treatment with 60 mg. daily, but occurred once only in each of the other groups and then after five weeks' treatment. The mooning was severe in only one patient and rapidly regressed when the dose of prednisone was reduced. Dyspepsia was an early side-effect and occurred in all the treatment groups: three patients stopped taking the tablets on this account.

Discussion

Our results suggest that in these mild cases of colitis treated as out-patients definite advantage is to be gained by using 60 or 40 mg. of prednisone daily rather than 20 mg. daily. There is some disadvantage in using 60 mg. daily in that side-effects may be more frequent than with the lower doses. The incidence of side-effects with 40 mg. daily was not greater than with 20 mg. daily, and in view of the therapeutic advantage 40 mg. could perhaps be regarded as the most useful of the three doses tested.

This trial was conducted openly and withdrawals from it on account of worsening symptoms could have been influenced by knowledge of the dose given: the results at two weeks are largely unaffected by this factor because only two patients had been withdrawn by this time. Differences in composition of the treatment groups could have affected the results, particularly as the groups were small. The composition differed in three ways (Table I), but analysis of the results at the end of treatment suggests that these differences were not important. Thus, of the four patients with a first attack of colitis in the 20-mg. group, one was well at the end of treatment, one was unchanged, and two were worse; of the patients who had had other treatment without success in the 20-mg. group, two were well, one was unchanged, and three were worse; all but one of the nine patients with extensive disease involving the transverse colon downwards were well at the end of treatment.

The findings reported here using prednisone 60 and 40 mg. daily are very similar to those reported in two previous trials of out-patient treatment at this clinic using similar doses (Lennard-Jones *et al.*, 1960). In this trial 4 out of 20 patients given prednisone 20-mg. daily were in remission at two weeks compared with 14 out of 40 patients reported in an out-patient trial using prednisolone in the same dose for the same time (Truelove, 1960); part of this difference may be due to slight differences in the definition of "remission." The results using 20 mg. daily for five weeks are similar to those reported by Watkinson (1961a, 1961b) using the same dose for one month. It is difficult to compare results in different published series, as factors such as the severity of the disease (Truelove and Witts, 1959) greatly affect the results.

It has been pointed out that most patients who improved during this trial began to do so within two weeks. If improvement had begun by this time, the disease might pass into remission as treatment was continued. These observations may be compared with those of MacDougall (1959), who showed in a series of 115 patients with colitis treated with corticosteroids in hospital for up to six weeks that about two-thirds of those who improved began to do so within eight days. Conversely, two-thirds of those who showed no signs of improvement by the eighth day remained resistant to treatment.

Summary

The results of treatment with three doses of oral prednisone have been studied in an open randomized trial during 60 courses of treatment for out-patients with ulcerative colitis.

Symptomatic improvement during the first two weeks of treatment occurred more often among patients given prednisone 60 or 40 mg. daily than among those given 20 mg. daily. The remission rate was apparently twice as great among patients given 60 or 40 mg. daily as among those given 20 mg. daily.

Side-effects from treatment were most frequent among patients given 60 mg. daily, and thus prednisone 40 mg. daily appears the most useful of the three doses tested.

We thank Nurse T. James for her help in the clinic and Mrs. I. M. Prentice for the diagram.

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RECURRENT MITRAL STENOSIS

AN ANALYSIS OF FINDINGS IN 32 CASES SUBMITTED TO REOPERATION

BY

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It is more than ten years since mitral valvotomy became the accepted treatment for the majority of patients suffering from mitral stenosis. While many difficulties have been overcome some await solution, and among these the problem of restenosis seems to us to be the most important.

This paper describes the findings at 32 repeat valvotomies for recurrent stenosis.

Material and Incidence.—One of us (K.F.) carried out 270 valvotomies during the period 1951 to end of 1961. Of 231 survivors (1 not traced) 32 (29 females, 3 males) have required reoperation. All of these patients had had their primary valvotomy more than five years previously.

Details of First Operation

In all the cases requiring reoperation the primary valvotomy was carried out by the transatrial route and the "split" achieved with the finger or a Brock's knife. Table I shows the number of cases of restenosis in patients who have survived to the present time. The valve sizes before and after the first operation are shown in Table II.

Calcification of the valve was described as absent in 17 cases, slight in 9, moderate in 2, and severe in 4.

If one accepts the finding, on histological examination, of poorly or well-formed Aschoff bodies in the

TABLE I.—Incidence of Restenosis

Year	No. of Operations	No. of Survivors	Restenosis
1951 and 1952	13	8	3 (37.5%)
1953	27	21	4 (19%)
1954	31	25	6 (24%)
1955	29	25	6 (24%)
1956	30	24	8 (33.3%)
1957	20	13	5 (38.4%)
	150	116	32 (27.5%)

TABLE II.—Primary Valvotomy. Valve Sizes Before and After Operation (32 Cases)

Valve Size (cm.):	0.5	1	1.5	2	2.5	3	3.5
Before operation	3	18	7	4	16	9	2
After				5			

atrial appendage as pathological evidence of rheumatic activity, 14 cases (43%) belonged to this category. In 17 cases the biopsy was negative and in one case the removal of tissue for examination was not feasible. In the entire series 58% were positive. Thus we found that the appendage biopsy was unhelpful in forecasting the likely development of restenosis. When the operation notes were examined critically we came to the conclusion that 27 of the 32 cases had not had an adequate valvotomy. Although in nine cases the final valve size was 3 cm., when other factors relating to valve configuration were taken into account we regarded only three as having had a satisfactory valvotomy. The most common cause of an incomplete valvotomy was the nature of the posterior commissure, which, when thickened and shelving, was difficult or impossible to "split" with the finger or a Brock's knife. The five cases which were regarded as having had an adequate operation had a full split of the anterior and a partial split of the posterior commissure—that is, none of the five had a separation of anterior and posterior commissures to the atrio-ventricular ring. Since 1957 Logan's method of transventricular valvotomy using a Tubb's dilator has been adopted and a complete separation of both commissures has practically always been achieved, and to date no such case has required reoperation.

Diagnosis of Recurrent Stenosis

All patients who have undergone mitral valvotomy should be followed up carefully for a number of years, as Lowther and Turner (1962) showed that a deterioration of 10% per annum occurs after five years. Failure to maintain improvement after operation may be due to factors such as myocardial degeneration, the onset of atrial fibrillation, irreversible changes in the pulmonary arterioles, bacterial endocarditis, disease of the aortic or tricuspid valves, mitral incompetence, or recurrent stenosis. Deterioration in exercise tolerance due to restenosis may occur several months after operation or may take some years. Logan *et al.* (1962) found that symptoms from restenosis rarely became evident in less than four years. This was not our experience, as deterioration became apparent in the first two years after operation in 18 cases and a further 11 cases deteriorated during the next two years. In the remaining three recurrence of symptoms did not take place for five, seven, and nine years respectively.

The physical signs of restenosis were no different from those of primary mitral stenosis—that is, a tapping apex beat, right ventricular thrust, and diastolic thrill on palpation, and an accentuated shortened first mitral sound, a loud second pulmonic sound, and a mitral

diastolic murmur on auscultation. An opening snap was sometimes present. In all the cases of this series the diagnosis was made on clinical grounds, and in only one instance was cardiac catheterization and left atrial puncture undertaken in order to confirm the diagnosis. Reoperation is indicated when restenosis of the mitral valve is suspected and the patient's symptoms are thought to be sufficiently disabling to justify the operative risk.

The Second Operation

Twenty-eight reoperations were performed by one of us (K.F.); the remainder were carried out in other centres, but full operative findings are available. At the second operation seven of the patients were aged 20–30, 10 were 31–40, 13 were 41–50, one was between 51 and 60, and one was over 60. The time interval between operations was 1–2 years in three, 2–4 in 12, 4–6 in 11, 6–8 in five, and 9 years in one.

The valve sizes found at the second operation were compared with those at the conclusion of the first and are shown in Table III.

TABLE III.—Comparison of Valve Size at First and Second Operation (32 Cases)

Valve Size (cm.):	0.5	1	1.5	2	2.5	3	3.5+
At end of primary operation							
At second operation	7	12	12	5	16	9	2

In all cases the valve orifice at the second operation was smaller than at the conclusion of the first; in 11 cases it was smaller at the second operation than it had been before splitting at the first.

A Tubb's dilator was employed, by the transventricular route, to achieve the split in the 28 reoperations carried out in this unit. In common with other workers we have found that when a good split of the commissures is achieved with the dilator the resultant valve orifice is a quite obvious crescent reaching to and limited by the atrio-ventricular ring. The sizes of the valve orifice achieved at reoperation were 3.5 cm. in 7, 4 cm. in 14, and 4.5 cm. in 7. These measurements were estimated on the postero-lateral edge of the crescent.

Discussion

Factors that have been held to be partly responsible for restenosis after operation are rigidity, with or without calcification of the valve, continuation or recrudescence of the rheumatic process, and individual variation in response of patients to splitting of the valve commissures. From our observations the valve cusps were regarded as mobile in 8 cases, fibrous and thickened in 21, and in 3 the operation notes did not indicate precisely the state of the valve. The role of calcification in the causation of restenosis is difficult to assess. Calcification *per se* was a major contributory factor in preventing a good split at the first operation, so it is not possible to assess its importance as an aetiological factor. In this series calcification of the valve was present in 15 of the 32 cases. Definite evidence of increase in calcification in the interval between operations was found in only one case.

The part played by rheumatism in restenosis is uncertain, as the rheumatic process may "smoulder" in the heart and not declare itself in the joints. Certainly

the appendage biopsy results failed to give any indication of prognosis. In two of our cases the comment had been made at the first operation that "it would not be surprising if the rheumatic process were still active," and in these two cases the appendage biopsies showed numerous Aschoff bodies suggesting continued rheumatic activity. Another patient had several attacks of subacute rheumatism in the interval between operations.

Logan *et al.* (1962) found that 36% of patients who had cusps completely separated anteriorly and posteriorly developed restenosis after an interval of more than five years.

This was not the experience of Belcher (1960, 1962), who found that only 4% of patients who had a complete split of both commissures had restenosed when followed up for eight years. Furthermore, he is convinced that an inadequate first operation is of prime importance in causation, and he has not known of restenosis in any case in which he has used the dilator.

Can these diverging views be reconciled? Before expressing an opinion several variable factors require to be considered, such as the critical assessment of operation notes, completeness of follow-up studies, criteria accepted for the diagnosis of restenosis, and the time interval between operations.

Our findings tend to support those of Belcher (1960, 1962). In 27 of the 32 cases the primary operation was undoubtedly inadequate. No case had a complete separation of both anterior and posterior commissures. We believe that after every valvotomy there is some re-fusion at the outer ends of the commissurotomy, and this is certain to occur. It would seem logical that a poor split followed by this inevitable restenosis would in most cases lead to a recurrence of symptoms. On the other hand, a similar amount of restenosis in a case having had a wide split would not decrease the size of the valve orifice by the same proportion. When we examined the decrease in valve size in the interval between operations we found that it amounted to 1 to 1.5 cm. in 23 (72%) cases, 2 cm. in 4 (12.5%), 2.5 cm. in 4 (12.5%), and 3 cm. in one case (3%). This possibility of inevitable reduction in valve size, say from 1 to 1.5 cm., would explain our finding that stenosis recurred most often in cases in which the primary valvotomy was inadequate. When restenosis occurred in patients believed to have had a reasonable split the process had been more extensive (2 to 3 cm.).

Is this theory of inevitable partial re-fusion compatible with the common experience that many patients who have had an inadequate valvotomy make good progress and have no recurrence of symptoms for many years? We believe that in some cases it is possible that a degree of restenosis may occur without giving rise to symptoms, for it must be borne in mind that in some patients the actual valve stenosis may be the main or only feature, while in others the effects of prolonged back pressure and myocardial damage are so extensive as to bear a much greater influence on the result of any valvotomy carried out. In other words, there are two groups of patients—the one in which the size of the valve orifice is the dominant feature, and the one in which other factors are of equal or of more importance. Wood (1954) stressed that in the latter group the size of the valve orifice in mitral stenosis bore no relation to the liability to develop symptoms such as pulmonary oedema and auricular fibrillation.

Summary

In a series of 270 valvotomies the case records of 32 patients requiring reoperation have been reviewed.

In more than half the cases deterioration occurred within the first two years after operation. In several cases this deterioration was not sufficient to warrant operation for a further two years.

In all cases the valve orifice at the second operation was smaller than at the conclusion of the first, and in 11 the valve size was smaller than before splitting at the first.

The primary commissurotomy was regarded as inadequate in 27 cases.

It is suggested that after mitral valvotomy all cases develop some degree of re-fusion, and in consequence recurrence of symptoms is most likely in those that had an inadequate valvotomy.

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CUSHING'S SYNDROME AND SKIN PIGMENTATION

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The role of the pituitary in Cushing's syndrome has been debated since the syndrome was first described (Cushing, 1932). Adenoma formation in the pituitary, found in 34 out of 58 cases collected by Knowlton (1953), is no proof of excess endocrine activity, as such tumours are not uncommon in the absence of adrenal dysfunction (Susman, 1935). A strong pituitary stimulus is suggested by the manner in which minute adrenal fragments may hypertrophy after adrenalectomy (Mason, 1957). Direct evidence of pituitary hyperfunction was provided by Clayton (1958) and Davies *et al.* (1960), who recorded high levels of plasma A.C.T.H. in Cushing's syndrome, although Paris *et al.* (1954) had previously reported negative results.

The relationship of Addisonian pigmentation to pituitary activity was demonstrated by Sulman (1956), who found raised concentrations of a melanophore-stimulating hormone (M.S.H.) in Addison's disease and also in some cases of Cushing's syndrome. The close similarity of M.S.H. and A.C.T.H. makes it impossible to determine the contribution of each hormone to the