Arrhythmias. Progressive MI. AI and SBE rare.	Early coronary disease. SBE.
Associated Lesions	Coarctation of Ao, PDA.	Bicuspid aortic valve	MI.	PPS. Hypercalcemia.

CHD-congenital heart disease; ♂-male; ♀-female; EC-ejection click; SEM-systolic ejection murmur; LSB-left sternal border; EDM-early diastolic murmur; AI-aortic insufficiency; LLSB-left lower sternal border; SM-systolic murmur; MI-mitral insufficiency; BP-blood pressure; LVH-left ventricular hypertrophy; LAH-left atrial hypertrophy; AS-aortic stenosis; CTR-cardio-thoracic ratio; Ao-aorta; SBE-subacute bacterial endocarditis; PDA-patent ductus arteriosus; PPS-peripheral pulmonic stenosis; JVP-jugular venous pressure.

TABLE I

HEMODYNAMICS

TABLE II

SUMMARY OF LEFT VENTRICULAR DYNAMICS IN PATIENTS WITH IHSS

AUTHORS	NUMBER OF PATIENTS	PEAK SYSTOLIC LEFT VENTRICULAR-ARTERIAL GRADIENT (mm Hg)		LEFT VENTRICULAR END DIASTOLIC PRESSURE (mm Hg)	
		Range	Average	Range	Average
Cohen *et al*	26	0-120	49	0-55	22
Wigle *et al*	10	20-113	50	7-35	22
Soulie *et al*	9	60-170	93	15-30	26
Stampbach and Senn	7	50-112	80	5-25	19
Menges *et al*	7	64-135	96	8-27	19
Bevegard *et al*	6	20-107	58	11-25	18
Hansen *et al*	4	80-157	122	6-17	10
Frank and Braunwald	126	0-175	54.3	0-44	17.8
Wilson and Criley	9	0-110	48	----	----
Boiteau	3	56-162	116	15-45	28
Rackley	5	50-75	64	15-28	18
TOTAL	212	0-175	65*	0-55	19

**patient weighted*

HEMODYNAMICS

TABLE III

MECHANISMS OF INTENSIFICATION OF OBSTRUCTION

(Reduction of ventricular systolic volume and/or augmentation of contractile state)

Intervention	Mechanisms
Postpremature contraction	Positive inotropic influence
Digitalis	Positive inotropic influence, ↑ arterial pressure*, ↓ rate*
Valsalva maneuver	↓ Venous return
Nitroglycerin	↓ Venous return, ↓ arterial pressure
Bleeding	↓ Arterial pressure, ↓ venous return, ↑ rate, positive inotropic influence (Reflex)
Isoproterenol (Isuprel)	Positive inotropic influence, ↓ arterial pressure, ↑ rate
Exercise	Positive inotropic influence, ↑ rate, ↑ arterial pressure*

Legend: ↑=increased, ↓=decreased, rate=heart rate.

*Effect which opposes intensification of obstruction, but is overridden by other effects.

TABLE IV

MECHANISMS OF RELIEF OF OBSTRUCTION

(Increase of ventricular systolic volume and/or depression of contractile state)

Intervention	Mechanisms
Methoxamine, Phenylephrine	↑ Arterial pressure, ↓ rate
Legs up	↑ Venous return
Hypervolemia	↑ Venous return
General anesthesia	Negative inotropic influence, ↓ venous return*
Propranolol	Blocks sympathetic stimulation

*Effect which opposes intensification of obstruction, but is overridden by other effects, intensification of obstruction.

RIGHT VENTRICULAR OBSTRUCTION

TABLE V

OBSTRUCTIVE CARDIOMYOPATHY: RIGHT VENTRICULAR GRADIENTS

AUTHORS	NUMBER OF STUDIES	NUMBER OF GRADIENTS	RANGE OF GRADIENTS
Soulie *et al* (1962)	8	6	7-48
Wigle *et al* (1962)	9	6	7-24
Bourdarias *et al* (1964)	28	14	10-118
Braunwald *et al* (1968)	128	18	10-61
Cohen *et al* (1964)	24	13	10-66
Taylor *et al* (1964)	4	3	27-78
Goodwin *et al* (1964)	8	7	7-55
Falcone *et al* (1967)	1	1	60
Lockhart *et al* (1965)	13	13	14-111

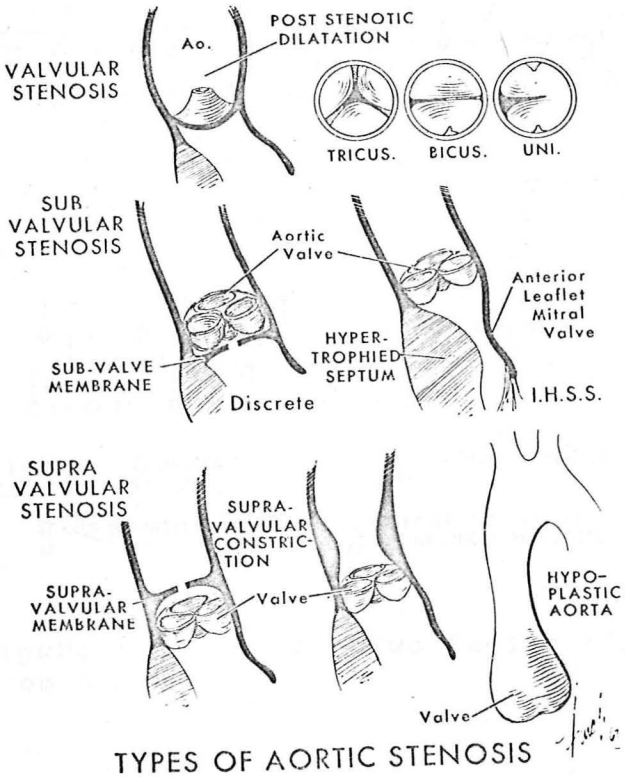


Figure 1
from *Braunwald*

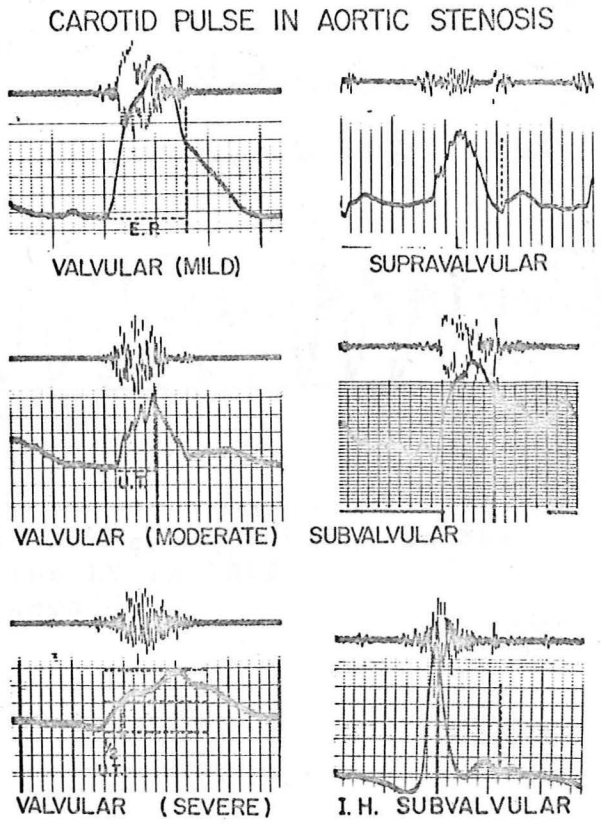


Figure 2
from *Braunwald*

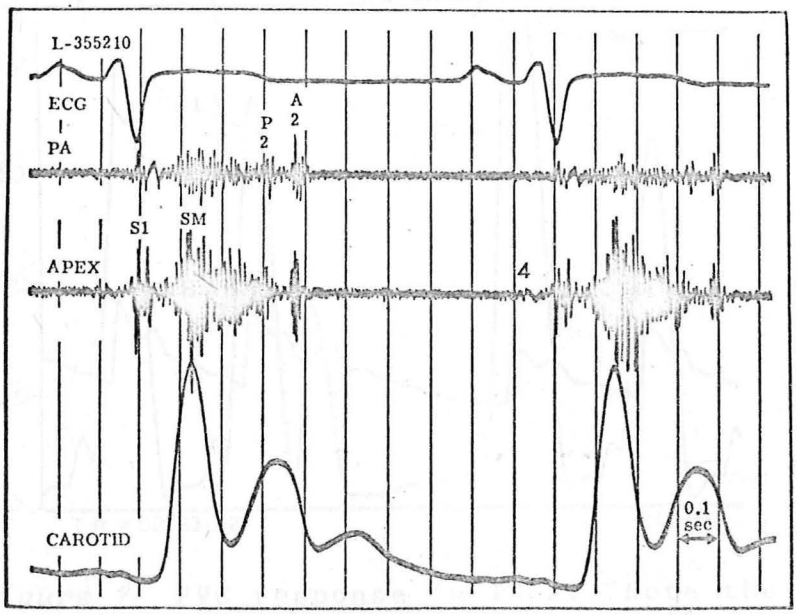
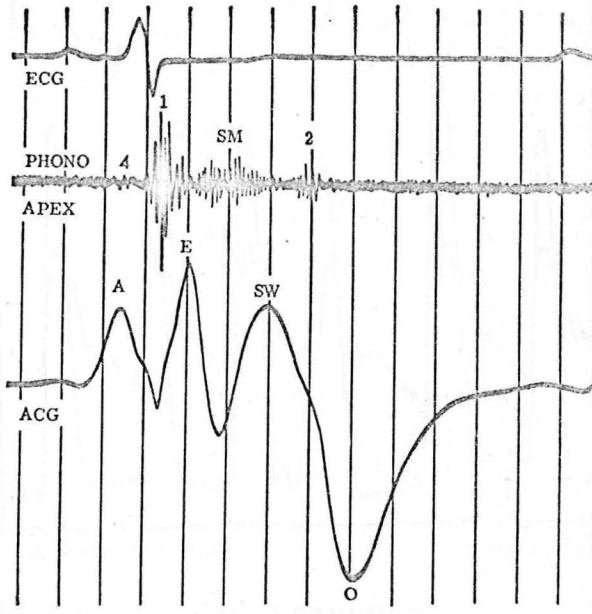


Figure 3 Carotid pulse. Note rapid upstroke and Bisferiens type. Ejection type murmur with paradoxical splitting of S_2.
from *Travel*



Apexcardiogram in IHSS. Both large A wave and midsystolic outward bulge (SW) are seen clearly. A fourth heart sound (4) is present.

Figure 4 A triple impulse is present.
from *Travel*

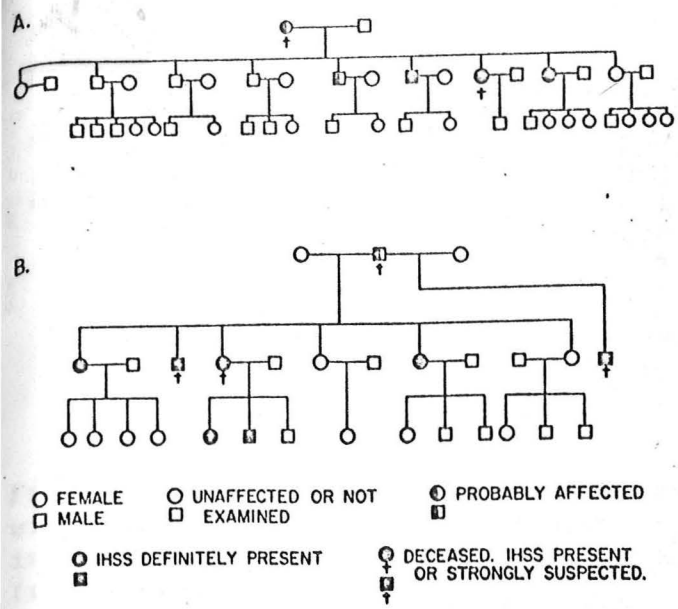


Figure 5 A and B - Two family trees.
from *Braunwald*

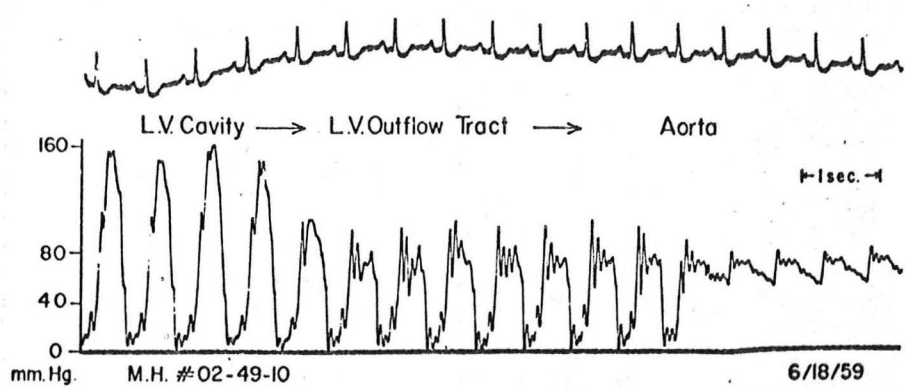


Figure 6 Pressure gradient in the body of the LV in IHSS.
from *Braunwald*

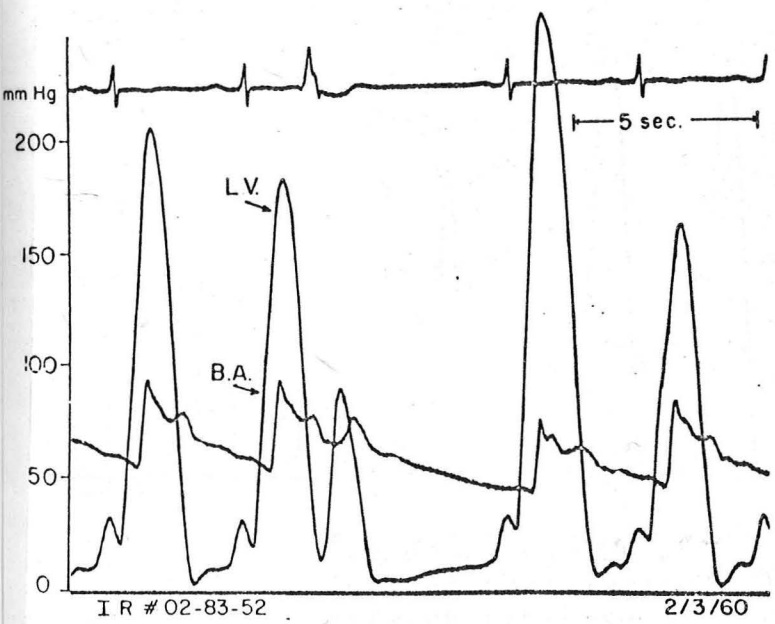


Figure 7 PVC response in IHSS. Note the pulse pressure fall in the B.A. in the post PVC beat.
from *Braunwald*

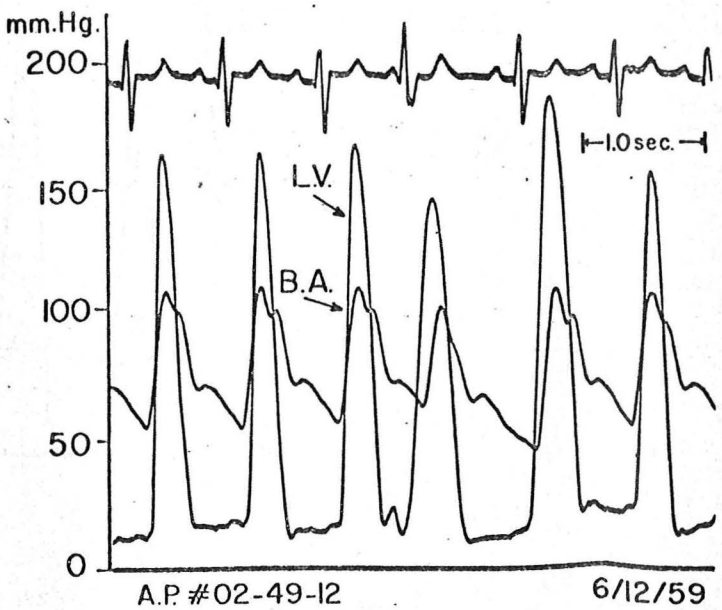


Figure 8 PVC response in valvular A.S. Note the pulse pressure rise in the post PVC beat.
from *Braunwald*

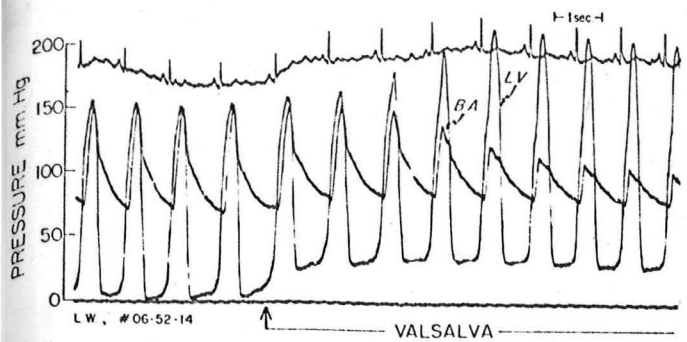


Figure 9 Note the gradient produced with Valsalva in IHSS. The murmur increases as the gradient increases. from *Braunwald*

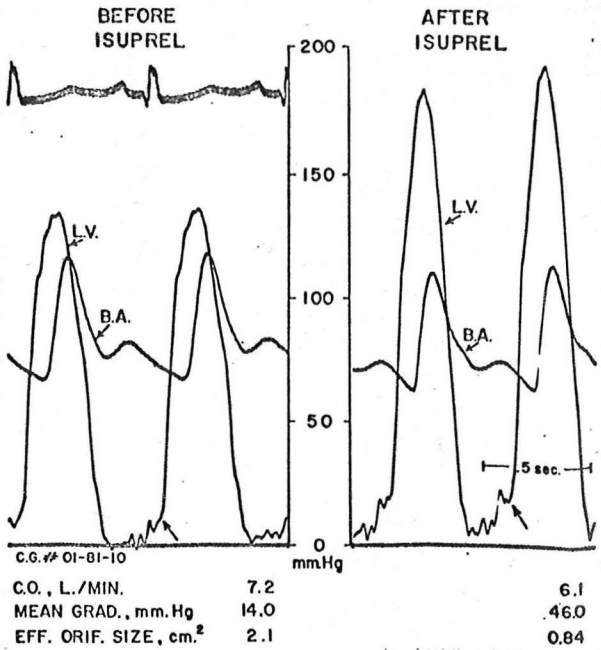


Figure 10 Response to isuprel in IHSS. Note the increase in gradient and decrease in orifice size with isuprel. from *Braunwald*

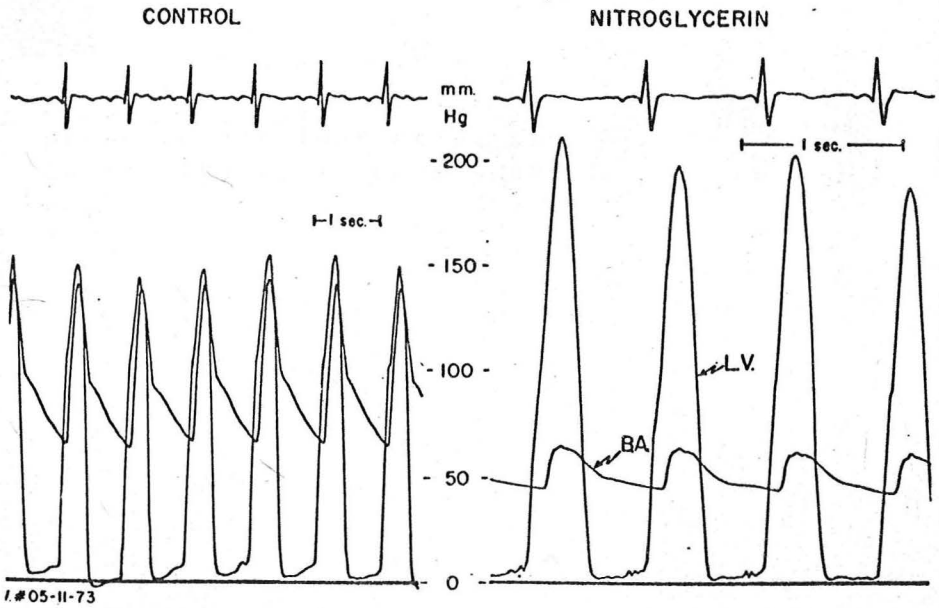
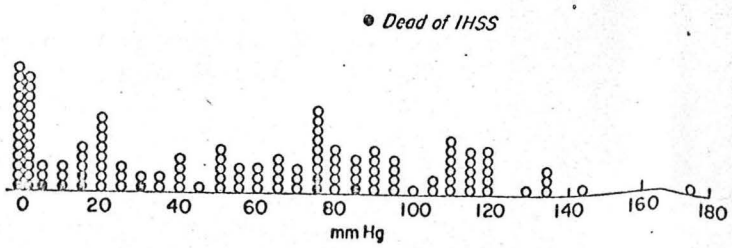


Figure 11 from *Braunwald*

Figure 12 Note the lack of correlation between pressure gradient and mortality from *Frank*



Peak basal left ventriculo-arterial systolic pressure gradient at the time of the initial catheterization. Only three of the 10 patients who died of IHSS had a systolic pressure gradient exceeding 30 mm Hg.

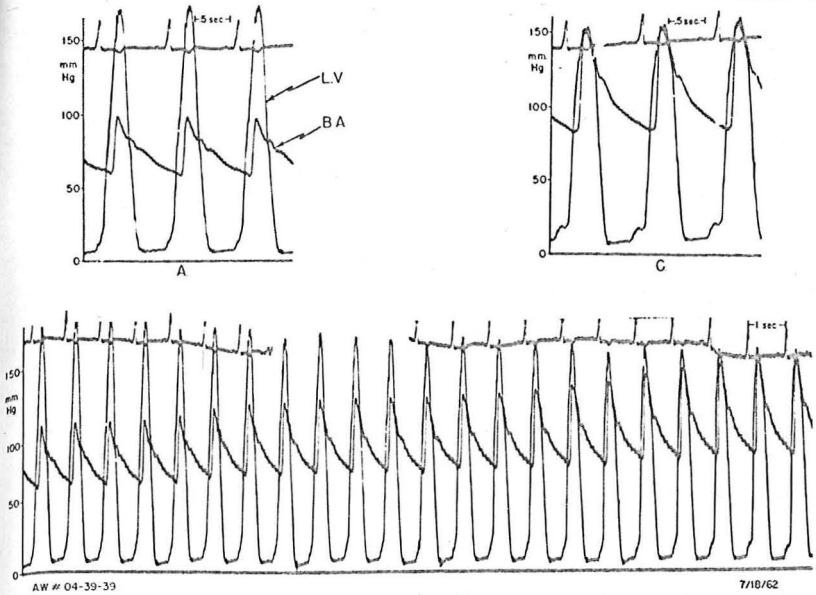


Figure 13 Response to methoxamine in IHSS. Note the obliteration of the gradient.
from *Braunwald*

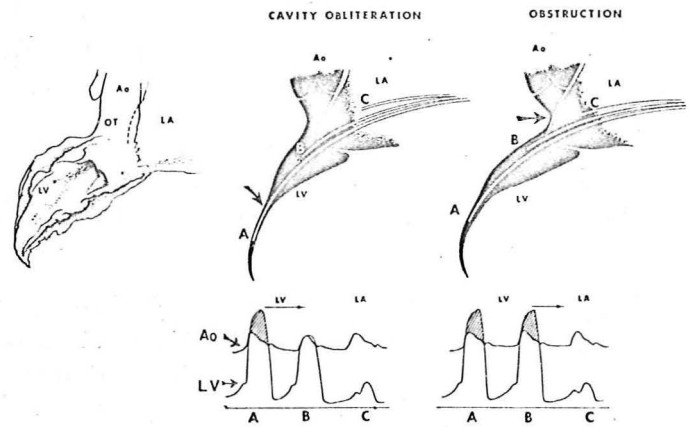
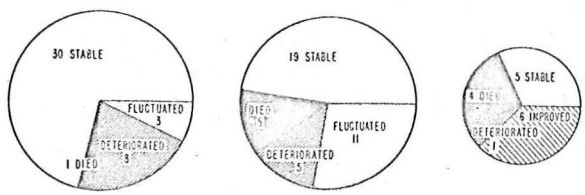


Figure 14 Note the loss of pressure gradient at B, the inflow tract, in cavity obliteration.
from *Ross*

	Class I	*Class II*	*Class III-IV*
Number	42	40	16
Av. Months Follow-up	38.2	33.0	31.1



The clinical course of patients in various functional classifications at the time of entry into the study. The patients in class I tended to remain stable, whereas those who were more disabled (classes II to IV) tended to pursue a more variable course.

Figure 15 Natural history.
from *Frank*

1. Schmincke, A.: Ueber Linkseitige Muskulose Conusstenosen. Deutsche Med. Wchnschr., 33:2082, 1907.

2. Bernheim, P.I.: De L'asystolie Veineuse Dans L'hypertrophic Du Cocur Gauche Par Stenose Concomitante Du Ventricule Droit. Rev. Med., 30:785, 1910.

3. Davies, L.G.: A Familial Heart Disease. Brit. Heart J., 14:206, 1952.

4. Brock, R.: Functinnal Obstruction of the Left Ventricle (Acquired Aortic Subvalvar Stenosis). Guy's Hosp. Rep., 106:221, 1957.

5. Brock, R.: Functional Obstruction of the Left Ventricle (Acquired Aortic Subvalvar Stenosis). Guy's Hosp. Rep., 108:126, 1959.

6. Teare, D.: Asymmetrical Hypertrophy of the Heart in Young Adults. Brit. Heart J., 20:1, 1958.

7. Morrow, A.G., and Braunwald, E.: Functional Aortic Stenosis: A Malformation Characterized by Resistance to Left Ventricular Outflow Without Anatomic Obstruction. Circulation, 20:181, 1959.

8. Livesay, W.R., Wagner, E.L., and Armbrust, C.A. Jr.: Functional Subaortic STenosis Due to Cardiomyopathy of Unknown Origin. Am. Heart J., 60:955, 1960.

9. Bercu, B.A., Diettert, G.A., Danforth, W.H., Pund, E.E. Jr., Ahlvin, R.C., and Belliveau, R.R.: Pseudoaortic Stenosis Produced by Ventricular Hypertrophy. Am. J. Med., 25:814, 1958.

10. Menges, H. Jr., Brandenburg, R.O., and Brown, A.L., Jr.: The Clinical Hemodynamic and Pathologic Diagnosis of Muscular Subvalvular Aortic Stenosis. Circulation, 24:1126, 1961.

11. Wigle, E.D., Heimbecker, R.O., and Gunton, R.W.: Idiopathic Ventricular Septal Hypertrophy Causing Muscular Subaortic Stenosis. Circulation, 26:325, 1962.

12. Manchester, G.H.; Muscular Suboartic Stenosis. N.E.J.Med., 269:300, 1963.

13. Cohen, J., Effat, H., Goodwin, J.F., Oakley, C.M., and Steiner, R.E.: Hypertrophic Obstructive Cardiomyopathy. Brit. Heart J., 26:16, 1964.

14. Pare, J.A.P., Fraser, R.G., Pirozynski, W.J., Shanks, J.A., and Stubington, D.: Hereditary Cardiovascular Dysplasia: A form of familial cardiomyopathy. Am. J. Med., 31:37, 1961.

15. Braunwald, E., Morrow, A.G., Cornell, W.P., Aygen, M.M., and Hilbish, T.F.: Idiopathic Hypertrophic Subaortic Stenosis: Clinical, hemodynamic and angiographic manifestations. Am. J. Med., 29:924, 1960.

16. Brent, L.B., Aburano, A., Fisher, D.L., Moran, T.J., Myers, J.D., and Taylor, W.J.: Familial Muscular Subaortic Stenosis: An unrecognized form of "idiopathic heart disease", with clinical and autopsy observations. Circulation, 21:167, 1960.

17. Bjork, V.O., Hultzuist, G., and Lodin, H.: Subaortic Stenosis Produced by Abnormally Placed Anterior Mitral Leaflet. J. Thoracic and Cardiovas. Surg., 41:659, 1961.

18. Dinsmore, R.E., Sanders, C.A., and Harthorne, J.W.: New Eng. J. Med., 275:1225, 1966.

19. Ewy, G., Marcus, F., Bohajalian, O., Burke, H., Roberts,W.: Muscular Subaortic Stenosis in the Elderly. Am. J. Cardiol., 22:126, 1966.

20. Simon, A.L., Russ, J., Gault, J.: Angiographic Anatomy of the Left Ventricle and Mitral Valve in Idiopathic Hypertrophic Subaortic Stenosis. Circulation, 36:852, 1967.

21. Morrow, A.G., Fogarty, T.J., Hannah, H., Braunwald, E.: Operative Treatment in Idiopathic Hypertrophic Subaortic Stenosis. Circulation, 37:589, 1968.

22. Frank, S., Braunwald, E.: Idiopathic Hypertrophic Subaortic Stenosis: Natural history. Circulation, 37:759, 1968.

23. Braunwald, E., Lambrew, C.T., Rockoff, S.D., Ross, J. Jr., and Morrow, A.G.: Idiopathic Hypertrophic Subaortic Stenosis: Description of the disease based upon an analysis of 64 patients. Circulation 29 (suppl. IV):IV-1, 1964.

24. Nasser, W.K., Williams, J.F., Mishkin, M.E., Childress, R.H., Helman, C., Merritt, H.D., and Genoresa, P.D.: Familial Myocardial Disease With and Without Obstructinn to Outflow. Circulation, 35:638, 1967.

25. Tavel, M.E.: Clinical Phonocardiography and External Pulse Recording. Chicago Year Book Medical Publishers, Inc., 1967, pp 140-172.

26. Tafur, E., Cohen, L.S., and Levine, H.D.: The Apexcardiogram in Left Ventricular Outflow Tract Obstruction. Circulation, 30:392, 1964.

27. Oakley, C.M., and Hallidie-Smith, K.A.: Assessment of Site and Severity in Congenital Aortic Stenosis. Brit. Heart J., 29:367, 1967.

28. Tavel, M.E.; Clinical Phonocardiography, It's Use in Diagnosis of Idiopathic Hypertrophic Subaortic Stenosis. J.A.M.A., 203:123, 1968.

29. Rosenblum, A., and Delman, A.J.: Valsalva Maneuver and the Systolic Murmur of Hypertrophic Subaortic Stenosis. Am. J. Cardiol., 15:868, 1965.

30. Prescott, R., Quinn, J.S., and Littmann, D.: Electrocardiographic Changes in Hypertrophic Subaortic Stenosis Which Simulate Myocardial Infarction. Am. Heart J., 66:42, 1963.

31. Cohen, R.J., Kaljot, V., and Czarnecki, S.W.: Septal Hypertrophic Subaortic Stenosis Simulating the Electrocardiographic Pattern of Myocardial Infarction. Vasc. Dis., 1:269, 1964.

32. Estes, E.H. Jr., Whalen, R.E., Roberts, S.R. Jr., and McIntosh, H.D.: Electrocardiographic and Vectorcardiographic Findings in Idiopathic Hypertrophic Subaortic Stenosis. Am. Heart J., 65:155, 1963.

33. Hollister, R.M., and Goodwin, J.F.: Electrocardiogram in Cardiomyopathy. Brit. Heart J., 25:357, 1963.

34. Braudo, M., Wigle, E.D., and Keith, J.D.: Distinctive Electrocardiogram in Muscular Subaortic Stenosis Due to Ventricular Septal Hypertrophy. Am. J. Cardiol., 14:599, 1964.

35. Wigle, E.D., and Baron, R.H.: Electrocardiogram in Subaortic Stenosis. Circulation, 34:585, 1966.

36. Klein, M.D., Mathur, V., Levine, H., and Gorlin, R.: Electromechanical Correlation in Hypertrophic Subaortic Stenosis. Circulation, 38:635, 1968.

37. Brachfield, N., and Gorlin, R.: Subaortic Stenosis: A revised concept of the disease. Medicine, 38:415, 1959.

38. Klein, M.D., Lane, F.J., and Gorlin, R.: Unusual characteristics of the Left Ventricular Chamber in Subaortic Stenosis. Clin. Res., 12:186, 1964.

39. Lewis, R.P., Bristow, J.D., Farrehi, C., Kloster, F.E., and Griswold, H.E.: Idiopathic Left Ventricular Hypertrophy. A Hemodynamic Reappraisal. Am. J. Med., 38:842, 1965.

40. Brockenbrough, E.C., and Braunwald, E.: Hemodynamic Technic for the Detection of Hypertrophic Subaortic Stenosis. Circulation, 23:189, 1961.

41. Whalen, R.E., Cohen, A.I., Sumner, R.G., and McIntosh, H.D.: Demonstration of the Dynamic Nature of Idiopathic Hypertrophic Subaortic Stenosis. Am.J. Cardiol., 11:8, 1963.

42. Braunwald, E., and Ebert, P.A.: Hemodynamic Alterations in Idiopathic Hypertrophic Subaortic Stenosis Induced by Sympathomimetic drugs. Am. J. Cardiol., 10:489, 1962.

43. Bourdarias, J.P., Lockhart, A., Ourbak, P., Ferrane, J., Scebat, L., and Lenegre, J.: Hemodynamique des Cardiomyopathies Obstructives (abstract). Arch. Mal. Coeur, 57:737, 1964.

44. Soulie, P., Joly, F., and Carlotti, J.: Les Stenoses Idiopathiques de la Chambre de Chasse du Ventricule Gauche. (A propos de 10 observations). Acta Cardiol. (Brux.), 17:335, 1962.

45. Taylor, R.R., Bernstein, L., and Jose, A.D.: Obstructive Phenomena in Ventricular Hypertrophy. Brit. Heart J., 26:193, 1964.

46. Goodwin, J.F., Shah, P.M., Oakley, C.M., Cohen, J., Yipinstoi, T., and Pocock, W.: The Clinical Pharmacology of Hypertrophic Obstructive Cardiomyopathy. In Cardiomyopathies. A Ciba Foundation Symposium, ed. G.E.W. Wolstenholme and M. O'Connor, p 189, J.& A.Churchill, London, 1964.

47. Lockhart, A. et al: Right Ventricular Involvement in Obstructive Cardiomyopathies: Haemodynamic studies in 13 cases. Brit. Heart J., 28:122, 1966.

48. Falcone, D., Moore, D., and Lambert, E.: Idiopathic Hypertrophic Cardiomyopathy Involving the Right Ventricle. Am. J. Cardiol., 19:735, 1967.

49. Mason, D., Braunwald, E., and Ross, J. Jr.: Hemodynamics with Isuprel in Right Ventricular Obstruction. Brit. Heart J., 27:884, 1965.

50. Wigle, E.D.: Discussion in Ciba Foundation Symposium on Cardiomyopathies. Boston, Little, Brown, and Co., 1964.

51. Soulie, P., Joly, F., and Carlotti, J.: Les Stenoses Idiopathiques de la Chembre de Chasse du Ventricule Gauche. Acta Cardiologica, 17:335, 1962.

52. Stampbach, V.O., and Senn, A.: Die Idiopathische Hypertrophische Subaortenstenose. Schweiz, med. Wchnschr., 92:125, 1962.

53. Menges, H. Jr.: Muscular Subvalvular Aortic Stenosis. Am. Heart J., 64:137, 1962.

54. Menges, H. Jr., Brandenberg, R.O., and Brown, A.L. Jr.: The Clinical, Hemodynamic, and Pathological Diagnosis of Muscular Subvalvular Aortic Stenosis. Circulation, 24:1126, 1961.

55. Bevegard, S., Jonsson, B., and Karlof, I.: Low Subvalvular Aortic and Pulmonic Stenosis Caused by Asymmetrical Hypertrophy and Derangement of Muscle Bundles of the Ventricular Wall. Acta med. scandinav., 172:269, 1962.

56. Hansen, P.F., Davidsen, H.G., and Fabricius, J.: Subvalvular Aortic Stenosis of Muscular Type. Acta med. scandinav., 171:743, 1962.

57. Boiteau, G.M., Bourassa, M.G., and Allenstein, B.J.: Upstroke Time Ratio: A new concept in differentiating valvular and subvalvular aortic stenosis. Am. J. Cardiol., 11:319, 1963.

58. Rackley, C.E., Whalen, R.E., and McIntosh, H.E.: Ventricular Volume Studies in a Patient With Hypertrophic Subaortic Stenosis. Circulation, 34:579, 1966.

59. Wilson, W.S., Criley, J.M., and Ross, R.S.: Dynamics of Left Ventricular Emptying in Hypertrophic Subaortic Stenosis. Am. Heart J., 74:4, 1967.

60. Stampbach, V.O., Wyler, F., Rentsch, M., and Schupbach, P.: Diagnostische und Hamodynamische Probleme bei der Aortenstenose. Cardiologia, 38:112, 1961.

61. Manchester, G.H.: Muscular Subaortic Stenosis. N.E. J. Med., 269:300, 1963.

62. Stewart, S., Mason, D., and Braunwald, E.: Impaired Rate of Left Ventricular Filling in Idiopathic Hypertrophic Subaortic Stenosis, and Valvular Aortic Stenosis. Circulation, 37:8, 1968.

63. Wigle, E., Marquis, Y., and Auger, P.: Pharmacodynamics of Mitral Insufficiency in Muscular Subaortic Stenosis. Caned. Med. Ass. J., 97:299, 1967.

64. Brockenbrough, E.C., Braunwald, E., and Morrow, A.G.: A Hemodynamic Technic for the Detection of Hypertrophic Subaortic Stenosis. Circulation, 23:189, 1961.

65. Mason, D., Braunwald, E., and Ross, J.: Effects in Changes in Body Position on the Severity of Obstruction to Left Ventricular Outflow in IHSS. Circulation, 33:374, 1966.

66. Braunwald, E., Oldham, H.N. Jr., Ross, J. Jr., Linhart, J.W., Mason, D.T., and Fort, L.,III: The Circulatory Response of Patients with Idiopathic Hypertrophic Subaortic Stenosis to Nitroglycerin and to the Valsalva Maneuver. Circulation, 29:422, 1964.

67. Marcus, F.I., Westura, E.E., and Summa, J.: The Hemodynamic Effect of the Valsalva Maneuver in Muscular Subaortic Stenosis. Am. Heart J., 67:324, 1964.

68. Taylor, R.R., Bernstein, L., and Jose, H.D.: Obstructive Phenomena in Ventricular Hypertrophy. Brit. Heart J., 26:193, 1964.

69. Whalen, R.E., Cohen, A.I., Sumner, R.G., and McIntosh, H.D.: Demonstration of the Dynamic Nature of Idiopathic Hypertrophic Subaortic Stenosis. Am. J. Cardiol., 11:8, 1963.

70. Sloman, G.: Propranolol in Management of Muscular Subaortic Stenosis. Brit. Heart J., 29:783, 1967.

71. Criley, J.M., Lewis, K.B., White, R.I., and Ross, R.S.: Pressure Gradients Without Obstruction: New concept of "hypertrophic subaortic stenosis". Circulation, 32:881, 1965.

72. Morrow, A.G., Vasko, J.S., Henney, R.P., and Brawley, R.K.: Can Outflow Obstruction be Induced Within the Normal Left Ventricle? Am. J. Cardiol., 16:540, 1965.

73. Blundell, P., Bedard, P., Baron, R., and Wigle, E.D.: Nature of Intraventricular Pressure Differences Induced by Pharmacological Agents in Dogs. Am. Heart J., 74:652, 1967.

74. White, I, Criley, J., Lewis, K., and Ross, R.: Experimental Production of Intracavity Pressure Difference. Am. J. Cardiol., 19:806, 1967.

75. Adelman, A., Wigle, E.: Two Types of Intraventricular Pressure Difference in the Same Patient. Circulation, 38: , 1968.

Page Missing in Original Volume

88. Cohen, L.S., and Braunwald, E.: Amelioration of Angina Pectoris in Idiopathic Hypertrophic Subaortic Stenosis with Beta-Adrenegic Blockade. Circulation, 35:847, 1967.

89. Mason, D., Cohen, L.S., Ross, J. Jr., and Braunwald, E.: Idiopathic Hypertrophic Subaortic Stenosis. Am. J. Cardiol., 19:797, 1967.

90. Rosenblum, R., Friedon, J., Dalman, A.J., and Berlpwotz. W.D.: Long Term Propranolol Therapy in Patients with Idiopathic Hypertrophic Subaortic Stenosis. Circulation, 35/36(suppl.II):226, 1967.

91. Bliss, H.A., Moffet, J.E., and Gautt, C.L.: Effects of Chronic Oral Propranolol Therapy in Idiopathic Hypertrophic Subaortic Stenosis. Circulation, 35/36(suppl.II):72, 1967.

92. Gorlin, R., Cohen, L.S., Elliott, W.C., Klein, M.D., and Lane,F.J.: Hemodynamics of Muscular Subaortic Stenosis (Obstructive Cardiomyopathy). In: Ciba Foundation Symposium: Cardiomyopathies, p 76, Edited by Wolstenholme, G.E.W., and O'Connor, M. London, 1964. J. & A. Churchill, Ltd.

93. Brink, A.J., Lewis, C.M., and Van Heerden, P.D.R.: Coronary Blood Flow and Myocardial Metabolism in Obstructive Cardiomyopathy. Am. J. Cardiol., 19:584, 1967.

94. Bowuer, A.F., Hanashiro, P.K., Garr, W.R., Carleton, R.A., and Graettinger, J.S.: Idiopathic Hypertrophic Subaortic Stenosis: Treatment with guanethidine. Am. J. Med., 42:189, 1967.

95. Goodwin, J.F., Hollman, A., Cleland, W.P., and Teare, D.: Obstructive Cardiomyopathy Simulating Aortic Stenosis. Brit. Heart J., 22:403, 1960.

96. Morrow, A.G., and Brockenbrough, E.C.: Surgical Treatment of Idiopathic Hypertrophic Subaortic Stenosis. Technic and Hemodynamic Results of Subaortic Ventriculotomy. Ann. Surg., 154:181, 1961.

97. Kirklin, J.W., and Ellis, F.H.: Surgical Relief of Diffuse Subvalvular Aortic Stenosis. Circulation, 25:739, 1961.

98. Lillehei, C.W., and Levy, M.J.: Transatrial Exposure for Correction of Subaortic Stenosis: A new approach. J.A.M.A., 186:8, 1963.

99. Julian, O., Dye, W., Javid, H., Hunter, J., Muenster, T., and Najafi, H.: Apical Left Ventriculotomy in Subaortic Stenosis Due to a Fibromuscular Hypertrophy. Circulation, 31(suppl.I):125, 1965.

100. Cooley, D., Bloodwell, R., Hullman, G., LaSorte, A., Leachman, R., and Chapman, D.: Surgical Treatment of Muscular Subaortic Stenosis. Circulation, 35(suppl I):22, 1967.

101. Trimble, A.S., Bigelow, W.G., Wigle, E.D., and Chrysohou, A.: Simple and Effective Surgical Approach to Muscular Subaortic Stenosis. Circulation, 29(suppl.):125, 1964.

102. Bentall, H., Cleland, W., Oakley, C., Shah, P., Steiner, R., and Goodwin, J.: Surgical Treatment and Postoperative Hemodynamic Studies in Hypertrophic Obstructive Cardiomyopathy. Brit. Heart J., 27:585, 1965.