the count was repeated a week later it was found to be normal and there was no recurrence. No other toxic effects in the blood-forming organs were noted.

The frequent alterations in the biochemical investigations were studied carefully, but statistically significant alterations were found only in the case of the serum alkaline phosphatase estimations at the third and sixth months of treatment. Camerini-Davalos *et al.* (1962) have reported that the serum alkaline phosphatase and other liver-function tests are abnormal in 10% of diabetic patients irrespective of therapy. In this series nearly half the group showed a rise in the alkaline phosphatase during some stage of the trial, while in 20% (all but one of whom were untreated) the level was raised before aceto-hexamide was started. We do not know what importance to attach to this observation, which has been described by other workers (Boshell *et al.*, 1962; Field and Tyroler, 1963). Our patients showed no clinical evidence of ill-health, and we did not discontinue the drug as a result of this finding. Certainly, the evidence of an abnormal alkaline phosphatase level suggests a possible deleterious effect of the drug on the liver, but we did not observe any other significant biochemical disturbance or clinical findings to support this conclusion. It is conceivable that aceto-hexamide might possess an extrahepatic activity, so that an effect on kidney or osteoblast metabolism remains a hypothetical possibility. It is clear that further investigation into the importance or otherwise of the alkaline phosphatase response during aceto-hexamide therapy is needed. It is because of this finding that we hesitate to give the drug our unqualified recommendation.

Summary

An investigation into the clinical use of aceto-hexamide in the treatment of 50 patients with diabetes mellitus has been carried out: 35 (70%) showed a good response, 6 (12%) a

fair response, 7 (14%) a poor response, while the response could not be adequately determined in 2.

Toxic effects of aceto-hexamide were not severe and treatment had to be discontinued in two (4%). A statistically significant rise in the level of the serum alkaline phosphatase was found at three and six months in treated patients. This finding could not be correlated with any clinical disturbance or other hepatotoxic effects and its cause is not understood. Nevertheless its occurrence underlines the necessity for more extensive clinical trials before aceto-hexamide can be recommended unreservedly for treating patients with diabetes mellitus.

We are grateful to Dr. F. Latham, of Messrs. Eli Lilly, for generous supplies of aceto-hexamide used throughout the trial; to Mr. J. B. Merrett, of the department of social and preventive medicine, Queen's University of Belfast, for advice about the statistical analyses; and to Dr. M. G. Nelson and Mr. D. W. Neill for the haematological and biochemical investigations which were carried out in their respective laboratories. We wish to thank the clinic dietitians and other members of the metabolic unit staff for their assistance and Miss L. Carroll for secretarial help.

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Restenosis of Mitral Valve: A Study of 100 Cases Treated by Operation

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Brit. med. J., 1964, **1**, 871-875

Papers about restenosis of the mitral valve have been principally concerned with the incidence and cause of the condition. The results of operative treatment have been mentioned only in passing.

As an increasing number of patients who were operated on before the introduction of transventricular valvotomy by Logan *et al.* (1962) are now presenting with a recurrence of their symptoms, it seemed worth while to find out what had happened to those who had undergone a second operation, and, if possible, what factors had an adverse influence on the results.

Material

We have studied 100 patients who have had second operations for mitral stenosis. The results have not been as good as those

obtained after primary valvotomy, and the various factors which may have accounted for this have been considered.

The first patient in the series had his second operation in 1956, and the last in September 1961. There were 15 men and 85 women, their average age at the time of the second operation being 41, with extremes of 25 and 61.

Operation

Sixty-six of the patients had their first operation done by one of us (J. R. B.); all of these came from a group of 376 patients whose valvotomy had been carried out by the finger-and-knife method, giving an incidence of restenosis of 17.6% so far. The remainder had their first operation done elsewhere. One patient had a third valvotomy. Her second operation was done with the transventricular dilator; this was an early case, and it is now known that the dilatation was quite inadequate. Apart from this case, no patient who has had a valvotomy by

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the transventricular method has yet required another operation. This includes 108 primary operations done by the same surgeon during the past six years as well as the second ones considered here.

In 92 patients the second operation was done by the transventricular method, in the remaining eight an adequate valvotomy was thought to have been achieved with the finger. In nearly all cases the approach was made via the atrial wall, as the appendage had been amputated at the first operation; this method presented few difficulties. One purse-string suture was used.

Finally, in one patient an unsuccessful attempt was made to relieve her organic tricuspid incompetence.

Method of Assessment

While recognizing the difficulty of precisely assessing the result of any operation for mitral stenosis, it was thought that objective assessment by cardiac catheterization, even if practicable, might not be completely reliable, and that although in general the physical signs correlated well with the exercise tolerance, there were divergences: on the one hand, in some patients the disability seemed less than the physical signs indicated; on the other, there were patients with almost no physical signs in whom the operation had apparently been a failure. For these reasons subjective assessment has been used throughout.

Patients were seen by one of us (J.R.B.) at some time during 1962 as near as possible to the anniversary of their operation. One patient went abroad and was lost track of. Two could not be traced during the year; the results given for these two are those of their last visit. One patient who died of carcinoma of the breast has been classified according to her exercise tolerance before she died, not as a late death.

Patients were put into one of four groups according to their exercise tolerance at the time of interview: "excellent," "good," "fair," and "poor" as in previous papers (Belcher, 1958, 1960). On this basis the results in the 100 cases were: excellent in 21, good in 27, fair in 21, and poor in 13; there were 12 late deaths and 5 operative deaths, and 1 was lost to follow-up.

Operative Deaths

An operative death was one which occurred while a patient was still in hospital; all of the five deaths happened within 14 days of the operation. The causes of death were calcium embolus (Adams, 1961), pulmonary embolus, the creation of severe mitral incompetence, bronchopneumonia, and cardiac arrest on the table respectively.

Late Deaths

There were 12 late deaths: two occurred in patients with severe aortic valve disease, two followed cerebral embolism, and the remainder were due to congestive cardiac failure. Six had had short-lived good results, but the others had for various reasons been little improved by their second operation. The average length of time between the second operation and death was two years.

Deterioration

So far deterioration of exercise tolerance has occurred in 18 patients who had excellent, good, or fair results initially. Six of these have died.

In many cases factors were present which might have been responsible for a bad result, but the proportion was no greater than that in the remainder of the series. However, one fact stood out: none had had their second operation less than three

years previously, and 15 had had it four or more years before (Table I). Moreover, the proportion of the patients who had their second operation three or more years ago and who now have a decreasing exercise tolerance is high (42%). Thus, although the second operation has often given relief, it may well be that this will prove temporary despite the transventricular valvotomy. The figures also suggest that the deterioration may develop more quickly than it did after the first operation.

TABLE I.—Proportion of Patients Operated on in Individual Years Who Show Deterioration

Year of Second Operation	No.	Deterioration	
		No.	%
1956	9	4	44
1957	13	3	23
1958	18	9	50
1959	12	4	33

Systemic Emboli

In seven cases cerebral emboli occurred immediately after the second operation; in one it was shown at necropsy that the emboli were pieces of calcium originating from a calcified valve (Adams, 1961); in the other six the signs of hemiplegia soon disappeared. The incidence of cerebral emboli (7%) was much higher than after the primary operations (2.5%), but the mortality was similar in the two groups.

There were six cases of late emboli in 100 patients with restenosis—four between the two operations and two, both of which were fatal, after the second operation. The incidence of late emboli in those who had not required a second operation was only 1%. All the patients had had the atrial appendage amputated at the first operation, and, although these numbers are small, they suggest that the presence of an appendage may be of less importance than stenosis of the valve in the causation of systemic emboli.

Factors Responsible for Unsatisfactory Results

As Ross (1959) has said, there are often several adverse factors in any given case when valvotomy has not brought a good result or when there has been deterioration after the primary operation. These factors may have been mitral incompetence and inadequate valvotomy, calcification of the valve, or pulmonary disease. These and others have been studied in the present group.

After the 100 second operations two factors which may lead to a poor result may have been almost eliminated. Only three patients had an inadequate valvotomy, as almost all had had a transventricular operation. Secondly, although it is often difficult to estimate the importance of bronchitis when it is associated with mitral valve disease, it was easier to estimate its importance after valvotomy had been done. The group of patients whose disability was chiefly due to pulmonary disease could be eliminated, and only 2 out of 100 were thought to have had bronchitis bad enough to contribute to their symptoms.

Two groups have been compared: those who still have good or excellent results, and those who have fair or poor results, or who have died since their second operation (excluding those who died at operation). Table II shows the comparative figures for some of the factors already referred to.

Age Factor.—The average age of the patients who had unsatisfactory results was six years higher than that of the successful group, and only 4 of the 16 who were over 50 at the time of their operation did well. Secondly, a much larger proportion of those who did badly were over 40 when they had their first operation: half the patients with unsatisfactory results were over this age, as against 19% of those who did well. Thus, although advancing age has often been said to have little effect

on the results of primary valvotomy, it does appear to militate against the success of a second operation.

Cardiothoracic Ratio.—Although the average size of the heart was greater in the failures, there was such a wide "scatter" in the two groups that no obvious trend was apparent. Of the seven patients whose ratios exceeded 70%, almost half fell into each group.

TABLE II

	Good and Excellent	Poor, Fair, and Late Deaths
Total	48 (8 M. 40 F.)	46 (7 M. 39 F.)
Average age at second operation ..	38 years (25–54)	44 years (28–61)
Average C.T.R.	55%	59%
Atrial fibrillation:		
At first operation	14 (29%)	24 (52%)
At second operation	29 (60%)	37 (80%)
Calcification	15 (32%)	20 (42%)
Severe mitral incompetence	2	7
Inadequate split	0	3

Atrial Fibrillation.—The development of atrial fibrillation is one of the landmarks in the progress of mitral stenosis. It was common in this group of patients: 40% had it at the first operation and 70% by the time the second one was done. Although it is unlikely that this alone had a major effect on the results, it was much commoner among the failures.

Calcification.—There was some degree of calcification of the valve in 35 of the patients, but it is probable that it was important only when it was extensive. There were 23 such cases, and 17 of them did badly; but it is difficult to say whether this was primarily due to the calcification and the consequent immobility of the valve, or whether it was due to the higher incidence of mitral incompetence and other complicating factors in this group. It was, however, more common in the group of patients who failed to do well for no good reason than it was among those in which success was achieved.

Influence of Time

Influence of Time.—Table III shows the years in which the second operations were done. Sixty-three were done more than two years ago, and 22 more than five years ago. Fig. 1 shows the length of time between the two operations; half of the second ones were done between four and six years after the first one—almost half of these in the first five years. This is unlike the experience of Lowther and Turner (1962), but similar to that of Fraser and Kerr (1962).

TABLE III

Year	1956	1957	1958	1959	1960	1961	1962
No. of second operations ..	9	13	18	12	11	21	16

FIG. 1.—Length of time between the first and the second operation.

The temporal factors which might have an influence on the results have been considered: the passage of time since the second operation and the interval between the two operations. Fig. 2 shows the adverse influence of the passage of time on the results of the second operation. The proportion of unsatisfactory results increased as the time after the second operation lengthened; this is chiefly due to the deterioration already

referred to. Secondly, the length of time between the first and second operation was related to the results, divided as before into two groups. Although the difference was not great, it seems that the results tended to improve as the length of time between the two operations increased (Fig. 3).

FIG. 2.—Influence of passage of time on result of second operation. Continuous line=good or excellent results. Broken line=fair or poor results or late deaths. Results are seen to deteriorate as period after second operation increases. Actual numbers given.

FIG. 3.—Influence of length of time between first and second operations on the results. Continuous line=good or excellent results. Broken line=fair or poor results or late deaths. Actual numbers given.

Mitral Incompetence

Mitral incompetence may be expected to have the same influence on the results of second operations as it does on primary ones (Belcher, 1956). It was very common in the patients under consideration here: no fewer than 63 had some degree of incompetence at the end of the second operation (Table IV).

TABLE IV.—Mitral Incompetence

	Grade I	Grade II	Grade III
Before operation ..	23	6	5
After	23	30	10

In no case was incompetence found where it had not been recorded at the end of the first operation, and in none had it disappeared. What is more, where it had been graded it had seldom changed between the two operations.

The classification of the incompetence was the same as that already published (Belcher, 1956). Only those in grade III were thought to have haemodynamically significant leakage. In 29% incompetence was either created or worsened by the transventricular dilator. This is a high incidence, but it has been lessened since the dilator has not been opened so widely. The incidence of traumatic mitral incompetence is commoner when this method is used, being 23% in the series described by Lowther and Turner (1962) as against 14% with the finger-and-knife method.

Calcification of the valve seemed to have some significance in that it was described in 46% of those in whom there was pre-operative incompetence and those in whom this was worsened, as against 30% of those in whom it was created and 24% in the remaining 37 patients in whom there was no incompetence at all.

The subjective results in the patients with the various grades of incompetence at the end of the operation are shown in Table V. These figures show that, as in the case of primary operations, in grades I and II the incompetence had little influence on the results, but only two patients with severe incompetence did well; a slightly higher proportion of those with no incompetence were much improved.

TABLE V.—Subjective Results of Mitral Incompetence

	Excellent	Good	Fair	Poor	Late Death	Operative Death
Grade III	1	1	2	4	1	1
" II	6	12	5	3	1	3
" I	3	4	6	4	6	0
None ..	11	10	8	2	4	1
Total	21	27	21	13	12	5

Other Factors

Various other factors that might have had an influence on the results were studied. In the first place, more patients who had good results had minor or moderate disability before both their first and second operations, and more of those with severe disabilities before both operations did not do well.

Secondly, more patients who did well after the first operation also did well after the second; on the other hand, those who had a poor result after their first operation tended to do badly after their second. The efficacy of the commissurotomy at the first operation had an influence on the incidence of restenosis but none on the result of the second operation. Almost all the patients had a transventricular valvotomy at the second operation, but the split was thought to have been complete in only 67 of those available for follow-up. In three the split was classed as "fair" and in the remainder as "fair to good." Table VI shows that even this small difference between the efficacy of the split influenced the results, there being a greater proportion of the patients who had complete valvotomies among those with good or excellent results. The importance of the extent of the commissurotomy already stressed in previous papers, although denied by Logan *et al.* (1962), seems to be shown here again.

TABLE VI.—Influence of Split on Result

Result	Good	Fair to Good	Fair
Excellent or good ..	40	7	1
Fair, poor, or late death ..	27	16	3

Lastly, it was thought that the tightness of the stenosis found at the second operation might have an influence on the result. This was not so, except that a slightly higher proportion of those who were found not to have a significant stenosis at the second operation did badly.

Causes of Failure

Among the 46 patients who did not do well there were fairly obvious causes in 24 (Table VII).

TABLE VII.—Causes of Failure

Important mitral incompetence ..	7
" aortic valve disease ..	5
" tricuspid valve disease ..	3
Inadequate valvotomy ..	3
Emboli ..	3
Bronchitis ..	2
Thyrototoxicosis ..	1

In the remaining 22 patients there was no obvious cause of failure. It may have been due to erroneous assessment or to a summation of adverse factors any one of which would not by itself have led to a bad result—the multifactorial degeneration of Lowther and Turner (1962).

Of the 22 patients, 5 were over 50, 9 had calcification of the valve (in 6 this was severe), 5 had C.T.R.s of more than 65%, 17 were in atrial fibrillation, 5 had mitral incompetence, 6 had imperfect splits, and 8 had had their second operation more than three years previously.

Thus although the differences between the group of failures and those with good results were not large, all the adverse factors except enlargement of the heart were commoner in the less satisfactory group and each may have played some part in the result (Table VIII).

TABLE VIII.—Comparison of Cases Which Failed for No Obvious Reason With Those Having a Good Result

Factor	Failed	Good
Over 50 ..	25%	16%
Operation more than three years ago ..	38%	25%
C.T.R. more than 65% ..	25%	29%
Fibrillation at second operation ..	80%	60%
Calcification of valve ..	45%	35%

Discussion

Analysis of the operations discussed here shows that the risk of the second operation is no greater than that of the first, but that the results in terms of improvement in exercise tolerance were not as good despite the fact that the valvotomy was almost complete in a high proportion of cases.

Ellis *et al.* (1959), following up 1,000 patients operated on more than five years previously, found that 66% had good or excellent results and that there had been 9.5% of late deaths. Despite the shorter follow-up, the comparable figures in our series were 48% and 12% respectively (Table IX).

TABLE IX

	Total	Good or Excellent	Fair or Poor	Late Deaths	Operative Mortality
Logan <i>et al.</i> (1962) ..	80	56	38	4	2.4
Ellis <i>et al.</i> (1962) ..	51	45	20	18	17
Jose <i>et al.</i> (1962) ..	43	51	19	7	23
Belcher and Gupta ..	100	48	34	12	5

The figures presented here are comparable with those in other series: these all showed that about half the patients did well after a second operation, although the length of the follow-up and the method of operation varied.

The transventricular operation was used in almost all the patients in this series and also in that of Logan *et al.* (1962) and of Fraser and Kerr (1962). Ellis *et al.* (1962), who also used the right-sided approach and the open method, agree that it is the method of choice, but they suggest that the open method should be used where other methods have failed, where there is mitral incompetence, or where there is gross calcification of the valve. Although it is true that the results in the second two groups are not perfect, there is as yet not enough evidence to suggest that they will be any better with the open method.

Bailey (1961) suggests that the open method should be used in all second operations, but the results which he quotes compare unfavourably with those in the present series.

The low mortality, the proportion of good results, and the simplicity of the transventricular operation suggest that at the moment it remains the method of choice in treatment of restenosis of the mitral valve. The value of obtaining a complete commissurotomy has been reaffirmed by the figures given here, and although the incidence of mitral incompetence was high it has been confirmed that it is seldom of much importance.

Analysis of the figures in this series has shown that the factors affecting the result of second operations are much the same as those affecting primary ones; they confirm the finding of Lowther and Turner (1962) that more patients needing second operations have a number of adverse factors. It has been

shown that the expectation of a good result is increased if the patient is young, is in sinus rhythm, has no calcification of the valve, and has had a perfect valvotomy; also if the result of the first operation has been good and if a long period separates the two valvotomies.

The follow-up has shown that with the passage of time there has been the same tendency to deterioration after the second operation as after the first. This has occurred despite the use of the transventricular dilator in almost all the cases, although it has not yet been seen in primary cases done by the same method. This observation supports the view that mitral stenosis is a progressive disease and that though surgery may slow the process it cannot halt it. This should not allow the possibility of a third valvotomy to be forgotten, and it may well be that many patients who have had good results from second valvotomies followed by deterioration will require yet another operation.

It may be concluded that while the results of second operations for mitral stenosis are not as good as those of the first the operative mortality is the same, and almost half the patients are much improved. The operation of choice at present seems to be blind transventricular valvotomy, and this should be recommended to all patients with restenosis of the mitral valve.

Summary

The results of 100 second operations for mitral stenosis are analysed: 48 were regarded as "excellent" or "good," 34 as

"fair" or "poor." There were 12 late deaths, and the operative mortality was 5.

The factors responsible for the unsatisfactory results have been studied. Advancing age, increasing heart size, atrial fibrillation, and calcification of the valve all proved to be slightly adverse factors.

Mitral incompetence was common but seldom had an adverse influence on the result.

Deterioration appeared to be more rapid after the second operation than after the first.

The results of second operations, although not as good as those of primary ones, more than justify them in the treatment of restenosis of the mitral valve.

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Thalassaemia, Glucose-6-Phosphate Dehydrogenase Deficiency, Sickling, and Malarial Endemicity in Greece: A Study of Five Areas*

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Brit. med. J., 1964, **1**, 875-879

For the last few years the concept that a balanced polymorphism maintains high frequencies of the genes for abnormal haemoglobins, thalassaemia, and glucose-6-phosphate dehydrogenase deficiency has been the stimulus for intensive studies, and many important contributions have clarified some aspects of this problem; these studies have been reviewed by Allison (1961), Motulsky and Campbell-Kraut (1961), and Neel (1962). The main effort of scientists has been concentrated on the exploration of the polymorphisms concerning the abnormal genes for sickling, for haemoglobin C, and for glucose-6-phosphate dehydrogenase deficiency (G-6-P.D.d.).

The indications that haemoglobin S and G-6-P.D.d. genes confer on their carriers considerable genetic resistance against *Plasmodium falciparum* malaria (Allison, 1954; Motulsky, 1960; Allison and Clyde, 1961) provided grounds for the hypothesis that malarial endemicity is the main factor maintaining a balanced polymorphism of these two genes. These positive findings have led to broad acceptance of the malarial theory for thalassaemia also. This last hypothesis, introduced by Haldane (1949) and favoured by the similar geographical distribution of malaria and thalassaemia in the Mediterranean basin,

has been tested practically only once (Carcassi *et al.*, 1957). That study was carried out in Sardinia; and its results agree well with the malarial hypothesis; however, the need for similar studies in other thalassaemic areas is evident.

The present investigation was undertaken to test the malarial hypothesis by studying thalassaemia, G-6-P.D.d., and Hb S frequencies in certain areas of Greece, which in the past were either non-malarious or moderately to severely malarious. Four out of the six areas discussed here were chosen because in each there had been several zones of different malarial endemicity in close proximity. In addition, thalassaemia-trait frequencies between older and younger age-groups were compared in a part of the sample.

Material and Methods

This study was carried out in 1961 and 1962. A total of 2,143 subjects were studied for thalassaemia trait; of these, 1,474 were also examined for G-6-P.D.d. and 1,021 for Hb S. Five areas were screened: Karditsa, Elasson, Corfu, Petromagoula, and Serifos (see Map). The characterization of the malarial endemicity in each area before 1945 was based on older data (Livadas and Sphangos, 1940) and on information obtained through the local public health centres. This information was checked and found accurate by Dr. G. Belios, Professor

* Supported by grants from the U.S. Public Health Service, National Institutes of Health, National Heart Institute (H-4541), and from the Royal Hellenic Research Foundation (1478).

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