# Natural History of Mitral Stenosis: A Review

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THE INTRODUCTION of cardiovascular surgery has profoundly influenced the natural history of many cardiac diseases. Availability of surgical means of benefiting serious heart disease—regardless of whether these means are curative of palliative—provides a powerful temptation to take advantage of such an opportunity. It is evident, however, that in many instances medical therapy may carry a much smaller risk than that of surgical intervention. It is therefore crucial to consider the natural history of a disease before a decision regarding surgery is made.

The natural history of many diseases can no longer be observed, since it would be improper to withhold surgical help in certain advanced stages. Consequently, natural history often has to be extrapolated from older studies, which are incomplete by today's standards, and from observations of patients who for various reasons were not subjected to surgical therapy. In this review, we have attempted to analyze critically the natural history of mitral stenosis as it can be reconstructed today, and from these observations have attempted to formulate a rational therapeutic approach to this disease.

### Etiology

The traditional view that diseases of leftsided cardiac valves are late consequences of rheumatic fever no longer holds true, for isolated lesions of the aortic valve and pure mitral regurgitation, more often than not, are caused by other etiologic factors. Mitral stenosis, alone or in combination with other forms of valvular disease, is the only lesion attributed principally to rheumatic disease.

The relationship between strentococcal in-

The relationship between streptococcal infection and rheumatic fever is well supported by epidemiologic, clinical, and experimental observations.<sup>1-4</sup> A recent piece of supporting evidence is by Goldstein et al.5 who showed that group A streptococci have antigens which cross react with the structural glycoprotein of the heart valves, thus directly linking this organism with rheumatic valvular disease. Rheumatic fever tends to be mimetic: hence, in a recurrent attack the host generally remains free of carditis if he was initially free of it and to have recurrent carditis when this was present initially.6 Of equal importance has been the observation that permanent valvular damage generally appears only in those patients with previous acute carditis; patients having arthritis but no carditis are usually spared chronic valvular damage.6 These findings have rendered support for prophylactic penicillin therapy in some patients with prior rheumatic fever, although the value of this prophylaxis in patients who had no evidence of carditis remains debatable. After several years have elapsed from the last rheumatic attack, the probability of a recurrence diminishes and the need for penicillin lessens.

Involvement of the mitral valve represents the most common of all locations of the rheumatic process. Nevertheless, some puzzling aspects have engendered an inquiry into the *exclusive role* of the rheumatic process in causing mitral stenosis. A large proportion of patients with mitral stenosis—as many as half in some series—have no history of rheumatic

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fever. The usual and most plausible explanation given is that patients with mitral stenosis who have no recollection of acute rheumatic fever suffered from subclinical rheumatic carditis; rheumatic fever is particularly apt to escape attention if unassociated with polyarthritis. Burch and Colcolough, searching for an alternate etiologic factor, brought out the possibility of viral infection producing the anatomic changes leading to mitral stenosis. An exceedingly rare form of mitral stenosis is congenital stenotic malformation of the mitral valve; this is associated with serious circulatory disturbances and is seldom seen beyond the age of 3 years.

The association of mitral stenosis with congenital defects of the atrial septum has been widely recognized since the description by Lutembacher. Mitral stenosis as a part of this syndrome is usually considered to be rheumatic in origin.9 Edwards10 suggested that the interatrial communication may be a foramen ovale, stretched secondarily to left atrial hypertension, as a result of mitral stenosis. Recently an interesting possibility was suggested by Okada et al.,11 who postulated that mitral valve changes in the Lutembacher syndrome are caused by a nonrheumatic fibrosis of the mitral valve, representing a response to trauma from altered stresses and abnormal flow patterns through the mitral orifice. Each of these mechanisms is probably capable of producing the Lutembacher syndrome.

### Clinical Evolution of Mitral Stenosis

The course of mitral stenosis, from its inception during acute carditis to the point where surgical treatment becomes mandatory, usually spans a period of several decades. Little factual information is available regarding the early stages of mitral stenosis. During the initial attack of rheumatic carditis, the mitral valve leaflets are commonly affected; however, such changes are incapable of producing actual narrowing of the valve orifice. Clinical signs of mitral regurgitation are found in these initial stages, although such findings do not necessarily indicate permanent

damage to the mitral valve, often being caused by temporary malfunction of the mitral valve-papillary muscle-chordal apparatus.

It is generally agreed that a time interval of several years has to elapse between the initial attack of carditis and the time when definite clinical evidence of mitral stenosis becomes apparent. The traditional view<sup>12</sup> that this time interval varies from 2 to 8 years is probably an underestimate. Bland and Jones,<sup>13</sup> in their 20-year follow-up study of children with acute rheumatic fever, showed that nearly two thirds of those who had mitral stenosis at the termination of the study did not show it at the 10-year half point. Hence, it appears that in the majority of cases the process of development of mitral stenosis takes longer than a decade.

The majority of patients with fully developed mitral stenosis remain asymptomatic for a varying length of time. Thus, there is a "latent" period of mitral stenosis, which might be subdivided into two stages: first, the stage of formation of mitral stenosis, and second, the asymptomatic stage of fully developed mitral stenosis. Wood's<sup>14</sup> series showed that the latent period lasted an average of 19 years: the mean age for the attack of carditis was 12 years and the age at the appearance of symptoms, 31 years. Wood<sup>14</sup> also estimated that from the onset of symptoms to the stage of total disability, an average of 7 years elapsed.

The subject of clinical progression of mitral stenosis was investigated in two longitudinal studies. Rowe et al<sup>15</sup> followed a group of 250 patients with pure mitral stenosis for 20 years, or until death. About half of the patients were under 30 years of age at the inception of study; 52% were asymptomatic (class I). At the end of the study, 79% of the patients were dead, and 13% remained unchanged. After the first 10 years, 39% were dead. Of the patients who were initially asymptomatic, 59% remained unchanged after 10 years, and 24% did so after 20 years. The other study<sup>16</sup> dealt with patients who were already symptomatic (average age at inception of study was 41.5

vears). After 11 years, 11% remained unchanged, and 70% were dead; after 18 years, 3% were unchanged, and 83% were dead. These observations plainly show the potentially serious nature of mitral stenosis. When mitral valvulotomy was introduced, it was clearly demonstrated on the basis of the above figures that the course of patients with significant symptoms was favorably influenced by the operation.<sup>17</sup> However, it is equally apparent from such figures that a proportion of patients with mitral stenosis may remain clinically unchanged for many years, or, to put in other terms, asymptomatic patients may remain asymptomatic indefinitely, while mildly symptomatic patients may remain unchanged for as long as 20 years.

Most patients with mitral stenosis tend to develop symptoms in the fourth or fifth decade of life. In about half, symptoms develop gradually, and, in the other half, abruptly—often precipitated by a complication such as atrial fibrillation, in our experience. When patients become symptomatic, some can still be controlled adequately by medical management for long periods of time; others may deteriorate rapidly into uncontrollable disability such that surgical treatment becomes necessary.

During the past few years, important new information has unfolded showing that the course of mitral stenosis in areas with a lower standard of living differs greatly from that summarized above. In "depressed" areas, 18-23 mitral stenosis tends to progress rapidly and may lead to serious disability early in life, so that surgical treatment becomes necessary. Using the percentage of mitral valve operations performed in patients under 20 years of age as an index, the comparison of data between various areas is presented in table 1. It is seen that economically deprived areas of this country may also produce an altered epidemiologic pattern of rheumatic heart disease: University of Kentucky Medical Center, which draws its clinical material heavily from the population of the neighboring Appalachia, has seven to 15 times higher

Table I

Mitral Valve Operations Performed in Patients under 20 Years of Age

Location	% of operations
San Francisco*	0.5
Philadelphia <sup>24</sup>	1.0
Edinburgh <sup>25</sup>	1.0
Italy <sup>18</sup>	3.0
Poland <sup>23</sup>	5.0
Lexington, Kentucky†	7.5
Israel <sup>19</sup>	8.0
India <sup>22</sup>	27.0
India <sup>20</sup>	34.0
$Iraq^{21}$	40.0

<sup>\*</sup>Our own series.

incidence of symptomatic juvenile mitral stenosis than most other centers.

### Complications in the Natural History of Mitral Stenosis

Atrial fibrillation is the most common complication, perhaps even sequel, to mitral stenosis. The overall incidence of atrial fibrillation in this condition is estimated to be about 40%.14 Atrial fibrillation often develops first in a paroxysmal form; later, it may appear in persistent form, but responds to antiarrhythmic therapy. Eventually atrial fibrillation establishes itself permanently in a therapyresistant form. Atrial fibrillation is related to left atrial enlargement and left atrial hypertension. Initially appearing as a functional disturbance in the electrophysiologic mechanism, perhaps as a response to stretching of the atrial musculature, it eventually is perpetuated by organic changes, namely, a disintegration of the architecture of the atrial muscle.26 Patients with very large left atria and those who have had atrial fibrillation for longer than 5 years are likely to have extensive disruption of their atrial musculature (i.e., atrial fibrosis and muscle atrophy) therefore are unlikely to respond to DC shock or antiarrhythmic therapy, even after a satisfactory surgical correction of the mitral stenosis.

Atrial fibrillation has a profound effect upon the natural history of mitral stenosis. Hemodynamically, it causes lower resting cardiac

<sup>†</sup>Noonan JA: Personal communication.

output at comparable ventricular rates.<sup>27</sup> The onset of atrial fibrillation is the most common factor bringing a previously asymptomatic patient into a stage of disability. The rapid ventricular rate of a suddenly appearing atrial fibrillation produces many emergencies in patients with mitral stenosis. Furthermore, even after the ventricular rate is brought under control, patients often find themselves in a lower effort capacity than prior to the onset of the arrhythmia, due to loss of the atrial "kick" mechanism.

Systemic emboli are among the most dreaded complications of mitral stenosis. Their incidence is given as 9–14% of patients with mitral stenosis, with 60–75% of those having cerebral embolism. 14, 28–30 Systemic embolization occurs primarily in the presence of atrial fibrillation. It is not known whether atrial fibrillation is a sine qua non of this complication, with those reported as having embolism while in sinus rhythm possibly suffering from an unrecognized paroxysm of fibrillation, or whether mural thrombi may actually develop in the contracting atrium.

The disastrous consequences of cerebral embolization are often compounded by the fact that patients with mitral stenosis who are asymptomatic, or even unaware of their disease, may be stricken. The occurrence of systemic emboli in patients who are not disabled by mitral stenosis poses a significant dilemma regarding surgical therapy, especially if mitral stenosis is shown to be mild. It is evident that mitral valve operation does not eliminate the danger of embolism. Whether the incidence of embolization is reduced by valvotomy has not been answered; studies purporting to show such beneficial effect lack statistical design to make preoperative and postoperative comparison valid.30 Several studies have indicated the favorable effect of anticoagulant therapy upon the incidence of recurrent emboli; the evidence for this is at best suggestive, for the experimental design of available studies and controls is not adequate for a conclusive answer.

"Myocardial factor" is considered by some an additional cause of cardiac failure, unrelated to the mechanical effects of mitral stenosis.31 An impairment of left ventricular function, although detectable by sensitive hemodynamic techniques, is generally inconsequential from the clinical standpoint, except in some elderly female patients with chronic atrial fibrillation, in whom obstruction at the mitral valve is mild and clinical disability is related to a low cardiac output. The myocardial factor is often blamed for the failure of patients to show satisfactory improvement after cardiac surgery.32 However, such interpretation should be questioned unless hemodynamic proof of nearly complete elimination of mitral block is present. Patients who undergo open-heart surgery occasionally develop myocardial damage sustained at the time of perfusion, which should not be confused with the "myocardial factor" mitral stenosis.

Other complications of mitral stenosis should be mentioned as affecting its natural history: respiratory infections occur more frequently in patients with mitral stenosis than in the general population and may precipitate cardiac failure. Infectious endocarditis is very rare in pure mitral stenosis,<sup>33</sup> but its incidence is significant in the patients who, in addition, have aortic or mitral regurgitation. Occasionally, patients with mitral stenosis develop massive pulmonary hemorrhage ("pulmonary apoplexy").<sup>14</sup> Some reports indicate that emergency operation upon the mitral valve may be lifesaving in severe, exsanguinating pulmonary hemorrhage.<sup>34</sup>

### Hemodynamic Evolution of Mitral Stenosis

Studies performed with the aid of cardiac catheterization show in a most reliable manner the severity of mitral stenosis and its consequences upon the circulation. The importance of hemodynamic evaluation of mitral stenosis cannot be overemphasized in patients in whom surgical treatment is being contemplated, for both the symptomatology and the clinical signs of mitral stenosis are often misleading.

The degree of physiologic stenosis of the mitral valve can be assessed with the aid of

the formula by Gorlin and Gorlin.35 In spite of certain oversimplifications and assumptions in the application of the hydraulic formula (e.g., constant flow through the valve), the calculation of the mitral valve orifice gives reproducible values, which check reasonably well with surgical estimates of it. The accuracy of the Gorlin formula depends upon the care with which measurement of cardiac output is performed. The pressure gradient across the valve is now most often measured directly, although the formula was originally described with the use of an assumed level of left ventricular diastolic pressure. Inasmuch as the valve area is related to the square root of the pressure gradient, its accuracy and reproducibility are best in the presence of large gradients, i.e., higher degrees of stenosis, and least in mild stenosis.

In the early stages of mitral stenosis, findings at cardiac catheterization may be entirely normal and there may be no pressure gradient, or one too small to be measured with available instrumentation. The normal atrioventricular filling occurs through a valve orifice of approximately 3 cm². Mildest degrees of valve obstruction (between 2 and 3 cm²) are virtually unmeasurable. Mild mitral stenosis (a label usually applied to valve areas between 2 and 1.4 cm²) seldom produces symptoms. Moderate stenosis (in the range between 1.4 and 0.9 cm²) and severe stenosis (less than 0.9 cm²) constitute the population from which surgical candidates are selected.

The most important consequence of mitral stenosis is left atrial hypertension, which in turn elevates pressures in the pulmonary vascular system and is largely responsible for dyspnea, the principal cause of patient's disability. Since mitral stenosis develops very slowly and gradually, pressure increments in the pulmonary capillary system are small, permitting adaptive processes to take place. The most effective compensatory mechanism preventing excessive fluid from being driven out of the pulmonary capillaries under high hydrostatic pressure (pulmonary edema) is the increased capacity of the lymphatic system to drain excess fluid. Thus the degree of

dyspnea and the incidence of attacks of pulmonary edema are much lower in mitral stenosis than in the suddenly appearing left ventricular failure with equivalent left atrial hypertension.

The level of left atrial pressure is related to the severity of mitral stenosis. However, it is materially modified by such factors as cardiac output and cardiac rate, and indirectly influenced by atrial size and compliance as well as by the circulating blood volume (hence, the influence of diuretics). Pronounced swings of left atrial and pulmonary capillary pressure may occur in patients who happen to have a relatively high-output state, wherein, even with mild mitral stenosis, pulmonary edema may develop during exercise or tachycardia. On the other hand, some elderly individuals with chronic atrial fibrillation and low, relatively fixed, cardiac output may have minimal symptoms in the presence of significant mitral stenosis.

As mitral stenosis progresses and reaches the "severe" stage, some individuals develop secondary pulmonary arteriolar constriction, leading to severe pulmonary hypertension.<sup>14, 36</sup> An index of this "reactive" pulmonary hypertension is the level of pulmonary vascular resistance, which can reach a level as high as five to 10 times the normal level. This "active" component is superimposed on "passive" pulmonary hypertension, i.e., that produced as a direct effect of increased left atrial pressure. Pulmonary arterial pressures may reach systemic levels in some cases.

The hemodynamic consequence of such severe pulmonary hypertension is an overload upon the right ventricle, often producing right ventricular failure and tricuspid regurgitation. Inasmuch as low cardiac output limits the elevation of pressure in the left atrium and in the pulmonary capillaries, pulmonary hypertension has been considered by some a "protective" mechanism, preventing pulmonary edema. Convincing evidence for this is not available, and the "protective" effect of high pulmonary vascular resistance may be more a fallacy than a reality. Although sudden episodes of frank pulmonary edema probably

occur more often in patients with normal or only slightly elevated pulmonary arterial resistance, patients with very high resistance do manifest high resting and exercise pulmonary capillary pressures and have disability from pulmonary congestion and edema.<sup>37</sup> Thus, they are in no way protected from most of the ravages of severe mitral stenosis. High pulmonary arterial resistance is reversible if improvement of left atrial pressure occurs after surgical treatment, in contrast to congenital heart disease, where organic and irreversible pulmonary vascular disease is usually responsible for the high pulmonary arterial resistance.<sup>38</sup>

Previous knowledge of the progression of mitral stenosis was mainly based upon comparison of hemodynamic findings in patients with varying severity of mitral stenosis. Recently, we have undertaken a longitudinal study of patients with mitral stenosis, in order to develop more insight into the modes of hemodynamic progression of this disease.<sup>39</sup> Serial studies performed for periods of from 1 to 10 years reveal that mitral stenosis progresses in some patients at a rapid rate, while in others it remains relatively stable. Progression, defined as a narrowing of the mitral valve orifice, is usually associated with aggravation or development of clinical disability. In the nonprogressive form, where the mitral valve area remains stable, symptoms develop less frequently and, when present, are usually related to complications, most commonly atrial fibrillation. It is noteworthy that such progressive and nonprogressive forms have been demonstrated not only in patients who never underwent surgical valvotomy, but also in those following such operations ("restenosis").

### Pathologic Evolution of Mitral Stenosis

During acute rheumatic fever with carditis, involvement of the mitral valve consists of tiny, translucent nodules located along the line of closure of the valve, occasionally also involving subvalvular parts of the chordae.<sup>40</sup> Aschoff bodies are not usually encountered upon the valve tissue. Microscopic sections of

these nodules show largely nonspecific proliferation of fibroblasts and macrophages. These translucent vegetations later become opaque and grav, and eventually more of the valve leaflet becomes thickened. Changes within the valve structure involve deposition of fibrin upon the cusps with loss of the normal morphology, hyalinization, and eventually the covering of the leaflets with endothelium.41 This process may lead to fusion of the valve commissures. Brock<sup>42</sup> postulated that the initial point of fusion of the two leaflets occurred at the "critical area of tendon insertion," i.e., the point where the shortest and most direct chordae connect with the cusps. When fusion occurs at these points, portions of the cusps lateral to them are immobilized, thereby facilitating more commissural fusion.

Virtually no information is available regarding early progression of pathological changes in the mitral valve. When mitral stenosis is fully developed, three distinct types have been recognized:<sup>43</sup> (1) commissural type, consisting of fusion of the commissures with little involvement of cusps or chordae; (2) cuspal type in which the leaflets are converted into stiff, rigid, leathery (later calcified) structures; and (3) chordal types in which the chordae are fused, thickened, and shortened, thereby interfering with the mobility of the leaflets. In addition to the pure forms, combinations of these types occur.

The various anatomic forms of mitral stenosis may affect atrioventricular filling in similar manner. The degree of mitral valve obstruction is often fixed, due to commissural fusion, and possibly, to the chordal abnormalities (fig. 1B). However, in the pure cuspal form (fig. 1C) of mitral stenosis, the degree of apparent valve narrowing, as evidenced clinically and hemodynamically, appears more severe than that found anatomically. This physiologic-anatomic dissociation is likely related to stiffened and possibly calcified valve cusps; these cusps, while potentially mobile, may fail to open in response to a given left atrial pressure, regardless of whether the commissures are fused or not. It is therefore

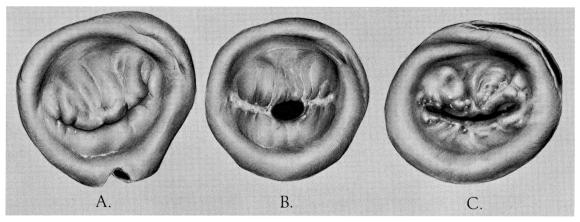


Figure 1

Drawing of three mitral valves: (A.) Normal mitral valve in a closed position, viewed from the atrium. (B.) Stenotic mitral valve with commissural type of stenosis, showing maximum opening; commissural fusion joins leaflets of normal thickness and mobility. (C.) Cuspal type of mitral stenosis: only minimal fusion of commissures is present, but the stiff, fibrocalcific leaflets cannot open under physiologic pressure.

possible to have the mitral valve "wide open" on surgical or pathologic inspection, and yet to have the valve remain severely stenotic under in vivo conditions.

## Progression of Mitral Stenosis: A New Concept

It is evident from the foregoing discussion that clinical, hemodynamic, and pathologic observation all point to the fact that mitral stenosis is often a continuously progressive, life-long disease. The clinical course shows that most patients with mitral stenosis, who become disabled, do so relatively late in life, sometimes as late as in their fifties and sixties: hemodynamic studies revealed that such patients may show rapid progression in the degree of mitral valve stenosis. Pathologic studies indicate that pure commissural mitral stenosis with thin, mobile leaflets is found mostly in young individuals, while in older patients valve calcifications are almost always present. One should ask the question: How does this course fit into the generally accepted rheumatic origin of mitral stenosis? Very little attention has been paid to the pathogenesis of later stages of mitral stenosis. Initiated by acute rheumatic carditis, mitral stenosis is believed to be the consequence of healing of the rheumatic process. It is generally assumed that active rheumatic process plays a role in the progression of mitral valve changes, either as repetitive rheumatic insults or as a "smoldering" chronic rheumatic activity, both usually subclinical. This last view has received a boost by the frequent findings of Aschoff bodies in atrial muscle biopsies at the early stage of the surgical era.

It should be pointed out that many known facts about the natural history of mitral stenosis are not compatible with the "unitarian" rheumatic pathogenesis of mitral stenosis. If low-grade rheumatic activity were a prerequisite to the scarring of mitral valve, then the pathologic process would be most active in the early years after the acute attack, and then would gradually subside, for it is well recognized that both signs of rheumatic activity and recurrences of rheumatic carditis are most constantly and frequently found during the first two decades after the initial attack. Yet, our study has clearly demonstrated that progression of mitral stenosis in the fourth and fifth decades of life often occurs at a rate that only an acceleration of the process could explain. Otherwise patients would not have survived to that age. Furthermore, restenosis of the mitral valve, occurring at any

age, would be difficult to fit into the active rheumatic concept.

Considering an alternate explanation for progression of mitral stenosis beyond its early stages, the most attractive hypothesis is to abandon the postulate of continuing rheumatic activity and to accept a theory that the initial rheumatic valvulitis and its early scarring consequences produce changes upon the valve that are capable later of perpetuating themselves in a nonspecific manner. The key issue to this is the view proposed by Edwards<sup>44</sup> in connection with calcific aortic stenosis, that a valve can be traumatized by abnormal flow patterns, and that such trauma can lead to thickening, fibrosis, and calcification of valve cusps. The clinical course of calcific aortic stenosis, now believed largely due to congenitally abnormal cusps (mostly bicuspid), suggests that the narrowing of the aortic orifice is not a continuous, even process, but one likely to progress in an exponential manner. It may take 40 or 50 years of traumatic damage to a bicuspid aortic valve to produce barely discernible aortic stenosis; in the next 5 to 10 years, the process may accelerate itself rapidly, producing a lifethreatening, severe stenosis.

The probability exists that an analogous pathologic process accounts for the later stages of mitral stenosis. The view that the rheumatic process is the only mechanism producing changes upon mitral valve cusps has recently been contradicted by Pomerance, 45 who found nodular thickening upon the leaflets of elderly individuals, resembling rheumatic changes, attributed to trauma of valve closure, the two leaflets hitting each other. Similarly, mitral valve disease in Lutembacher's syndrome (see above) may be due to nonspecific trauma.

One should thus visualize the rheumatic process as one responsible for the early changes upon the leaflets leading eventually to their fusion. Such fusion, producing the commissural type of mitral stenosis, may cause only minimal trauma or none at all, because the normal atrioventricular filling pathway may not be affected. In such cases, mild mitral

stenosis may persist for life. Slight alteration of flow pattern producing minimal trauma to the valve may be analogous to a bicuspid aortic valve, i.e., produce progressive valve changes over a period of many decades. More severe involvement of the commissures and the involvement of the cusps and chordae by the early rheumatic process would alter flow patterns through the mitral orifice to a degree that progressive valvular deformity would ensue earlier in life. To produce clinically and hemodynamically significant mitral stenosis, further fusion of the commissures may take place, stiffening and calcification of the cusps with or without fusion may develop, or a "funnel-type" deformity of the mitral valve may take place, in which case major participation of the chordae occurs, all of which may be "traumatic."

All observations regarding the natural history of mitral stenosis can be explained by the nonspecific pathogenesis as proposed above, including the persistence of nonprogressive mild mitral stenosis for life, its late rapid progression, its accelerated course in underdeveloped and depressed areas, the effect of mitral valvotomy: permanent relief in some, delayed restenosis in others, immediate restenosis in still others.

### Surgical and Postsurgical Stages of Mitral Stenosis

The introduction of mitral valvotomy in 1948 was a major breakthrough in the treatment of mitral stenosis. The dramatic effect of such an operation on seriously ill patients with mitral stenosis was immediately evident, but soon its limitations became apparent as well. The operation was clearly not a curative one, such as is the case in some congenital cardiac lesions. It was limited to patients with pure or almost pure mitral stenosis, eliminating cases with all but trivial degrees of regurgitation. Furthermore, it was unsuccessful in some individuals, or even capable of making the patients worse in a few (by the production of mitral regurgitation). Later developments included the performance of valvotomy under direct vision by means of

open-heart surgery, and eventually, mitral valve replacement.

Even though more than 20 years has elapsed from the earliest mitral valve operations, the full impact of cardiac surgery upon the natural history of mitral stenosis is as yet to be determined. It is obvious, however, that in terms of risk, rate of complications, and long-term fate of patients, mitral valvotomy belongs in an entirely different class from mitral valve replacement, and the two have to be discussed separately.

The evaluation of the results of mitral valvotomy presents considerable difficulty. The overall beneficial results, in terms of large series of cases, can best be demonstrated by the survival rate, which shows postvalvotomy patients, originally in functional classes III and IV, surviving a 10-year period at a higher rate than medically treated patients.<sup>17</sup> However, wide discrepancies exist between the various series in regard to the clinical conditions of patients, as well as to the rate of restenosis of the mitral valve. It is highly probable that earlier studies, based on clinical evaluation, overestimated the results ("excellent results" in 65-85% of cases).46,47 Later reports agree that deterioration occurs frequently in patients with initial improvement. The incidence of restenosis of the mitral valve, as the basis for deterioration, was estimated as low as 10%17, 46 and as high as 50%48 both in a 10-year time period. Although the existence and frequency of restenosis of the mitral valve have been questioned from time to time<sup>49</sup>since many such suspected cases were thought to represent merely unsuccessful valvotomies-hemodynamic studies indicate clearly that restenosis does occur and may take place in those patients in whom mitral valvotomy widened the orifice only slightly, as well as in those in whom the stenosis was nearly totally relieved.39

Hemodynamic studies performed in only a small fraction of patients included in the various clinical series revealed important information. First, it is shown that mitral valvotomy may indeed produce a dramatic improvement in circulatory dynamics, includ-

ing a regression of disappearance of reactive pulmonary hypertension.<sup>36, 38</sup> It was demonstrated, furthermore, that in many patients valvotomy produces a change from severe to only slightly less severe mitral stenosis. The majority of patients show a moderate reduction of the mitral valvular obstruction, and only a handful end up with an almost complete relief of mitral stenosis (entirely normal dynamics under all conditions are probably not attainable). Finally, a number of patients fail to show any improvement whatsoever, even though the patient may have felt much better. Thus, subjective evaluation of the effect of the operation by the patients need not reflect the true anatomic success of the operation. For example, it has been shown that abrupt deterioration in patients with mitral stenosis may develop in response to a small increment in the severity of stenosis, as if a patient would "turn a corner" at a critical point. Equally dramatic disappearance of disability can occur when the operation attained only a minimal success but managed to take the patient below his critical point of stenosis.50

How do pathologic findings correlate with clinical and hemodynamic data? There seems to be general agreement that mitral leaflets with good mobility offer the best target for conservative surgical approach. Thus, pure commissural type of mitral stenosis can be successfully relieved, in some cases permanently. It seems likely that involvement of the cusps and chordae in the stenotic process would permit the attainment of only temporary relief of mitral valve obstruction, with restenosis becoming only a matter of time. Finally, severe fibrocalcific disease of the valve cusps may make relief of the obstruction impossible, for here physiologic stenosis is produced by inability of mitral leaflets to move under available filling pressure. Hence, it may become irrelevant to the degree of resistance to flow whether the commissures remain fused together or are cut all the way to the annulus. (Such cases illustrate the occasionally observed paradox of the surgeon

accomplishing a wide orifice, but hemodynamic studies showing no improvement.)

In response to the question whether mitral valvotomy is still a worthwhile operation, the answer appears to be an unequivocal yes. The beneficial effect of mitral valvotomy in properly selected cases is well proven. The major prerequisite is evidence of good mobility of mitral cusps. On the other end of the spectrum of mitral stenosis are patients with heavy calcification of the valve cusps, in which case valvotomy is ineffective. Regarding cases in between these two extremes, the choice of operation deserves most careful consideration. Equating the low risk (3-5% in the case of closed valvotomy and slightly higher in open valvotomy), and the lack of late complications, other than the possibility of restenosis, against the high risk in valve replacement with a continuous risk of late complications and as-yet-unknown average life of the valve, a good case could be made in favor of the performance of mitral valvotomy as a first try in select cases. The alleged advantages of open valvotomy over closed valvotomy are based entirely upon the surgical impressions. No "hard data" are available to compare results of the two techniques. Hemodynamic follow-up studies have amply demonstrated the capability of closed valvotomy of achieving spectacular improvement so that the value of closed valvotomy in properly selected cases is established beyond doubt.

The introduction of artificial mitral valve constituted one of the breakthroughs of cardiac surgery by providing the opportunity to save and rehabilitate many seriously ill patients with mitral stenosis nonresponsive to more conservative surgical treatment. Nevertheless, the effect of valve replacement upon the natural history of mitral stenosis cannot be assessed as yet. What's more, the critical student of the natural history of mitral stenosis has to ask the question whether the net effect of valve replacement may not be a shortening rather than a lengthening of the life of average patients with mitral stenosis. On the positive side, hemodynamic studies after valve replacement may show normal or near-normal values at rest, but abnormal responses to exercise are still the rule.<sup>51</sup> The pulmonary vascular resistance falls and the cardiac output rises within hours after the operation.<sup>52</sup> On the negative side, artificial valves have not vet reached the point of resistanceless atrioventricular filling and are really equivalent to a mild mitral stenosis. The risk of the operation is considerably higher than that of conservative mitral surgery. Prosthetic mitral valves introduce the added risk of late complications; thromboembolic phenomena. periannular leaks, hemolysis, ball variance, and erosion of the cage through the wall of a small left ventricle (hence, preference of disc valves by some surgeons). The possible need for anticoagulant therapy introduces another risk factor. To be sure, many technical advances in the manufacture of prosthetic valves have been made and the use of homo- and heterografts is being investigated. Yet, only time will ultimately tell how many patients will have uneventful 10 years of life after mitral valve replacement and how often valve failure, if present, will give enough warning time to permit reoperation to exchange valves.

Perhaps the most revealing point about present use of valve prosthesis is statistical, pertaining to the operative risk. In large cumulative series a fall in mortality of more recent cases is emphasized, and figures of 4% mortality for mitral valve replacement are shown.53,54 Yet, a recent truly consecutive series in a cooperative study of six major surgical centers shows the overall hospital mortality for mitral valve replacement of 22%.55 It is pointed out that mortality figures of other operations in this cooperative study are comparable with those of other centers. Therefore, surgical skill could not account for the difference between a 4 and a 22% surgical risk of mitral valve replacement. A reasonable possibility may be that the series with a 4% mortality contains a much higher number of low-risk individuals with early forms of mitral stenosis, who would not be subjected to mitral valve replacement in the other centers, or that seriously ill patients with mitral stenosis are being turned down, or both! In centers

participating in the cooperative study patients are selected for surgery after hemodynamic evaluation. In many centers this is not the case and only clinical evaluation is performed. While it is usually stated that valve replacement is performed on class III patients, functional classification is largely subjective, and the variability of the course of mitral stenosis makes a patient with rapid atrial fibrillation and class IV disability often return to class I under adequate medical treatment.

Figures pertaining to late mortality after valve replacement are also difficult to interpret. Such figures are estimated at from 7 to 20%. Assuming a 15% late mortality and a 22% immediate risk, the 5-vear survival of about two thirds is similar to the average 70% survival in the series of Rowe et al.15 dealing with medical therapy. The argument that early operations lower the risk of valve replacement<sup>56</sup> is weakened by the fact that late deaths, complications, and the ultimate fate of the patients have not been demonstrated to differ in those operated at early stages from those operated in later stages of mitral stenosis, so that medical treatment may carry an overall lower risk.

#### General Discussion

The main thesis presented here is based on indirect evidence, but is consistent with all known facts about the course and the natural history of mitral stenosis. The view is proposed that mitral stenosis is initiated by a rheumatic insult to the mitral valve, which accounts for the early changes. The later progression of the anatomic changes of the mitral valve is a nonspecific process resulting from trauma to the valve structures caused by altered flow patterns, analogous to the now universally accepted mechanism of calcific aortic stenosis developing upon a bicuspid aortic valve or one showing other congenital deviation from the norm. It is believed that the progression of mitral stenosis does not occur in a uniform fashion, but goes through a stage of stability, which at some point turns into progressive stage, often at an accelerated rate. Severe rheumatic insults, such as those seen in underdeveloped parts of the world, may produce such accelerated progression early in life. In our area this stage is likely to occur in the fourth, fifth, or sixth decade of life. Patients may also remain unchanged for a lifetime with mild or moderate mitral stenosis, if more favorable anatomic conditions exist.

The application of this thesis to management of patients with mitral stenosis justifies a conservative approach and caution, especially when committing the patient to such an irrevocable form of surgical treatment as valve replacement. Many misconceptions regarding mitral stenosis are prevalent among physicians and the public alike. The patient's primary physicians often believe that mitral stenosis is a "surgical disease" and that he should be channeled directly to a cardiac surgeon. Patients may be under the impression that they suffer from a condition for which there is a "surgical cure," and begin to press for an operation whenever the slightest inconvenience related to mitral stenosis occurs. If we are to influence the natural history of mitral stenosis in a most favorable way, it is necessary to follow the team approach, with experienced clinicians, physiologists, and surgeons critically reviewing each case individually. Medical treatment and surgical treatment are two parallel modes of management of mitral stenosis, the choice of which needs to be carefully defined. Surgical candidates must have reasonable hemodynamic evidence of significant valve obstruction. Clinical symptomatology should be clearly related to mitral stenosis per se, rather than to some of its secondary complications, preferably should be progressive (the value of serial hemodynamic evaluations is self-evident), and nonresponsive to a good medical regimen.

Further studies are needed to provide more detailed information regarding the pathologic stage of mitral stenosis and its hemodynamic progression, as well as angiocardiographic identification of its varieties. Such studies might help provide rational and scientifically based guidelines for the timing and type of

surgical treatment that would most favorably affect the course of the various forms of mitral stenosis.

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