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DETERIORATION AFTER MITRAL VALVOTOMY

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Many patients with mitral stenosis are greatly improved by surgical treatment because widening of the valve orifice, and in varying degree restoration of mobility to the cusps, results in a fall in intrapulmonary pressures. Symptoms may be relieved, but it is known that after valvotomy pulmonary arterial and venous pressures, and in particular the pulmonary vascular resistance, usually remain raised, especially on exercise. Often the cardiac output changes less than might be expected and in particular the right ventricle continues to pump against a raised resistance (Wade, Bishop, and Donald, 1954).

Experience has shown that after initial improvement, which may last for several years, many patients deteriorate. Deterioration may be due to restenosis, but it must be remembered that valvotomy does nothing to arrest the natural history of rheumatic heart disease, which is often a continuing process in the form either of active carditis or of the progressive fibrosis that follows activity. This may be evident in the mitral valve itself, which becomes more sclerotic or calcified; in the aortic or tricuspid valve, where damage may become evident or increase; or in the myocardium, as shown by the development of cardiac enlargement, cardiac failure and, possibly, atrial fibrillation.

The number of patients who deteriorate increases year by year. In some this is due to re-fusion of the cusps and in others to progressive sclerosis and rigidity of the valve, resulting in functional stenosis. An important factor may be an inadequate first operation in the early days when experience was relatively small.

In some patients deterioration is associated with a single dominant factor such as traumatic (operative) mitral incompetence. In some, deterioration is attributable to multiple adverse factors which can be grouped under the general heading of progress in the natural history of rheumatic heart disease. In a few there is unequivocal evidence of active rheumatic carditis, but more often such activity can only be suspected. In others deterioration or limitation in the degree of improvement is due to unrelated disease in the lungs or elsewhere and sometimes to psychological factors. Sometimes deterioration is precipitated by respiratory infection, pulmonary infarction, pregnancy, or bacterial endocarditis.

The effects of increasing age itself are difficult to define, but it is reasonable to suppose, without trying to be more precise than the evidence warrants, that with passage of time there is a general decline in performance of the rheumatic heart. Certainly age would seem to be an important factor. The incidence of atrial fibrillation increases with age and fibrillation has a number of disadvantages, as discussed below. The incidence of valvular calcification and of intracardiac clot also increases with age.

Deterioration after valvotomy then may be due to a combination of adverse factors, including re-fusion of the cusps, progressive sclerosis of the valve, a relatively inadequate first operation, other valvular disease, or myocardial failure.

The Present Series

This paper is concerned with the *first 500* patients from the cardiac department of the Western General Hospital in Edinburgh who have been treated by valvotomy for proved severe mitral stenosis during the past 11 years and more than 12 months ago.

Nineteen patients have been excluded in order to restrict the analysis to those with tight stenosis. In all but one of these, who was pregnant, the error in assessment was due to associated mitral incompetence, and the valve orifice admitted more than the proximal half of the terminal phalanx of the index finger. The incidence of error as regards the degree of stenosis was 3.8% in all cases for the first five years and 2.8% in the last five years. This indicated that an accurate diagnosis of tight stenosis can be made in 97% of all cases despite such difficulties as associated mitral incompetence, aortic valvular disease, and pregnancy.

In this series of 500 patients the valve orifice accepted less than the terminal phalanx of the index finger in 480 cases (96%) and just admitted the terminal phalanx in the remainder.

This paper is not so much concerned with those who have maintained a good functional result as with the general problem of those who subsequently deteriorated after operation. An analysis has been made of operative mortality and other immediate ill-effects in the whole series of 500 patients, and of the subsequent progress of the first 200 patients to be treated, more than six years

ago. Throughout significance has been accepted at the 99% level ($P=0.01$ or less). A particular study has also been made of all patients so far who have required a second operation (Logan, Lowther, and Turner, 1962).

The series is uniform in that, as previously described (Logan and Turner, 1953; Turner and Fraser, 1956), all patients were admitted to the same medical ward, were assessed in a similar manner by three of the same four observers and almost all were operated on by the same surgeon (Mr. Andrew Logan).

The fact that during the period of 11 years since our first patient was treated surgically a standard method of assessment has been made by the same small team has facilitated the recording and analysis of data and all patients become well known to us as individuals. In most cases one of us has been present in the operating-theatre, which has also facilitated discussion and the correlation of data, and incidentally provided an additional stimulus to achieve accuracy in pre-operative diagnosis. It is important to emphasize that the 200 patients who have been followed for more than six years were all operated upon before the introduction of the transventricular dilator (Logan and Turner, 1959) and during the period when almost all surgeons were also using a finger-and-knife technique.

All have been examined in a regular follow-up clinic except one who is living abroad. Five patients who live at a distance have been examined by other physicians, who have kindly sent us detailed reports.

Post-operative results have been divided into three groups: "good," "fair," and "poor." Good implies great functional improvement with ability to carry out normal housework or a previous occupation. Fair implies considerable improvement but with some dyspnoea on moderate exercise and usually the necessity for some home help or an occupation involving little physical exertion. A poor result implies slight or no improvement or actual deterioration due to the operation, such as from traumatic mitral incompetence or systemic embolism.

That the series is fairly representative of rheumatic heart disease is evident from Table I. It will readily be seen that the selection of patients for operation was not confined to what might be described as "good risks." To have done so would have resulted in a lower operative mortality and a higher proportion of good results but would also have denied a new lease of life to many.

From the beginning we have offered the prospect of surgical relief to many severely disabled patients with tight stenosis despite relative contraindications, including an age over 50, considerable cardiac enlargement, heavy calcification of the valve, or aortic valvular disease, and appreciate that these might be regarded as absolute contraindications in centres where different

TABLE I.—*Mitral Valvotomy (500 Cases), Clinical Features*

	No.	%
Males	110	22
Females	390	78
Age < 30 years	99	20
Age 30-49	344	69
" 50-60	57	11
Atrial fibrillation	197	39
Cardiothoracic ratio $\geq 60\%$	111	22
Calcification of valve	179	36
Heavy calcification	92	18
Associated valvular disease:		
Mitral incompetence	137	27
Aortic	262	52
stenosis	103	21
Intracardiac clot	107	21

criteria are adopted. Undoubtedly a few patients have died as a direct result of this policy when otherwise they might have lived their restricted lives for a longer period. However, in this group there has been a large proportion of worth-while results, and on balance we believe that our policy as regards selection of cases for operation has been justified by the results.

Operative deaths are considered first before dealing with our main topic, which concerns those who did not maintain a good result throughout the six-year period.

Operative Mortality

The overall operative mortality has remained constant at 6-7% over the 11-year period, which compares favourably with many published series, especially when considered in relation to the type of case being treated.

The relative incidence of adverse factors in those who died at operation and those who survived is shown in Table II.

It will be seen that incidence of atrial fibrillation, aged 50 and over, cardiac enlargement, and heavy calcification of the valve was two to three times higher in those who died at operation. The apparent effect of each of these factors on operative mortality is shown in Table III. However, these features frequently occur in combination, and a more detailed analysis is shown below, in which an attempt is made to evaluate each individually.

In this series of 500 patients there were 31 operative deaths (Table IV). It will be seen that the principal causes of death were systemic embolism and traumatic mitral incompetence, but the actual incidence of each is low. The incidence of intracardiac clot increases with age and with heart size, and is much higher in those with atrial fibrillation than in those with sinus rhythm as discussed below. Therefore in some measure the risk of systemic embolism is predictable. Traumatic mitral incompetence is related chiefly to the precise pathological changes in the valve, and this is not predictable. It is related to surgical technique only in the sense that

TABLE II.—*Mitral Valvotomy (500 Cases). Incidence of Adverse Factors*

	No. in Group	Heavy Calcification	Atrial Fibrillation	Age 50 and Over	C.T.R. $\geq 60\%$
Operative deaths	31	15 (48%)	26 (84%)	10 (32%)	15 (48%)
Survivors of operation ..	469	77 (16%)	171 (37%)	47 (10%)	96 (20%)

TABLE III.—*Mitral Valvotomy (500 Cases). Factors Influencing Operative Mortality*

Factor	Operative Mortality (%)
Sinus rhythm	2
Atrial fibrillation	13
Age < 50 years	5
" 50	18*
Cardiothoracic ratio $< 60\%$	4
" $\geq 60\%$	14
No heavy calcification	4
Heavy calcification	16

* 11% in 36 cases in the last eight years.

TABLE IV.—*Mitral Valvotomy (500 Cases). Causes of Operative Death*

Systemic embolism	13
Traumatic mitral incompetence	6
Circulatory failure	5
Cardiac arrest	2
Haemorrhage	3
Pneumonia	2
Total	31 (6.2%)

it is more likely to follow strenuous efforts at commissural division in difficult cases. In our experience the incidence of important incompetence has not been higher since the introduction of the transventricular dilator. Circulatory failure is apt to occur in the early days after operation in severely advanced cases and cardiac arrest at the time of operation may occur in the same group. Haemorrhage for technical reasons is now rare.

Death at operation tends to be a more dramatic event than death in the course of medical treatment and consequently gives rise to more comment. Nowadays, if patients for surgical treatment are properly selected, death at or shortly after operation is infrequent and usually occurs either from the largely unpredictable hazards of systemic embolism or from traumatic mitral incompetence or in those known to be relatively poor risks. These risks having been considered and accepted, a few such deaths can hardly be avoided. On the other hand, death frequently occurs in patients with tight mitral stenosis who have not had the opportunity of surgical treatment and in whom a good result would have been expected. Such deaths are reprehensible in the sense that surgical treatment either has not been considered or has been rejected on inadequate grounds. It is very important that surgical treatment should at least be considered in every patient in whom the diagnosis of mitral stenosis is made, and if symptoms cannot be attributed to some other condition, operation should usually be advised. The decision is often difficult, so that in practice this means that almost all patients should be referred to a centre with special experience.

Results

The results after six years in 200 patients are shown in Table V. The proportion of unsatisfactory results in survivors (72) at six years appears rather high (39%), but it is emphasized that this includes not only those who subsequently required a second operation and did well, but also those who maintained a good result for

TABLE V.—*Mitral Valvotomy (200 Cases): Results After Six Years*

Operative deaths	14
Untraced	1
Good result	113
Unsatisfactory result	72
Operation repeated	13
Fair	39*
Poor	3
Dead	17

* In 23 of these operation was subsequently repeated.

several years before deteriorating and those who deteriorated with important but unrelated disease. In addition, six patients were difficult to classify because of cerebral embolism or psychological disorders. Hemiplegia obviously limits the capacity for physical exertion and hence the opportunity to become breathless. Cerebral embolism may also be associated with mental changes. Psychological disorders of constitutional origin and unrelated to rheumatic heart disease may make the assessment difficult. In all these cases it seemed desirable to classify the patients conservatively as less than good results, although their status was not really attributable to deterioration as regards the heart. In view of these facts it is concluded that the results of valvotomy itself are really rather better than is indicated by an overall percentage.

A clearer impression of the post-operative progress in this group is shown in Fig 1. The proportion of good

results, beginning at 84% after the first year, falls by only 10% over the first five years but by another 10% during the following year. Thereafter deterioration is progressive, and by the end of eight years less than 50% have maintained a good result without interruption. In the inevitably small group who have been followed for more than nine years the proportion maintaining a good result without interruption has fallen as low as 20%, but many of these have passed into the reoperation column and are again improved. It is emphasized that a fair result implies definite and worth-while improvement in patients who previously were progressively disabled.

It is noteworthy that of the 72 who were less than good at the end of six years, 30 were in this category by the end of the first 12 months. An analysis of this latter group shows that six subsequently required a second operation, in 13 multiple adverse factors were present and the operation did no more than change for a time the natural course of severe rheumatic heart disease, and in 11 a variety of single factors (included in Table VII) precluded benefit derived from the relief of severe stenosis.

It is evident from our experience that mitral valvotomy materially benefits the majority of patients for five to six years but thereafter the proportion who deteriorate steadily increases. The reasons for this are discussed below.

In Table VI the 72 patients who failed to maintain a good result are divided into two groups. The first consists of 35 patients in whom deterioration by six years was shown to be due to restenosis and who had had or were about to have a second operation. The second consists of 37 patients who did not have a second

FIG. 1.—Progress after mitral valvotomy in 185 survivors of the operation observed for six to nine years.

TABLE VI.—*Mitral Valvotomy (185 Cases): Deterioration by Six Years (72 Cases)*

Reoperation	35
Within 6 years	13
After 6	22
No reoperation	37
Single dominant adverse factor	19
Multiple adverse factors	18

operation (but in many of whom nevertheless some degree of continuing or increasing obstruction of the mitral valve was probably present), either because of a single dominant adverse factor or because of multiple adverse factors.

Restenosis of the Mitral Valve

In our experience restenosis of the mitral valve has been the most frequent single cause for deterioration after valvotomy. It is also the most important cause, being the only one for which potentially satisfactory treatment is available.

Recurrence of symptoms similar to those which preceded the first operation and the absence of any other condition which might be responsible for deterioration are the usual circumstances which have led us to consider the need for a second operation.

Often the first operation was carried out in the early days when experience was limited and a relatively incomplete valvotomy was achieved. This might be expected to favour re-fusion of the cusps. Another important factor may be heavy sclerosis or calcification of the valve preventing separation of the cusps or maintaining them in rigid apposition after they have been separated.

Nevertheless restenosis has frequently occurred after an apparently satisfactory valvotomy; and also, despite a very sclerotic valve, many patients have maintained a good result for six or more years without recurrence of symptoms. It would seem likely that the prognosis is not only related to the size of the valve orifice produced and to restoration of mobility to the cusps but that other factors must also be important. Presumably these include differences in the rate of deposition of the fibrin which is responsible for the refusion of the cusps and progression in the natural history of rheumatic heart disease, particularly as regards the heart muscle.

Our experience in relation to these and other factors is reported elsewhere (Logan, Lowther, and Turner, 1962) because the problem has become one of increasing importance and complexity.

Of the first 268 patients in the present series of 500 to be followed for more than five years after valvotomy, 92 have now been subjected to a second operation and severe stenosis was found in all but six. The incidence of restenosis increases year by year and has risen from 5% after five years to no less than 70% in the relatively few (37) patients who have been followed for nine years. The average interval between operations has been seven years.

We have analysed the incidence of other potentially adverse factors, such as age, atrial fibrillation, considerable cardiac enlargement, calcification of the valve, associated mitral incompetence, and aortic valvular disease in those who have had a second valvotomy and in those who have not, but found no significant difference. The operative mortality for the second valvotomy (2.4%) and operative incidence of systemic embolism and traumatic mitral incompetence have not been higher than for the first valvotomy. In most cases a better valvotomy has been achieved owing to greater surgical experience and improved technique after the introduction of the transventricular dilator. However, the indications so far are that long-term results may be less satisfactory and that this may be attributable to the relentless progress of rheumatic heart disease.

Single Dominant Factor as a Cause of Deterioration

The single dominant factors which were responsible for deterioration and which precluded consideration of a second operation in 19 patients are shown in Table VII. These factors are self-explanatory and each occurs so infrequently as not to warrant detailed discussion.

TABLE VII.—*Single Dominant Factors Precluding Reoperation (19 Cases)*

Early death	9
Cardiac arrest	2
Influenza pneumonia	1
Bacterial endocarditis	1
Malignant pulmonary hypertension	1
Severe systemic hypertension	1
Myocardial infarction	1
Carcinoma	1
Transfusion reaction	1
Active carditis	2
Traumatic (operative) mitral incompetence	1
Chronic bronchitis	1
Systemic embolism	3
Psychological disorders	3

Two patients died suddenly and seven died from an unrelated condition which failed to respond to treatment. Two had clear evidence of active carditis. One is awaiting surgical treatment for traumatic mitral incompetence. One had severe chronic bronchitis.

Multiple Adverse Factors

In 18 patients multiple factors were present, such as atrial fibrillation, considerable cardiac enlargement, calcification of the valve, and aortic valvular disease, and seven of them were aged 50 or more, but, as discussed below, none of these factors individually precludes a good operative result. Half of them, despite tight stenosis, had had palpable reflux at operation. Thirteen have since died. Five of 12 patients who were examined at necropsy showed evidence of cardiac cirrhosis of the liver. This may be a difficult diagnosis to make in life, but we now believe that when the diagnosis seems definite the risk of post-operative circulatory failure is so high that surgical treatment should not be advised. Continued rheumatic activity was probably a factor in some, but the difficulties of being certain of this are well known.

In addition some degree of mitral stenosis doubtless persisted in all, and in a few of these with very rigid valves this was shown at necropsy to be considerable. Severe pulmonary hypertension as measured by cardiac catheterization or assumed from an electrocardiographic pattern of right ventricular hypertrophy or considerable enlargement of the pulmonary artery as judged radiographically was present in some.

It may be questioned whether valvotomy is justified in patients with evidence of such severe heart disease. However, Fig. 2 shows that in this series a worth-while degree of improvement was obtained and persisted in most cases for several years. The difficulties in this group are so great and of such importance that after the long-term results have been discussed in relation to individual adverse factors the problem of this by no means uncommon group with multiple adverse factors will be considered in more detail.

Atrial Fibrillation

The proportion of patients with rheumatic heart disease of sufficient severity to bring them under observation who develop atrial fibrillation increases with age (Table VIII). Sometimes fibrillation is precipitated by

exercise, emotion, respiratory infection, or active carditis, but often it develops without obvious reason and the condition is attributed to advancing years.

The cause of fibrillation is uncertain. An analysis of our material shows that it bears no direct relationship to the degree of mitral stenosis or incompetence or of pulmonary hypertension but that those with fibrillation tend to have larger hearts, as judged by the cardio-thoracic ratio, and also larger atria than in those with sinus rhythm. By a process of exclusion it seems clear that factors other than myocardial damage are unimportant and there is at least presumptive evidence that myocardial damage is in some way responsible, although the precise nature of the relationship is obscure (Fraser and Turner, 1955b).

It was known long before the days of surgical treatment that the prognosis for those with atrial fibrillation was worse than for those in sinus rhythm, so that it was only to be expected that the long-term outlook in these patients after operation would not be so good.

Atrial fibrillation is certainly not by itself a contra-indication to surgical treatment for the relief of tight mitral stenosis, and in the present series 39% of patients had established fibrillation before their operation. Nevertheless its significance is sometimes underestimated. Atrial fibrillation is an adverse factor which must be taken into account when considering both operative mortality and the prospects of lasting relief.

Operative Mortality.—The operative mortality has been significantly greater in those with atrial fibrillation (13%) than in those with sinus rhythm (2%) (Table IX) ($P < 0.01$). However, a causal relationship is valid only if the two groups do not differ in other respects. Table X shows that those with atrial fibrillation also have a higher incidence of other adverse factors. Therefore we have extracted from the series a group who differ only in respect of rhythm (Table XI). It is

evident that even without the other three commonly associated adverse factors which we have analysed—that is to say, in those who are not over 50 years of age and are without gross cardiac enlargement or heavy calcification of the valve—the operative mortality with fibrillation is much greater than in a similar group with sinus rhythm (Table XI). This is largely due to a higher incidence of clot and subsequent cerebral embolism as discussed below.

Good Results.—The proportion of patients who maintain a good post-operative result for more than six years is apparently lower in those with atrial fibrillation (46%) than in those with sinus rhythm (69%) (Table XII). However, this difference is not statistically significant ($P = 0.08$). Again it is important to remember that those with fibrillation have a higher incidence of other adverse features (Table X), and because of this these figures do not necessarily reflect the influence of fibrillation itself. However, when other analysable factors have been excluded the figures are too small for statistical analysis, and it has still to be shown that fibrillation itself has an adverse influence on long-term results. It will be seen from Fig. 3 that most patients in this group maintain worth-while improvement for at least five to six years. Nevertheless, if, as discussed above, fibrillation reflects myocardial damage it may be that over a longer period this group will do less well than those in sinus rhythm.

Post-operative atrial fibrillation—that is to say, within the first few days—developed in approximately 20% of all patients previously in sinus rhythm, and sinus rhythm either returned spontaneously or was restored with quinidine in all but a very few cases. In fact, in only four of our total series did this not occur. So far atrial fibrillation has developed subsequently in another 27% and, as would be expected, this incidence increases with each passing year.

Age 50 and Over

Advancing years must clearly be adverse. Most patients with untreated mitral valvular disease succumb before the age of 50 and those who do survive are liable to have atrial fibrillation, considerable cardiac enlargement, rigidity and calcification of the valve,

FIG. 2.—Progress of 18 patients with no second operation.

TABLE VIII.—Atrial Fibrillation and Age

Age-group	Total No. of Cases	Atrial Fibrillation
10-19	9	0
20-29	89	13 (14%)
30-39	180	50 (28%)
40-49	165	93 (56%)
50+	57	41 (72%)
Total	500	197 (39%)

TABLE IX.—Atrial Fibrillation: Operative Mortality

	No. in Group	Operative Deaths
Atrial fibrillation	197	26 (13%)
Sinus rhythm	303	5 (2%)

TABLE X.—Atrial Fibrillation: Incidence of Associated Adverse Factors

	No. in Group	Age 50+	C.T.R. $\geq 60\%$	Heavy Calcification
Atrial fibrillation	197	43 (22%)	74 (38%)	48 (24%)
Sinus rhythm	303	14 (5%)	37 (12%)	44 (15%)

TABLE XI.—Atrial Fibrillation: Comparison of Operative Mortality in Two Groups

	No. in Group	Operative Deaths
Atrial fibrillation Age < 50 C.T.R. < 60% No heavy calcification	81	6 (7.4%)
Sinus rhythm Age < 50 C.T.R. < 60% No heavy calcification	222	1 (0.45%)

TABLE XII.—Atrial Fibrillation: Good Results at Six Years

	No. in Group	Good Results at 6 Years
Atrial fibrillation	65	30 (46%)
Sinus rhythm	120	83 (69%)

chronic cardiac failure sometimes with cirrhosis of the liver, intracardiac clot, and unrelated conditions such as chronic bronchitis, hypertension, or coronary atheroma.

It will be seen from Table XIII that there were 57 patients aged 50 and over, and 10 of these died as a result of the operation, giving a mortality rate of 18% compared with a mortality of 5% for all cases under 50. This is a significant difference ($P < 0.01$). However, in the last eight years there have been only four opera-

tive deaths in 36 patients over 50, so the operative mortality in this group should probably be assessed at about 10%. Perhaps this should be expressed by saying that 90% survive even at this age, and often with an advanced condition.

The incidence of the associated adverse factors analysed in the other groups is shown in Table XIV. It is impossible to make a valid comparison of operative mortality in those over and under the age of 50 in whom these other adverse factors are *not* present because the numbers are too small. There were only seven patients aged 50 or more with sinus rhythm, a cardiothoracic ratio under 60%, and no calcification of the valve, with one operative death from traumatic mitral incompetence, a complication which is not related to age.

Good Results.—Among the 185 survivors for more than six years were 17 aged 50 or more. The result at six years is classified as good in seven and fair in three—that is to say, still worth while in 10 of the 17. The good results compared with those under the age of 50 are shown in Table XV. Because the number of those aged 50 and over is small no statistical conclusion can be drawn, but it will be seen from Fig. 4 that a high proportion maintained a worth-while degree of improvement for several years.

In retrospect operation should probably not have been advised in three of the patients with an unsatisfactory result, on account of gross cardiac enlargement and other adverse features. Since there were only two patients in the group with sinus rhythm, a cardiothoracic ratio under 60%, and without calcification of the valve, a statistical comparison cannot be made as regards those in whom age was the only potential adverse factor. Some individuals aged 50 or more with many interests in life are most unwilling to accept progressive incapacity and restrictions without hope of improvement. They are anxious for something to be done despite the realization that there must be some risk. Others, having slowly come to accept their limitations, are content when it is explained that the chances of considerable improvement are relatively slight and there might even be none. If all relevant factors, including temperament and attitude, are taken into account the decision in the individual case is not usually difficult.

Conclusion.—No one should be denied the opportunity on account of age alone, because worth-while benefit can undoubtedly be obtained in most cases.

FIG. 3.—Progress of 65 patients with atrial fibrillation.

TABLE XIII.—Age and Operative Mortality

	No. in Group	Operative Deaths
Age 50+	57	10 (18%*)
„ <50	443	21 (5%)

* 11% in 36 cases in the last eight years.

TABLE XIV.—Age and Incidence of Associated Adverse Factors

	No. in Group	Atrial Fibrillation	C.T.R. $\geq 60\%$	Heavy Calcification
Age 50+	57	42 (74%)	15 (26%)	23 (40%)
„ <50	443	155 (35%)	96 (22%)	69 (16%)

TABLE XV.—Age and Good Results at Six Years

	No. in Group	Good Result at 6 Years
Age 50+	17	7 (41%)
„ <50	168	106 (63%)

FIG. 4.—Progress of 17 patients aged 50 or more years.

Calcification of Mitral Valve

This incidence of calcification increases with age (Table XVI) and is also higher in males (56%) than in females (22%). Different opinions are held on the importance of calcification of the mitral valve. Our views are unchanged and have been discussed previously (Turner and Fraser, 1956).

Since there is less disagreement as regards the importance of light calcification we have extracted from our series of 500 patients 92 who had *heavy* calcification for the purpose of analysing the operative risk.

TABLE XVI.—Calcification of Mitral Valve

Age	No. in Group	No. with Calcification
<30	99	16 (16%)
30-49	344	131 (38%)
50-60	57	32 (56%)
Total ..	500	179 (36%)

Twenty-seven have been followed for more than six years after the operation and have been analysed as regards good results.

Operative Mortality.—Table XVII shows the operative mortality in those with heavy calcification of the mitral valve compared with those without it. The risk is significantly greater in those with heavy calcification ($P<0.01$). However, it must be remembered that calcification is often associated with other adverse factors (Table XVIII). As in the case of atrial fibrillation any statement as regards the adverse influence of calcification *itself* holds only if the two groups analysed are equal in other respects. We have therefore extracted the group of 252 patients who were in sinus rhythm, aged under 50, and who did not have gross cardiac enlargement, and compared the operative mortality in those with and in those without heavy calcification (Table XIX). It is evident that there is no significant difference between those with and those without heavy calcification.

Good Results.—We have compared the good long-term results in the 185 patients who survived the operation for more than six years as regards the presence or absence of heavy calcification (Table XX). There is no significant difference ($P=0.25$) between the end-results in the two groups, and when other adverse factors are excluded the total numbers become too small for conclusions to be drawn. Nevertheless it is emphasized and shown in Fig. 5 that in 27 patients the post-operative result at the end of six years was still good in 9 and fairly good in a further 11—that is to say, worth while in more than two-thirds. In addition, other patients were much improved for a period of two to four years before deteriorating.

Perhaps the most important point to emphasize is that the significance of calcification from the operative point of view is impossible to predict by radioscopy or tomography. What matters is its precise distribution and relationship to the line of fusion of the cusps.

TABLE XVII.—*Calcification: Operative Mortality*

	No. in Group	Operative Deaths
Heavy calcification ..	92	15 (16%)
No heavy calcification ..	408	16 (4%)

TABLE XVIII.—*Calcification: Incidence of Associated Adverse Factors*

	No. in Group	Atrial Fibrillation	Age 50+	C.T.R. $\geq 60\%$
Heavy calcification ..	92	48 (52%)	26 (28%)	30 (33%)
No heavy calcification ..	408	149 (37%)	31 (8%)	81 (20%)

TABLE XIX.—*Calcification: Comparison of Operative Mortality in Two Groups*

	No. in Group	Operative Deaths
Heavy calcification Sinus rhythm Age < 50 C.T.R. < 60%	30	0
No heavy calcification Sinus rhythm Age < 50 C.T.R. < 60%	222	1 (0.45%)

TABLE XX.—*Calcification: Good Results at Six Years*

	No. in Group	Good Results at 6 Years
Heavy calcification ..	27	14 (52%)
No heavy calcification ..	158	99 (63%)

Some valves with heavy calcification are so rigid that little if anything can be done or, if some separation of the cusps is obtained, their mobility is little improved and functional stenosis remains severe. In other cases there is heavy calcification in the region of the valve, but its distribution is such that an adequate valvotomy can be achieved and considerable mobility of the cusps restored.

In some patients with heavy sclerosis but no actual calcification of the valve there is just as much rigidity and the valve is no more amenable to satisfactory surgical treatment than one with calcification. Likewise it is not predictable from the pre-operative assessment what the surgeon may be able to achieve. Fortunately in such cases there is usually no question of being turned down for operation as may happen to the patient in whom heavy calcification has been detected.

Conclusion.—In considering the significance of calcification in relation to operative mortality and long-term results the importance of associated adverse factors must be appreciated. It is clear from our analysis that heavy calcification *itself* should never be a contraindication to operation. In this group long-term results are less good than in those without such calcification; but this is acceptable in view of the fact that the operative mortality is no higher.

Cardiac Enlargement

In general, cardiac enlargement might primarily be due either to dilatation of the heart from the mechanical effects of severe valvular deformity or to weakened muscle, from rheumatic myocarditis, giving way in response to normal or raised pressures. If valvular defects were the most important factor there should be some correlation between individual chamber-size and the severity of stenosis or incompetence of the mitral, aortic, and tricuspid valves and the presumed duration of the rheumatic process. The latter factor can be roughly assessed by the age of the patient, the age at which rheumatic fever occurred, the age at which heart disease was first noted, and to some extent by the duration of symptoms.

In a previous analysis of our material we attempted to correlate these various factors but were not able to

FIG. 5.—Progress of 27 patients with heavy calcification of the valve.

demonstrate any close relationship between general cardiac or individual chamber size and the severity of valvular defects and this suggests that the myocardial factor is dominant (Fraser and Turner, 1955b).

Operative Mortality.—There were 111 patients with a cardiothoracic ratio of 60% or more and it will be seen from Table XXI that the operative mortality is significantly higher than in those with smaller hearts ($P<0.01$). However, it will be seen from Table XXII that the incidence of associated adverse factors is also higher in those with larger hearts. The importance of these other factors is shown if comparison is made with the group in which they are not present—that is to say, those with large hearts but in sinus rhythm, under 50 years of age, and without heavy calcification of the valve (Table XXIII). It is evident that there is no significant difference attributable to cardiac enlargement itself.

Good Results.—Similarly, if the late results are compared in those with and without large hearts (Table XXIV), it can be seen that there is no significant difference between them ($P=0.4$). Unfortunately the group with cardiac enlargement *alone* is necessarily small, but Fig. 6 shows that most of the 42 patients followed for six to seven years maintained worth-while results throughout the period.

Associated Aortic Valvular Disease

Patients are often denied operation for mitral stenosis on account of associated aortic valvular disease. We are here concerned only with operative results and not with differential diagnosis and theoretical concepts, but the problem is so important and of such frequent occurrence that it merits detailed consideration on another occasion.

Aortic Incompetence

Severe aortic incompetence in association with severe mitral stenosis must be a rare combination, and in the analysis of more than 1,500 patients with rheumatic

TABLE XXI.—Cardiac Enlargement: Operative Mortality

Cardiothoracic Ratio	No. in Group	Operative Deaths
$\geq 60\%$	111	15 (14%)
$< 60\%$	389	16 (4%)

TABLE XXII.—Cardiac Enlargement: Associated Adverse Factors

	No. in Group	Atrial Fibrillation	Age 50+	Heavy Calcification
C.T.R. $\geq 60\%$	111	74 (67%)	16 (14%)	31 (28%)
C.T.R. $< 60\%$	389	123 (32%)	41 (11%)	61 (16%)

TABLE XXIII.—Cardiac Enlargement: Comparison of Operative Mortality in Two Groups

	No. in Group	Operative Deaths
C.T.R. $\geq 60\%$ Sinus rhythm Age < 50 No heavy calcification	29	1 (3%)
C.T.R. $< 60\%$ Sinus rhythm Age < 50 No heavy calcification	222	1 (0.45%)

TABLE XXIV.—Cardiac Enlargement: Good Results at Six Years

Cardiothoracic Ratio	No. in Group	Good Results at 6 Years
$\geq 60\%$	42	21 (50%)
$< 60\%$	143	92 (64%)

heart disease, of whom approximately 40% have been treated surgically, we have not encountered a single instance. On the other hand, aortic incompetence of mild or moderate degree is often associated with tight mitral stenosis.

In this series of 500 patients treated by mitral valvotomy there were 262 patients (52%) with an early diastolic murmur audible down the left sternal border which persisted after valvotomy and was attributed to aortic incompetence. It is possible that there were a few errors in making this presumptive diagnosis and that the murmur was really due to pulmonary incompetence, but the inadvertent inclusion of a few such cases would not affect the conclusions drawn. Many of these patients had a loud murmur, a pulse of relatively full volume, and some degree of left ventricular enlargement, but none had a diastolic blood-pressure below 50 mm. Hg. None had an unequivocal electrocardiographic pattern of left ventricular hypertrophy.

Operative Mortality.—There were 17 operative deaths in these 262 patients (Table XXV). It is clear that there is no significant difference as regards the operative risk in those with and those without associated aortic incompetence.

Good Results.—In the present series of 185 patients followed for more than six years there were 82 in whom a diagnosis of associated aortic incompetence had been made pre-operatively. In no instance did mitral valvotomy apparently "aggravate" the haemodynamic effects of the aortic incompetence as judged clinically except that in a few cases the murmur was somewhat louder. The proportion of good results maintained for six years is similar to that in those who did not have aortic incompetence (Table XXVI).

So far as can be judged no patient has failed to benefit from the operation because of coexisting aortic

FIG. 6.—Progress of 42 patients with cardiothoracic ratio $> 60\%$.

TABLE XXV.—Associated Aortic Incompetence: Operative Mortality

Aortic Incompetence	No. in Group	Operative Deaths
Present	262	17 (6%)
Absent	238	14 (6%)

incompetence and no patient so far has subsequently deteriorated on this account. Over a longer period it would be surprising if patients who also have aortic valvular disease did not do less well than others; but the point we wish to emphasize is that some patients are on this account being denied the opportunity of relief from their mitral stenosis.

Over the past 10 years in our unit aortic incompetence has never by itself been accepted as a contraindication to surgical treatment for the relief of severe mitral stenosis, and so far there has been no reason to regret the adoption of this policy.

Aortic Stenosis

In the present series of 500 patients an associated aortic systolic murmur was recorded in 103 but no patient was turned down for mitral valvotomy on this account.

Severe aortic stenosis is often associated with severe mitral stenosis and is not a contraindication to mitral valvotomy, because aortic valvotomy can be carried out at the same thoracotomy. In 25 patients this combined valvotomy was carried out by the transventricular approach. In our experience the operative mortality for the combined procedure has not been higher than for mitral valvotomy alone.

Operative Mortality.—Altogether there were three operative deaths among the 103 patients, but in none was there anything to suggest that this was related to the associated aortic stenosis. It is clear that there is no significant difference between those with and those without an aortic systolic murmur (Table XXVII).

Good Results.—In the series of 185 patients followed for more than six years there were 23 in whom an aortic systolic murmur had been recorded pre-operatively. In a few cases it was thought probable that the aortic systolic murmur was somewhat louder post-operatively, but in no instance was there evidence of any immediate adverse effect, and after six years the proportion of good results as judged by symptoms was not significantly lower (Table XXVIII). However, in some patients there has been unequivocal evidence of increasing left ventricular hypertrophy or enlargement and two have subsequently required an aortic valvotomy.

Conclusion on Associated Aortic Valvular Disease

From the data presented it is clear that associated aortic valvular disease is not a contraindication to mitral valvotomy for the relief of symptoms due to severe mitral stenosis.

TABLE XXVI.—Associated Aortic Incompetence: Good Results at Six Years

	No. in Group	Good Result
Aortic incompetence	82	50 (61%)
No aortic	103	62 (60%)

TABLE XXVII.—Associated Aortic Stenosis: Operative Mortality

Aortic Stenosis	No. in Group	Operative Deaths
Present	103	3 (3%)
Absent	397	28 (7%)

TABLE XXVIII.—Associated Aortic Stenosis: Good Results at Six Years

Aortic Stenosis	No. in Group	Good Result
Present	23	15 (65%)
Absent	162	104 (64%)

Tricuspid Stenosis

It is not part of the purpose of this paper to discuss the diagnosis and treatment of tricuspid valvular disease. When suspected, the diagnosis should be confirmed by cardiac catheterization. Unless tricuspid incompetence is also present a gradient across the valve of more than a few millimetres should usually lead to exploration of the valve.

The diagnosis of significant tricuspid disease is important because if the stenosis is unrelieved there may be little improvement after mitral valvotomy.

In the present series of 500 patients treated by mitral valvotomy tricuspid valvotomy was also carried out 17 times. As with combined aortic valvotomy, it has not been possible to assess the individual benefit from each procedure. Two of these patients died at operation, but there is no reason to believe that either death was related to the tricuspid valvotomy. Too few have been followed long enough to assess long-term results.

Pulmonary Embolism and Infarction

Pulmonary infarction from embolism or from local thrombosis is a serious complication in all patients with rheumatic heart disease. In our experience there has rarely been any evidence of peripheral thrombophlebitis, and from this study and pathological studies it seems probable that local thrombosis in the pulmonary arterial tree occurs more often than is commonly supposed. Pulmonary arterial occlusion and pulmonary infarction contribute to pulmonary hypertension, respiratory embarrassment, and right heart failure, and constitute strong indications for considering valvotomy. After operation we have seen remarkable resolution of what can only be described as "chronic pulmonary infarction." In those with severe rheumatic heart disease these complications may be responsible for deterioration after initially successful valvotomy and, other things being favourable, constitute an indication for considering further surgical treatment.

Pulmonary Vascular Disease

Our studies have confirmed the general experience that the pulmonary vascular resistance (P.V.R.) is surprisingly variable in patients with similar degrees of severe mitral stenosis and that pulmonary hypertension, as directly measured or indirectly inferred from radiography or electrocardiography, is much more closely related to the P.V.R. than to the degree of obstruction at the mitral valve. It has been shown that, although always reduced by an adequate valvotomy and despite striking symptomatic relief, the P.V.R. after operation may remain much higher than normal, especially on exertion.

It might therefore reasonably be expected that the long-term prognosis would be largely dependent on the P.V.R., and over a long period of time this may prove to be the case. Nevertheless it is quite clear from our experience of patients with severe pulmonary hypertension that up to 10 years the results of valvotomy are not closely related to the P.V.R. as recorded directly or inferred.

In the group of 185 patients treated more than six years ago adequate catheterization data as regards pulmonary hypertension before operation were obtained in more than half the cases, and electrocardiographic signs of right ventricular hypertrophy and radiographic

evidence of enlargement of the main pulmonary artery were assessed in all.

We attempted to assess changes in the peripheral pulmonary arterial branches as recommended by Davies, Goodwin, Steiner, and Van Leuven (1953), but found in many cases this was too difficult to determine with sufficient certainty.

The three criteria we have used (pulmonary hypertension, E.C.G. signs of right ventricular hypertrophy, and enlargement of the pulmonary artery) as a reflection of the pulmonary vascular resistance are not of course exact, but, accepting the inevitable arbitrary grading, we have divided our patients into four grades of presumptive severity: nil, mild, moderate, and severe (Table XXIX).

TABLE XXIX.—*Pulmonary Vascular Resistance and Results at Six Years*

Raised Pulmonary Vascular Resistance*	No. of Cases	Long-term Results			
		Good		Fair	
		No.	%	No.	%
Nil	35	21	60	10	29
Mild	26	17	65	7	26
Moderate	81	55	68	20	25
Severe	43	33	70	5	12
				8	19

* See text.

Pulmonary hypertension was graded into four degrees depending on the mean pressure at rest and on exercise. Enlargement of the pulmonary artery was graded into four degrees as judged on a postero-anterior radiograph. Electrocardiographic criteria for the diagnosis of right ventricular hypertrophy in rheumatic heart disease and the difficulties of grading in degrees of severity have previously been fully discussed (Fraser and Turner, 1955a). It will be seen that there is no significant difference between the four groups.

Associated Pulmonary Disease

Bronchitis and sometimes chronic bronchitis and emphysema are not infrequently associated with mitral valvular disease, and the differentiation of the parts played by each as regards dyspnoea is not always easy to distinguish.

Bronchitis in the form of cough productive of mucoid sputum may be a manifestation of pulmonary oedema, and in any case by itself appears often to be improved by valvotomy. The real problem is that of emphysema. The diagnosis of emphysema by clinical means and radiography is often difficult or impossible and in the presence of rheumatic heart disease cannot be suspected from the history as might otherwise be the case. Pulmonary function tests are often useful and the results taken in conjunction with those of cardiac catheterization will usually indicate when symptoms are due to severe mitral stenosis.

[The conclusion of this article, together with a list of references, will appear in our next issue.]

The American Physiological Society has acquired ownership of the *Journal of Neurophysiology*, which was owned and operated from 1937 by the late Dr. J. F. Fulton and Charles C. Thomas, publisher, until the former's death in 1960. Dr. Fulton's one-half interest was left to Yale University, and the transfer has been effected by agreement between the society and the organizations concerned. (*J. Neurophysiol.*, January, 1962.)

TRIALS OF LIVE INFLUENZA VACCINE IN THE ROYAL AIR FORCE

A REPORT TO THE MEDICAL RESEARCH
COUNCIL COMMITTEE ON INFLUENZA AND
OTHER RESPIRATORY VIRUS VACCINES

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Formalinized influenza virus vaccine administered by subcutaneous injection is generally used in this country and the U.S.A. to immunize against influenza. Live influenza virus inoculated direct into the upper respiratory tract has been used extensively in the U.S.S.R. for this purpose (Smorodintsev, Drobyshevskaya, Ostrovskaya, and Shishkina, 1937; Smorodintsev, Tushinsky, Drobyshevskaya, Korovin, and Osetroff, 1937; Chalkina, 1938; and others). A number of trials of live vaccine were conducted by Burnet (1942, 1943), Mawson and Swan (1943), and Bull and Burnet (1943), but their vaccinated volunteers could still be infected experimentally, and they felt that the method was unsatisfactory.

Russian workers have used vaccine strains capable of multiplying in the nose and upper respiratory tract but causing few or no symptoms; they have selected virus strains obtained either by serial passage in the chick allantois or by passage through human embryonic lung tissue followed by culture in chick embryos. This vaccine in a strength of 10^6 50% egg-infective doses (EID_{50}) or more per ml. was introduced into the nose either by spraying or as drops, but they found that spraying gave better results.

Zhdanov and Solov'ev (1952) and Smorodintsev and Zhdanov (1957) stated what they believed to be the necessary conditions for the successful use of live attenuated influenza virus vaccine. These were: (1) that the vaccine should contain $10^6 EID_{50}$ or more per ml.; (2) that the virus could be recovered for two to four days from 50% or more of vaccinated subjects who were without antibody to the vaccine strain at the time of inoculation; (3) that there should be a fourfold or greater rise in haemagglutination-inhibiting (H.I.) antibodies in 50% or more of susceptible vaccinated subjects; and (4) that vaccine reinoculated two to three weeks later should fail to survive. It was stated that, up to 1960, vaccine meeting these requirements led to a reduction in morbidity rate to between a third and a half that in unvaccinated populations; furthermore, protection was obtained in the face of epidemic influenza (Smorodintsev, 1960).

In this country Isaacs and Roden (1956) and Isaacs, Negróni, and Tyrrell (1957) inoculated volunteers intranasally or by throat-swabbing with small doses ($10^3 EID_{50}$) of live influenza virus grown in eggs. In the first study, using A1 strains, they were unable to

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