Prosthetic Replacement of the Mitral Valve

Preoperative and Postoperative Clinical and Hemodynamic Assessments in 100 Patients

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SUMMARY

Mitral valve replacement was carried out in 100 patients with acquired mitral valvular disease. Preoperatively, two patients were in functional class I (NYHA), 64 in class III, and 34 in class IV. Fifty patients had predominant mitral stenosis, and 50 predominant mitral regurgitation. All were studied before operation by right and left heart catheterization, and the clinical and hemodynamic abnormalities were defined in detail and related to the valvular malformation. Seventeen patients died at or shortly after operation; seven others died in the late postoperative period. Operative methods employed, causes of death, and incidence and significance of nonfatal complications are presented. The 76 surviving patients have been followed for intervals of 15 months to 5 years; 47 are asymptomatic (class I), 26 are in class II, and three in class III. Postoperative hemodynamic assessments uniformly demonstrated regression of pulmonary hypertension, and intracardiac pressures and cardiac index were usually normal at rest. Hemodynamic responses to muscular exercise, however, were abnormal in most patients. Mitral valve replacement provides gratifying symptomatic and hemodynamic improvement in patients with mitral regurgitation or calcific mitral stenosis. Because prosthetic valves presently available are responsible for a significant number of late deaths and serious complication, operation is indicated only in severely disabled patients in whom life expectancy is limited.

Additional Indexing Words:
Mitr al stenosis Ventriculo-atrial regurgitation Mitral regurgitation
Hemodynamic response to exercise Anticoagulation Tricuspid regurgitation
Thromboembolism Aortic regurgitation

The Starr-Edwards prosthetic valve has provided the surgeon with an effective means for correcting stenotic and regurgitant malformations of the mitral valve that are not otherwise amenable to operative treatment, and the valve has had widespread clinical application. This prosthesis was first used at the National Heart Institute in November 1961, and between that date and August 1965 the Starr-Edwards valve was employed for isolated mitral replacement in 100 patients with acquired mitral valvular disease. In each of the 100 patients, detailed clinical and hemodynamic assessments were made before operation, and such studies have been carried out postoperatively in patients who survived. The findings at preoperative and postoperative study, the operative methods employed, and an evaluation of the late results of operation are presented.

Selection of Patients

The 100 patients to be described all had acquired mitral valvular disease that necessitated valve replacement. A definite history of acute rheumatic fever was obtained from 67 patients, and in 98 the appearance of the valve at operation was compatible with previous rheumatic valvulitis; in two patients mitral regurgitation resulted from ruptured

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chordae tendineae to otherwise normal valves, a sequel of infective endocarditis. A significant proportion of the 100 patients had associated tricuspid regurgitation, and they are included in the analysis. Excluded from present consideration are additional patients in whom mitral valve replacement was performed, but in whom aortic or tricuspid valve replacement, or both, was also necessary.

To permit correlations between the nature of the valvular malformation and various preoperative and postoperative findings, the mitral valve lesion in each patient was classified as predominantly stenotic or predominantly regurgitant. The mean left atrial pressure, the contour of the left atrial pressure pulse, the magnitude of the diastolic gradient across the valve, and the extent of mitral regurgitation evident on left ventricular cineangiocardiograms were utilized in the evaluation. In the classification of a given valve, however, greatest importance was given to the information obtained by palpation and direct examination at the time of operation. Among the 100 patients, 50 had pure or predominant mitral stenosis and 50 pure or predominant mitral regurgitation.

Preoperative Clinical Descriptions

Age and Sex

The 100 patients ranged in age from 10 to 64 years. The mean age of the entire group was 38 years, and the age distribution by decades is shown graphically in figure 1. Fifty-three of the patients were female, 47 were male. Among the 53 women, 18 had mitral stenosis and 35 mitral regurgitation; 32 of the men had mitral stenosis and 15 mitral regurgitation. These sex distributions are quite different from those of mitral stenosis and mitral regurgitation in the general population, mitral stenosis ordinarily being far more common in women and mitral regurgitation more common in men.

Severity of the Disease

All patients described symptoms attributable to mitral valvular disease and its sequelae, but the incidence and severity of symptoms were not subjected to detailed analysis because of the subjective nature of such information. Certain objective data, however, were utilized to characterize the severity of the disease. For example, in 87 of the 100 patients, hospitalization had been necessary on one or more occasions for the treatment of congestive heart failure; 38 patients had been hospitalized three or more times, and 10 had had five or more periods of hospital treatment. Previous operations upon the mitral valve had been performed in 35 patients; mitral commissurotomies had been carried out in 33 patients, in four of whom two commissurotomies had been performed. One patient with mitral regurgitation had had a mitral annuloplasty, and another the insertion of a posterior baffle. Twenty-two patients had experienced one or more systemic arterial emboli; 17 of these had mitral stenosis and five mitral regurgitation. Fifteen patients had been treated for infectious endocarditis; in two of them symptoms first appeared after the infection, and in seven others previously mild symptoms became severe. In 10 of the 15 patients who had had endocarditis, the predominant valvular malformation was mitral regurgitation.

At the time of the hospital admission at which mitral valve replacement was carried
out, two of the patients were considered in functional class II, 64 in functional class III, and 34 in functional class IV, according to the New York Heart Association classification system.

Physical Findings
On examination the usual physical findings indicative of mitral stenosis, mitral regurgitation, or a combined mitral valvular lesion were evident in every patient. In 36 patients pansystolic murmurs, which increased with inspiration, were audible along the left sternal border and were considered evidence of associated tricuspid regurgitation. In 24 patients blowing diastolic murmurs at the base of the heart were attributed to aortic regurgitation, while in four others such murmurs were thought to represent pulmonic regurgitation. Six patients had ejection murmurs indicative of aortic stenosis.

At the times of their admissions for operation, 23 patients had peripheral edema, 23 had gross hepatomegaly with the liver palpable four fingerbreadths or more below the right costal margin, and 12 patients had abdominal ascites. All three signs of severe congestion, that is, edema, ascites, and gross hepatomegaly, were present in nine patients on admission. Preoperative impairment of renal function, reflecting either serious congestive heart failure or associated primary renal disease, was indicated by a whole blood urea nitrogen level of 20 mg/100 ml or more in 11 patients.

Electrocardiographic Findings
Of the entire group of 100 patients, the cardiac rhythm was atrial fibrillation in 77, normal sinus rhythm in 21, and atrial fibrillation with complete heart block was present in the remaining two patients. Twenty-eight patients had left ventricular hypertrophy, electrocardiographically, 36 right ventricular hypertrophy, and in nine combined right and left ventricular hypertrophy was present.

Fluoroscopic and Radiographic Findings
Radiographic determinations of heart size, as reflected in the cardiothoracic ratio, were determined in relation to the predominant valvular malformation. Among the 50 patients with mitral stenosis, the cardiothoracic ratios ranged from 49 to 69%, and the mean value (±1 sd) was 58.3 ± 6.9. The cardiothoracic ratios ranged from 52 to 84% in the 50 patients with mitral regurgitation, and the mean value for heart size in this group, 67.0 ± 7.7%, was significantly greater than that in the patients with mitral stenosis (P < 0.001).

Calcification of the mitral valve was evident on fluoroscopic examinations, carried out with an image intensification system, in 63 patients, 44 of whom had mitral stenosis. In six patients fluoroscopic examinations revealed calcification of the left atrium, and in each of these patients a left atrial thrombus was subsequently found at operation. Contrast radiographic examinations were performed in 51 patients, and the results of these studies are described below.

Preoperative Hemodynamic Assessments
Each of the 100 patients was studied on one or more occasions preoperatively by means of right heart catheterization. Left heart catheterization, usually by the transseptal route, was also carried out in all but five patients; in these five patients valid measurements of the pulmonary capillary wedge pressure were obtained, and in subsequent analyses these measurements are included among the determinations of left atrial pressure obtained directly. The values obtained are presented separately for the groups of patients in whom the valvular malformation was predominantly stenotic and predominantly regurgitant. The values presented are average ones determined from three or more consecutive cardiac cycles.

Predominant Mitral Stenosis
The pertinent hemodynamic data, measured in the resting basal state at preoperative right and left heart catheterization in the 50 patients with predominant mitral stenosis, are summarized graphically in figure 2. Severe pulmonary hypertension, indicated by a pulmonary arterial or right ventricular
systolic pressure of 50 mm Hg or greater, was present in 36 patients. In only three patients in the entire group was the pulmonary arterial pressure normal (30 mm Hg or less), and the average value for the systolic pressure in the 50 patients was 63 mm Hg. With one exception, the mean left atrial pressure recorded in the resting state exceeded the normal value of 12 mm Hg, and the average mean left atrial pressure in the group was 24 mm Hg. In every patient in this classification, a diastolic gradient across the mitral valve was recorded; the mean diastolic gradients ranged from 7 to 27 mm Hg, and averaged 16 mm Hg. The left ventricular end-diastolic pressure was normal (12 mm Hg or less) in 44 of the 50 patients with predominant mitral stenosis. The cardiac index was determined, either by the Fick or by the indicator-dilution technique, in all of the 50 patients, and the value was abnormally low, less than 2.6 L/min/m² BSA in 39 of them. The average cardiac index in the group was 2.1 L/min/m² BSA.

Pure or Predominant Mitral Regurgitation

Pertinent preoperative hemodynamic data obtained in the 50 patients with mitral regurgitation are summarized in figure 3. A pulmonary arterial or right ventricular systolic pressure of 50 mm Hg or greater was recorded preoperatively in 33 of the 50 patients. Only four had normal pulmonary arterial or right ventricular systolic pressures,
and the average value in the group was 60 mm Hg. The left atrial mean pressures in the patients with mitral regurgitation ranged from 9 to 38 mm Hg, and the average value in the group was 20 mm Hg. The left atrial mean pressure was within normal limits in five patients. Simultaneous or sequential measurements of both the left atrial and ventricular pressure, enabling the calculation of a mitral valve gradient, were obtained in 41 patients in this group. In nine patients no mean gradient across the mitral valve was evident, whereas in the others mean gradients ranging from 1 to 24 mm Hg were recorded. The left ventricular end-diastolic pressure was normal in 34 of the 44 patients in whom this measurement was obtained, and the average value was 11 mm Hg. The resting cardiac index was measured in 39 of the 50 patients with predominant mitral regurgitation and was less than the normal value of 2.6 L/min/m² BSA in 35 of them; the average value was 2.2 L/min/m² BSA.

Preoperative Angiocardiographic Findings

In 51 patients the severity of mitral regurgitation was assessed by selective left ventricular injections of contrast media followed by serial biplane x-rays or a cineangiocardiogram. In only two patients in whom left ventricular angiography was performed was incompetence of the mitral valve not apparent. In the remaining 49 patients, varying degrees of left atrial opacification followed injection of dye into the left ventricle. The severity of reflux was estimated from the angiocardiograms as mild, moderate, or severe. Regurgitation was considered mild in eight patients, and in each the hemodynamic and operative findings indicated the predominant lesion to be mitral stenosis. In the remaining 41 patients, moderate or severe

Figure 3

Preoperative and postoperative hemodynamic data, recorded at rest, in the 50 patients with pure or predominant mitral regurgitation. Designations as in figure 2.
mitral regurgitation was evident angiographically, and in 30 of them the predominant lesion proved to be mitral regurgitation. Selective angiocardiology or cineangiography was carried out following injections of contrast medium into the aortic root in 43 patients. In 14 patients no evidence of aortic regurgitation was found on the angiographic study. In the remaining 29 patients mild or moderate aortic regurgitation was demonstrated.

Associated Cardiovascular Malformations

As noted, 29 patients had angiographic evidence of aortic regurgitation, but in none was regurgitation sufficiently severe to necessitate aortic valve replacement. Five of these same 29 patients had peak systolic gradients across the aortic valve of 2 to 8 mm Hg. In four patients left-to-right shunts entering the right atrium were detected in the course of cardiac catheterization by the results of inhaled foreign gas tests and arterial indicator-dilution curves. In each, a patent foramen ovale or atrial septal defect of the secundum type was found and closed at the time of operation. In three other patients left-to-right shunts at the atrial level were found to result from anomalous connections of single lobar or segmental pulmonary veins to the superior vena cava or coronary sinus. Operative correction of this associated congenital malformation was not carried out.

Operative Methods

The general operative methods utilized in each of the 100 patients were similar. Anesthesia was induced with sodium thiopental and maintained with nitrous oxide and succinyl choline, or halothane in a concentration of 0.5 to 1.0%. Systemic arterial pressure was measured during the operation and postoperative period through a catheter inserted into the radial artery, and central venous pressure was monitored through a catheter inserted from a branch of the saphenous vein into the abdominal inferior vena cava. All patients were given penicillin (1.2 million units daily) and streptomycin (1.0 g daily); the drugs were administered on the day preceding operation and for 7 days thereafter. All patients were on maintenance digoxin therapy at the time of operation. Cardiopulmonary bypass was provided by a disc oxygenator and roller pumps. In the initial part of the operative series, the extracorporeal circuit was primed entirely with heparinized whole blood, which had been drawn from donors 48 hours previously. Later, the perfusate was heparinized whole blood to which 1 L of isotonic glucose and saline and 0.5 L of low molecular weight dextran had been added. Perfusion rates were 2.0 to 2.2 L/min/m² BSA and, with few exceptions, were carried out with the patient at a normal body temperature. Mild general hypothermia was induced after the institution of bypass in an occasional patient in whom aortic regurgitation necessitated occlusion of the ascending aorta during the time that the left atrium was open.

Mitral valve replacement was most frequently performed (62 patients) through a left lateral thoracotomy; this operative approach has been previously illustrated. In the remaining patients the left atrium was opened from its right side through a median sternotomy, a bilateral anterior thoracotomy, or a right lateral thoracotomy.

When the left atrium is approached from its right side, the right atrium is dissected from the anterior wall of the left atrium through the plane of the interatrial septum (fig. 4). Two cannulae are usually passed from the right atrium into the superior and inferior venae cavae, but the cavae are not occluded during the period of bypass unless operative treatment of the tricuspid valve is required. The cannulae serve as stents within the venae cavae, and prevent angulation of these vessels when the right atrium is retracted to the left during exposure of the mitral valve. After the institution of bypass, ventricular fibrillation may be induced, as a precaution against air embolism, by myocardial electrodes through which a small alternating current stimulus is supplied. A left ventricular vent or drainage cannula is not utilized.
When the functional abnormality of the valve has been assessed, by palpation and by direct vision, and the necessity for replacement has been determined, the aortic leaflet of the valve is incised 1 or 2 mm from the annulus and the incision continued around the valve ring (fig. 5). The valve is excised in continuity with its chordae tendineae, and after it is freed from the annulus the papillary muscles are transected at their origins from the left ventricular wall (fig. 6). Every attempt is made to excise the valve and its supporting structures intact, to permit the most meaningful pathological study of the specimen. If a severely calcified valve is present, any residual calcific deposits in the annulus are removed with a rongeur and the ventricle is then carefully lavaged with copious quantities of saline solution to insure removal of all debris. After excision of the valve, the size of the left ventricular cavity is the principal determinant of the size of the prosthetic valve to be employed. This is assessed by means of calibrated obturators and a prosthesis selected. Starr-Edwards valves size 3M were employed in 59 patients, 4M valves in 31 patients, 2M valves in nine, and size 5M in the remaining patient. Almost without exception, the larger valves are utilized in patients with pure or predominant mitral regurgitation, and the smaller valves are necessary in the small left ventricle usually associated with pure or predominant mitral stenosis. The construction and orifice of the Starr-Edwards valve was altered in December 1963, and 45 of the prosthetic valves utilized were of the original configuration, and 55 were valves with the dimension of those available after April 1966.

The valve is anchored into the mitral annulus with a series of interrupted sutures of no. 0 Dacron, each suture being passed...
Figure 6

After the leaflets have been detached, the anterior and posterior papillary muscles are divided at their origins from the left ventricular wall. Every effort is made to exercise the valve and its supporting structures en bloc, to facilitate subsequent pathological examinations.

through the annulus twice, so that one end terminates on the ventricular aspect of the valve ring and the other on the atrial side (fig. 7). Fifteen to 20 individual sutures, comprising 30 to 40 attachments to the valve ring, are ordinarily employed. After the sutures have been placed in the valve ring, they are passed through the sewing margin of the prosthetic valve, which is held in a specially designed holder (fig. 8). One end of each suture is passed through the Teflon fabric of the valve near the metal ring, and the other near its edge. When all the sutures have been placed, the valve is detached from the holder and drawn into position as shown in figure 9. While the sutures are being tied and cut, the valve is kept incompetent by a Foley catheter passed through it. The atrium is closed with a continuous everting mattress suture followed by an over-and-over suture which approximates the everted edges.

Immediately before the everting suture is drawn tight, attention is directed to the evacuation of all air from the left atrium. Before the catheter is withdrawn, allowing the prosthesis to function, the apex of the heart is elevated, a stab wound is made, and air is also evacuated from the left ventricle. Normal rhythm is restored at this time if ventricular fibrillation has been induced. The mean duration of cardiopulmonary bypass in these 100 patients was 107 minutes.

In 18 of the 100 patients, regurgitant blood flow through the aortic valve during the operation necessitated single or multiple periods of occlusion of the ascending aorta. In 13 of these patients mild or moderate aortic regurgitation had been demonstrated angiographically prior to operation. Of interest is the fact that in 16 additional patients mild aortic regurgitation was evident on preoperative angiograms, but the magnitude
of regurgitant flow was not sufficiently great to require any period of aortic occlusion.

In 17 of the 100 patients, thrombi were present in the left atrium. In five the thrombus was confined to the atrial appendage, whereas in the remaining 12 an extensive thrombus extending into the main cavity of the atrium was present. In six patients who had left atrial thrombi, calcification of the thrombus had been appreciated on preoperative roentgenographic studies, and in another the presence of thrombus had been detected angiographically. Fifteen of the 17 patients with thrombi were in atrial fibrillation at the time of operation. Only four (24%) had a history of a previous embolic episode, an incidence of emboli not different from that in the patients without atrial thrombi (18/83, 22%). Twelve of the patients with thrombi had had a previous operation on their mitral valve, and all but one had a calcified valve. In the patients with thrombus confined to the atrial appendage, this structure was amputated. When the thrombus occupied the main cavity of the atrium, it was excised prior to valve replacement, care being taken to establish a cleavage plane between the organized base of the thrombus and the left atrial wall. When the thrombus was removed in this manner it could usually be extracted intact, and the underlying atrial wall was generally smooth.

In six of the patients in whom the preoperative and operative findings indicated severe tricuspid regurgitation, a tricuspid annuloplasty was performed following mitral valve replacement. In five of these patients the tricuspid valve appeared anatomically normal; in the other, in whom a tricuspid

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**Figure 8**

The size of the left ventricular cavity is assessed by means of calibrated obturators, and a prosthesis of appropriate size is selected. The sutures, which have been arranged sequentially in the arc-shaped holders, are passed in turn through the sewing margin of the prosthetic valve. The valve is held in the special device shown, and the orderly arrangement of the sutures is maintained by the clips on the holder. One end of each suture is passed deeply into the fixation ring near the valve orifice, and the other through the edge of the fabric.

**Figure 9**

The valve is detached from the holder, drawn into position, and while the sutures are being tied and cut the valve is kept incompetent by a Foley catheter through it. The left atriotomy is closed with a continuous everting mattress suture, and as it is drawn tight air is evacuated from the left atrium. Before the catheter is removed, air is also evacuated from the left ventricle through a stab wound in the apex.
commissurotomy was also performed, fusion of the commissures was apparent. The annuloplasty was usually accomplished with two figure-of-eight sutures approximating the tricuspid annulus for a distance of 1 to 1.5 cm in the commissure between the anterior and posterior leaflets of the valve. In the four patients in whom atrial septal defects had been demonstrated preoperatively, they were closed by direct suture.

Two patients had complete heart block before operation with ventricular rates ranging between 40 and 48 beats per minute. In them a catheter electrode was inserted into the right ventricle prior to induction of anesthesia, and the ventricular rate was maintained by a pacemaker during mitral valve replacement. At the conclusion of the operative procedure, permanent implanted pacemakers were inserted in each patient; in one a radio frequency unit was utilized, and in the other an internal battery-operated pulse generator.

Elective tracheostomies were performed in 34 patients at the conclusion of the operative procedure. A general indication for elective tracheostomy was severe pulmonary hypertension or associated pulmonary parenchymal disease, usually emphysema or both. In a large number of the remaining patients, the endotracheal tube was left in place for 18 to 24 hours. Ventilation was provided by a volume-controlled (Engstrom) respirator supplying a mixture of oxygen and 20 to 40% nitrous oxide. The application of this technique has obviated the necessity of tracheostomy in many patients, and narcotics were usually unnecessary during the period that nitrous oxide was administered. Anticoagulation with warfarin was initiated 48 hours after operation.

**Operative Deaths and Postoperative Complications**

Seventeen of the 100 patients in whom isolated mitral valve replacement was carried out died during the hospital admission at which operation was performed, and in each necropsy was performed. Two patients died at the time of operation. In one, bleeding from the incision in a thin, friable left atrium could not be controlled; the other patient had aortic regurgitation, which necessitated numerous periods of aortic occlusion, and effective ventricular contraction was never restored. Eight patients died between the first and seventh postoperative days after courses indicative of a progressively diminishing cardiac output. All of these eight patients had mitral stenosis and a small or normal-sized left ventricle; at necropsy there appeared to be a discrepancy between the size of the prosthetic valve and the ventricular cavity. The muscular ventricular septum was found to protrude into the cage of the valve, preventing full diastolic descent of the ball, suggesting that obstruction to left atrial emptying had been present during life. In five of these eight patients, massive thrombosis of the valve and atrium was found. Two patients had acute myocardial infarctions; one had thrombus on the prosthesis and was found to have had an embolus to the left circumflex coronary artery; the other had a congenitally hypoplastic circumflex coronary artery, and infarction probably occurred during a period of severe hypotension which occurred before the institution of bypass. One patient sustained a cerebral embolus from air that had not been evacuated from the left atrial appendage. One patient had been found at operation to have numerous pulmonary infarcts; postoperatively, the infarcted areas became infected with *Klebsiella pneumoniae*, liquefied, ruptured into the pleural spaces, and fatal empyema and epicarditis resulted.

The remaining three patients died 1 or 2 days postoperatively after evidencing cardiac failure, low cardiac output, and progressive hypotension. No anatomic cause of death was apparent at necropsy. All of these patients were women with pure mitral regurgitation, and they had been in severe and prolonged congestive heart failure. The norepinephrine content of the papillary muscles of two of these patients was analyzed, and in both the concentration was greatly reduced. A causal relationship between diminished cardiac output...
norepinephrine stores and the courses of patients after cardiac operations has not been established but is suggested by the failure to survive of the two patients in whom cardiac norepinephrine was depleted.

The courses of approximately half the patients were marked by one or more significant but not fatal complications. The general incidence of such complications, and the methods of management employed in this clinic, have been described elsewhere in detail.4 Arrhythmias requiring therapy occurred in 22 patients; five had ventricular fibrillation and all were successfully resuscitated. Eight patients developed hemothorax, which required evacuation, nine had pulmonary or wound infections, one developed pneumothorax necessitating drainage, and one had an episode of massive gastrointestinal bleeding. Two patients had cerebral emboli in the early postoperative period; the first patient in the series was not given anticoagulants, and on the seventh postoperative day had unilateral weakness and aphasia, which cleared after 6 hours; following this event anticoagulation was instituted. The other patient developed aphasia and right facial weakness, which persisted for 48 hours; in him warfarin administration had been discontinued 8 weeks after operation because of hemothorax.

There were no instances of classic acute renal failure, but six patients had transient hyperkalemia which required therapy. Three patients developed azotemia with blood urea nitrogens of 75 mg/100 ml or greater; these patients usually had a normal urinary output and did not have hyperkalemia. Three patients developed postoperative bilirubinemia, ranging from 17 to 30 mg/100 ml. All had only mild derangement of other tests of liver function, and had negative Coombs' tests. In one of these patients, red-cell survival was attenuated, and hemolysis was attributed to destruction of homologous erythrocytes. All of these patients were treated with mannitol to maintain an adequate urine flow, and all recovered without sequelae.

Late Deaths
Seven of the 83 patients who survived operation and the immediate postoperative period have died at intervals of 5 to 24 months after valve replacement. The hearts of six of the patients were returned to us for pathological study. Two patients died of bacterial endocarditis; one contracted the infection following a skin graft for a chronic leg ulcer, the operation being carried out at another hospital and without prophylactic antibiotics. The source of the infection in the other patient was not apparent. In both patients the organism was Staphylococcus aureus. One patient sustained a fatal cerebroembolus after anticoagulants had been discontinued, for unknown reasons, by his physician. One patient, who had complete heart block and an implanted pacemaker, died suddenly 6 months postoperatively. It is assumed that pacemaker failure and an Adams-Stokes seizure caused death, although some thrombus was evident on the prosthetic valve. One patient collapsed, was admitted to her local hospital, and was found to have subarachnoid bleeding; the prothrombin time was 72 seconds. She died, and autopsy revealed a massive cerebral hemorrhage; the heart and prosthetic valve were unremarkable. One patient died of congestive failure, and had a leak around the base of the prosthesis, which had been unsuccessfully closed at a second operation. The cause of death in the seventh patient is unknown; he died suddenly and his family was told by his physician he had had "a blood clot to the lung."

Late Complications of Operation
Anticoagulation and Thromboembolism
With three exceptions, an attempt has been made to maintain effective anticoagulation with warfarin in all patients. The drug was not given to two patients because estimations of prothrombin time were considered impractical or impossible; one was the youngest patient, a child of 10 years of age, and the other a narcotic addict who had no accessible peripheral veins. Anticoagulation was discontinued in a third patient after a massive
gastrointestinal hemorrhage. This latter patient and the child have had no emboli 18 and 12 months, respectively, after operation; both are in normal sinus rhythm. The third patient was one of those who died of infectious endocarditis. One additional patient had gastrointestinal bleeding necessitating transfusion of 2,500 ml of blood, but anticoagulation was resumed without incident thereafter. As noted, one patient died as a result of warfarin toxicity.

Anticoagulants have been discontinued for varying periods of time in virtually all of the remaining patients, and cessation of therapy has never been associated with embolization. In all patients in whom postoperative left heart catheterization was performed, warfarin was not administered for 2 to 4 days, and the prothrombin time was allowed to fall to near control levels. Warfarin was not administered for protracted periods in six patients in whom major operative procedures were performed: four had repair of residual ventriculo-atrial regurgitation, one had a cholecystectomy and common duct exploration, and the other bilateral ileofemoral endarterectomies. Therapy has also been interrupted without incident in patients undergoing diagnostic uterine curettage or dental extractions.

Eight patients have sustained definite cerebral emboli at intervals of 1 to 45 months after operation; one patient had a splenic infarct concurrently. Two patients have had two cerebral emboli each. One patient has severe neurological impairment with persistent flaccid hemiparesis; one has mild cerebellar dysfunction, and another has undergone personality changes that may or may not be sequelae of the embolus. The remaining five patients have no detectable neurological abnormality. Five additional patients have described transient episodes of vertigo, amnesia, or weakness, but no neurological abnormalities have ever been detected at the times of examination.

The physicians of all patients have been advised to maintain the dosage of warfarin at a level sufficient to increase the prothrombin time to approximately twice the control level. All of the patients who had emboli were receiving warfarin at the time, but it proved impossible to determine whether therapeutic levels of the drug had been consistently maintained prior to the embolic episode. Thus, meaningful conclusions cannot be drawn concerning the protection against embolism afforded by warfarin.

**Residual Ventriculo-Attrial Regurgitation**

Six patients were found, at the time of postoperative evaluation, to have regurgitant flow through ventriculo-atrial communications at the base of the prosthetic mitral valve. Clinical findings did not indicate the presence of residual regurgitation, but several of the patients evidenced less than usual symptomatic improvement. All had persistent hemodynamic abnormalities, and the communications were demonstrated by cineangiograms exposed after left ventricular injections. A detailed description of the findings in the six patients and the methods and results of angiographic study have been presented elsewhere.6

Operative correction of the regurgitation around the prosthesis was attempted in four of the six patients. In each, one or more fistulous communications between the left ventricle and left atrium were found and closed. In one patient, the first in whom the Starr-Edwards valve was used, the prosthesis had been secured with a continuous suture, and the communication clearly occurred between fixation points. In the other patients, in whom closely spaced interrupted sutures were used, the regurgitant orifices were adjacent to the aortic valve, and it appeared that the sutures had torn through the rim of mitral valve tissue in which they had been placed; in this area of the mitral annulus there is no true fibrous skeleton. In no patient was there evidence of active or previous infectious endocarditis. In each patient the ventriculo-atrial communications were closed with mattress sutures, reinforced with Teflon fabric. In one patient ventriculo-atrial regurgitation persisted after the second operation, but was effectively corrected at a third one. One patient referred to above died following reoperation, and a persistent defect was found.
at postmortem examination. The three surviving patients have shown marked clinical improvement, substantiating the impression that left ventriculo-atrial regurgitation was responsible for the recurrence or persistence of their disability. Two patients have not had residual regurgitation corrected. One is asymptomatic, and regurgitation appears mild by cineangiography. The other patient has marked regurgitation, but only moderate limitation of exercise tolerance, and reoperation has not yet been recommended.

These experiences indicate that when a patient fails to improve in a satisfactory manner following prosthetic mitral valve replacement, and when elevations of the pulmonary arterial and left atrial pressures persist, partial detachment of the prosthesis with ventriculo-atrial regurgitation should be suspected. Left ventricular catheterization and angiocardiography are then indicated to differentiate this lesion from residual impairment of left ventricular function.

No residual regurgitation occurred in the last 50 patients in whom mitral valve replacement was performed. This complication of the operation can probably be avoided if meticulous care is taken with the fixation of the valve. Figure-of-eight sutures are used, and particular attention is directed to the area near the aortic valve, especially when the mitral annulus is not heavily scarred. The fixation ring of the Starr-Edwards valve has also been redesigned, and is now made of more loosely knitted fabric, which probably permits better tissue ingrowth.

**Postoperative Hemodynamic Assessments**

In 74 of the 100 patients hemodynamic studies were carried out 6 weeks to 13 months after operation; the average interval was 8 months. Included are five patients who died at some time after the postoperative study was performed.

**Predominant Mitral Stenosis**

The pertinent hemodynamic data obtained postoperatively in 35 patients who had predominant mitral stenosis before operation are graphically compared to the preoperative values in figure 2. In all patients with competent prostheses, the resting pulmonary arterial or right ventricular systolic pressure fell postoperatively, and the average value was 35 mm Hg. The systolic pressure exceeded 50 mm Hg in only four patients, two of whom had persistent ventriculo-atrial regurgitation. Data concerning the changes in total pulmonary vascular resistance that follow mitral valve replacement have previously been presented in detail. In 10 of 11 patients who had mitral stenosis and systolic pulmonary arterial pressures of 50 mm Hg or more, pulmonary vascular resistance fell, and the average values before and after operation were 514 and 243 dynes sec cm⁻² respectively.

The left atrial mean pressure, measured at rest, was lower in every patient postoperatively, but in 13 of 32 patients with competent prostheses the mean left atrial pressure was still abnormal, greater than 12 mm Hg. In six patients the mean left atrial pressure was 20 mm Hg or greater; two of them were proved to have residual ventriculo-atrial regurgitation. In three of the other four patients the prostheses were competent, and the extremely high left atrial pressures reflected abnormal left ventricular end-diastolic pressures (16, 17, and 17 mm Hg, respectively). Data permitting calculation of the mean diastolic pressure gradient between the left atrium and left ventricle were obtained in 15 patients, and the average gradient was 6 mm Hg. Two patients had exceptionally large gradients, 14 and 15 mm Hg. One was found to have residual regurgitation; the other patient had a mean left atrial pressure of 23 mm Hg, and a left ventricular end-diastolic pressure of 11 mm Hg; electrocardiograms indicated that he had had a myocardial infarction several months after operation, but the relation of this finding to the pressure gradient is obscure. The left ventricular end-diastolic pressure was greater than 12 mm Hg in five of 20 patients in whom this determination was made. Two of these patients had associated aortic regurgitation, and two others had persistent ventriculo-atrial regurgitation. The

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cardiac index at rest was higher postoperatively in 31 of 33 patients, and was normal (2.6 L/min/m² or greater), in 21. The average value for the entire group was 2.8 L/min/m².

**Predominant Mitral Regurgitation**

Thirty-nine patients who had mitral regurgitation before operation were studied postoperatively, and the data measured in the resting state are summarized in figure 3. The pulmonary arterial or right ventricular systolic pressure was reduced in every patient in whom it had been elevated, and the average in the 37 patients was 35 mm Hg. Only two patients had pulmonary arterial systolic pressures 50 mm Hg or greater postoperatively, and one of them was shown to have persistent ventriculo-atrial regurgitation. In 11 patients who had had severe pulmonary hypertension, preoperative and postoperative measurements of total pulmonary vascular resistance were made. Resistance decreased in 10 of the 11 patients, and the average before and after operation values were 774 and 245 dynes sec cm⁻⁵ respectively.

The mean left atrial pressure was reduced postoperatively in 35 of the 36 patients with competent prostheses, and the average value was 10 mm Hg. The mean left atrial pressure was greater than 15 mm Hg in only two patients; one was found to have ventriculo-atrial regurgitation, and the other to have a markedly elevated left ventricular end-diastolic pressure (17 mm Hg). The mean gradient between the left atrium and left ventricle was determined in 15 of the patients, and the average value was 4 mm Hg. The left ventricular end-diastolic pressure was abnormally elevated in only two of the 18 patients in whom it was measured. One patient had ventriculo-atrial regurgitation, and the other had associated mild aortic regurgitation. The cardiac index was higher postoperatively in 32 of 34 patients with competent valves, and was normal in all but seven. The average cardiac index was 3.0 L/min/m².

**Hemodynamic Responses to Exercise**

Twenty-four patients, 11 with mitral stenosis and 13 with mitral regurgitation preoperatively, were exercised at the time of postoperative cardiac catheterization, and the hemodynamic data are summarized in figure 10. There were 13 patients with size 3M valves, nine with size 4M, one with size 2M, and one with a size 5m valve. All of the patients were able to increase their cardiac output with exercise; however, there was an associated increase in left atrial mean pressure in 23 of the 24 patients, and the mean left atrial-left ventricular pressure gradient also increased in 23 patients. The average increase in mean left atrial pressure was 8 mm Hg; there was no significant correlation between the size of the prosthetic valve and the magnitude of the rise in mean left atrial pressure. The average increase in the mean left atrial-left ventricular gradient with exercise was 4 mm Hg, a figure that also was not dependent on valve size. In 18 of the 24 patients oxygen consumption, as well as the cardiac output, was measured at rest and during exercise. In six, the exercise factor (Δ CO in ml/min/ΔO₂ consumption in 100 ml/min) was within the normal range, that is greater than 600. The exercise factor was moderately reduced (300 to 600) in nine patients, and strikingly low in the other three. Left ventricular end-diastolic pressure increased in 21 of 24 patients in whom it was measured before and after exercise, was unchanged in two, and decreased in the remaining patient.

**Current Clinical Status**

The 76 surviving patients have now (November 1966) been followed for intervals of 15 months to 5 years after operation, and the average period has been 34 months. All patients have returned to the Institute on one or more occasions for interview and examination, except five patients who live in Europe or Asia; information concerning these five patients has been obtained from correspondence with both them and their physicians. The current functional status of all 76 patients, determined within the past year, is summarized in comparison to the
preoperative functional classification in figure 11. Forty-seven patients are asymptomatic (class I), 26 are in functional class II, and three are in class III. Limitation of activity of one patient in class III is primarily related to severe pulmonary emphysema; another has severe impairment of left ventricular function (LVED of 12 mm Hg, cardiac index 1.1 L/min/m²); the third patient has normal pressures within the left atrium and ventricle, but has severe tricuspid stenosis and tricuspid regurgitation, which were not appreciated preoperatively, and tricuspid valve replacement may prove necessary. Fifty-three patients are employed full time or, in the case of some women, are managing homes and families without unusual assistance; the remaining seven patients state that they are seeking employment. Sixty-nine patients are on unrestricted diets, but 27 of them do not add salt to their food. The remaining seven patients must restrict sodium intake more stringently or require intermittent administration of diuretics or both; one of these is the patient with tricuspid stenosis, and another has residual ventriculo-atrial regurgitation.

**Associated Tricuspid Regurgitation**

Of the entire group of 100 patients, 28 were considered preoperatively to have both clinically and hemodynamically significant tricuspid regurgitation, without associated tricuspid stenosis or atrial septal defect. Mitral regurgitation was the predominant lesion in 21 of these patients, and mitral stenosis in seven. Preoperatively, the characteristic

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**Figure 10**

Postoperative hemodynamic observations made at rest, and at the conclusion of 6 minutes of supine exercise on a bicycle ergometer. The size of the prosthetic valve in each patient is designated. None of these patients had residual ventriculo-atrial regurgitation.
MITRAL VALVE REPLACEMENT

Four patients died; mortality rate (14%) was not different from that in the patients without tricuspid regurgitation.

Twenty-four of the patients with associated tricuspid regurgitation have been reassessed postoperatively. All evidence symptomatic improvement; 16 are on unrestricted diets, six on regular diets without added salt, and only two limit sodium intake more stringently. Postoperatively, mean right atrial pressures averaged 5 mm Hg, and systolic pulmonary arterial pressures 39 mm Hg. This experience, which has been presented elsewhere in greater detail, indicates that in most patients with mitral valve disease, tricuspid regurgitation is secondary to right ventricular hypertension and dilatation of the tricuspid annulus. In such patients tricuspid regurgitation will almost always improve or disappear after mitral valve replacement, and concomitant tricuspid replacement is seldom necessary.

**Associated Aortic Regurgitation**

As noted previously, 18 patients had aortic regurgitation sufficiently severe to necessitate intermittent occlusion of the aorta at operation. All of these 18 patients had blowing diastolic murmurs preoperatively, and aortic regurgitation of mild or moderate severity was demonstrated by angiography in the 13 patients in whom this study was carried out. Eight of the 18 patients died, but aortic regurgitation was a possible contributory cause of death in only three of them. Ten of the 18 patients are living, all have diastolic murmurs, but in none has there been evidence that the aortic regurgitation has progressed in severity, or that it is responsible for significant hemodynamic abnormalities.

**Maintenance or Restoration of Normal Sinus Rhythm**

Of the 76 surviving patients, 15 were in normal sinus rhythm at the time of operation; all are now in normal sinus rhythm, but two had transient episodes of atrial fibrillation postoperatively and were converted by quinidine or countershock. Sixty-one patients

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*As noted above, two other patients had tricuspid annuloplasties. One of these, however, also had tricuspid stenosis, and the other an atrial septal defect. These two patients are not included in this analysis, based on 28 patients with associated pure tricuspid regurgitation.

*Figure 11*

Functional classifications preoperatively and at most recent examination of 100 patients in whom mitral valve replacement was performed.

murmur of tricuspid regurgitation was present in 27 patients, 25 had abnormal venous distention, 14 peripheral edema, seven ascites, and in 27 the liver was enlarged more than 4 cm below the costal margin. The mean right atrial pressure was abnormally high in every patient (average 11 mm Hg), and 28 had severe pulmonary hypertension (average systolic pressure 75 mm Hg). At the time of mitral replacement, 24 patients had no operative procedure on the tricuspid valve, and in four a tricuspid annuloplasty was performed.
were in atrial fibrillation at the time of operation; 19 of these are now in normal sinus rhythm; five converted spontaneously, one after quinidine administration, and 13 after direct current countershock. Forty-two of the 61 patients who were in atrial fibrillation at operation persist in this rhythm (one with complete heart block and a pacemaker); in 27 conversion was attempted at some time postoperatively. In 10 of these 27 patients conversion was unsuccessful, and in the other 17 normal sinus rhythm was temporarily restored, but not maintained. A total of 18 patients with atrial fibrillation postoperatively had direct current countershock on more than one occasion, and only two ultimately remained in sinus rhythm. There was no correlation between the duration of time after operation and the long-term success of cardioversion.

**Radiographic Findings**

The cardiothoracic ratio was measured from films obtained approximately 6 months postoperatively. The ratio decreased slightly in 26 of 37 patients who had mitral stenosis; the postoperative ratios averaged 55, little change from the preoperative average of 57 in these patients. The cardiothoracic ratio decreased in 36 of 37 patients who had mitral regurgitation; the exception was a patient with residual regurgitation. In this group the ratios averaged 60, a substantial decrease from the preoperative mean value of 67.

**Comment and Conclusions**

Since the Starr-Edwards mitral prosthesis was made generally available in 1961, more than 15,000 such valves have been supplied by the Edwards Laboratories to surgeons in this and other countries. Thus, it is obvious that the results of operation in the 100 patients described may or may not accurately reflect the general experience with the prosthesis. Nevertheless, the data provided by these patients allow certain conclusions concerning the indications for and results of mitral valve replacement, and provide information concerning the extent to which the clinical and hemodynamic abnormalities present preoperatively may be expected to return toward normal.

In this clinic the long-term clinical and hemodynamic results of annuloplasty or other reconstructive operations for mitral regurgitation have been poor. Also, it has usually proved impossible to restore effective function to a stenotic mitral valve that is extensively fibrotic and calcified. In general, therefore, when operative treatment is contemplated in a patient with either mitral regurgitation or calcific mitral stenosis, it must be considered that valve replacement will be necessary. Since the total early and late mortality following mitral replacement among these patients was 24%, it seems clear that the operation should only be recommended to severely disabled patients, those in functional classes III and IV, in whom the operation can reasonably be expected to prolong life. If such patients are managed without operation, the risk of death within 2 years is equal to or exceeds the risk of valve replacement. It is likely, if not certain, that the immediate operative mortality associated with mitral valve replacement could be strikingly reduced if patients less severely ill were operated upon. At this time, however, there is no reason to believe that the incidence of late mortality and morbidity is less in such patients, nor is there evidence that total life expectancy is extended if operation is carried out early in the course of the disease. Hopefully, these conclusions may be altered if the incidence of late complication and death can be reduced by the development of improved prosthetic devices.

The major factors responsible for early or late death have been described above. Certain modifications of technique now obviate the likelihood of such complications as air embolism or bleeding from the atriotomy, and careful attention is directed to selecting a prosthetic valve that will be freely accommodated within the left ventricular cavity, particularly in patients with pure mitral stenosis. Other deaths after operation must, at
this stage of our understanding, be principally attributed to sequelae of the disease process. Two late deaths resulted from infectious endocarditis, and in one of these patients the infection followed an operative procedure performed without antibiotic prophylaxis. Rheumatic fever prophylaxis with penicillin is given only to patients less than age 30, but an intensive antibiotic regimen is now applied whenever a patient with a prosthetic mitral or aortic valve must undergo dental extractions, dental prophylaxis, or other operative procedure.9

Thromboembolism has been an important but not the major cause of death and disability in the late postoperative period. As noted, only one patient died of embolism, and one other has severe neurological impairment. Although one additional late death was a direct result of warfarin administration, all available clinical and laboratory evidence indicates that with prostheses of present design anticoagulation must be maintained unless a specific contraindication exists. Starr-Edwards valves modified so that autologous tissue covers all metal parts are presently being evaluated in this laboratory.10 It is hoped that this or other changes in the design of the valve will prevent thrombus formation and obviate the need for anticoagulants.

Finally, important consideration must be given to the gratifying symptomatic and hemodynamic improvement that was shown to follow mitral valve replacement. Virtually all surviving patients have been able to resume useful and productive lives and to carry on their activities without significant discomfort. Residual hemodynamic abnormalities are evident postoperatively in most patients, particularly their circulatory responses to muscular exercise. The residual abnormalities are usually of relatively minor importance, however, in comparison to those present before operation. Although present methods and prostheses employed for mitral valve replacement are less than ideal, continued application of the operation is clearly indicated in severely symptomatic patients, since a large proportion of them will survive and be substantially improved.

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Prosthetic Replacement of the Mitral Valve: Preoperative and Postoperative Clinical and Hemodynamic Assessments in 100 Patients
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