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LONG-TERM PROGNOSIS OF RHEUMATIC MITRAL REGURGITATION: PRESENTATION OF YEARLY PROGNOSTIC REGRESSIONS IN RELATION TO AFFECTING FACTORS*

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Studies have shown that the short or long-term results of the incidence of residual heart disease in acute rheumatic fever depend on the severity of the carditis, on the number of recurrences[1-6], on the duration of the pretreatment interval[2-10], which is debatable, and on the use of larger and longer doses of anti-inflammatory agents[9-10]. Therefore, in order to establish a more accurate prognosis, it is necessary to classify each individual case in relation to the factors that influence the prognosis of rheumatic fever.

The striking differences in the course and prognosis of this disease before[11-13] and after the penicillin era[1,2,4,14] show the importance of the beneficial effect of penicillin in treatment and in prophylaxis of recurrences[14-17]. Many studies have also shown that the degree of heart involvement is of importance[3-6,12,16,18].

Mitral regurgitation (MR), which is the most frequent manifestation of rheumatic heart disease[1,4-6], was found in 92% of our 144 patients with carditis[19]. Since pericardial involvement does not leave sequelae, the clinician is interested in the prognosis of the valvular lesion, and especially of the mitral regurgitation[5].

A clinical, objective, quantitative classification is needed which shows the severity of regurgitation. The well-known and established studies have used the following three criteria as a classification system which has to be revised since it may lead to errors or ambiguities: 1) Presence of congestive heart failure and/or pericarditis[1]; 2) Intensity of the apical systolic murmur as an index of the degree of MR[16,17,20]; 3) Electrocardiographic or radiologic criteria for the estimation of cardiac enlargement[1,21].

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In our experience, we encountered the following drawbacks in these criteria: 1) Rheumatic pericarditis has an excellent prognosis, while congestive heart failure has a poor prognosis. Thus, consideration of both in the same prognostic criterion is ambiguous. 2) Intensity of the apical systolic murmur does not correlate well with the grade of severity of MR, hence it is a poor index; 3) At the onset of carditis there is often a mild, pericardial effusion, which may at the start be clinically latent, but can be recognized by serial follow-up of the increase in the electrocardiographic voltage and by the simultaneous decrease in the cardiothoracic ratio on the chest X-ray or by echocardiography. The effusion leads to a false negative evaluation of the electrocardiographic and a false positive estimation of the radiographic left ventricular enlargement, which are clinical indices of the grade of severity of MR.

Another factor which greatly influences the degree of heart size is the respiratory phase[22]. An X-ray taken on expiration can show a false positive grade III enlargement, straight left cardiac border, and congestion in the lung fields in a normal individual[22].

After considering all the disadvantages of the afore-mentioned criteria, we decided to use other criteria for estimating the degree of MR. From the follow-up data, regressions were developed to estimate the yearly rate of disappearance of MR according to a classification system based on promptness of treatment, continuous or irregular prophylaxis, presence or absence of congestive heart failure, and grade of severity of MR. The method of estimating the latter yields considerably less false positive or false negative results, and is objective, since it is based on quantitative measurements. The results of 117 children with MR who were followed-up at a median 10 years (1028 patient years) were evaluated and those pertaining to 86 patients with isolated mitral regurgitation are presented in this paper.

Material and Methods

The material consisted of 117 children with an initial attack of MR due to rheumatic fever who were hospitalized in the Pediatric Cardiology Department of Cerrahpaşa Medical Faculty, between 1964-1983, and whose laboratory studies were complete with respect to the methodologies presented. They were followed up for 2-21 years by the same experienced pediatric cardiologist (T.O.), who was familiar with the results of earlier reports and had prospectively planned the follow-up in the Outpatient Clinic of the Division.

The course and prognosis of the condition were evaluated with respect to: 1) pretreatment interval; 2) strict compliance with penicillin prophylaxis; 3) presence of congestive heart failure; 4) degree of severity of MR.

1) The pretreatment interval was the time that had elapsed between the onset of symptoms attributed to acute rheumatic fever and the initiation of the antiinflammatory therapy. If proper therapy was instituted more than three weeks after the onset of the initial symptoms, these patients were classified as "late" in contrast to the "early" group. Proper treatment consisted of 800,000 U of a daily dose of penicillin for ten days, and 2 mg/kg/day of prednisone and 0.1 g/kg/day of aspirin for three weeks which was followed by a gradual reduction of doses for another six weeks. In our clinic, however, all patients with active carditis receive corticosteroid treatment with a weekly monitoring of the sedimentation rate.

2) Penicillin prophylaxis was started on the 11th day with the administration of 1,200,000 U benzathine penicillin. Those who received the drug every three to four weeks without fail were classed as the regular prophylaxis group while those who missed doses for a few months or a longer period but had later continued the drug on a regular basis were classed as the irregular prophylaxis group.

3) Patients with carditis were considered to have congestive heart failure if dyspnea not due to a respiratory infection was present and if enlargement of the heart was not due to pericarditis. Thus, the most common false positive diagnosis of congestive heart failure were avoided.

4) The presence and grade of severity of mitral regurgitation (MR): A persistent pansystolic murmur, maximum at the apex of grade II-IV intensity, which was transmitted towards the axilla during the hospitalization period of three to six weeks was accepted as MR in the presence of other major or minor criteria of acute rheumatic fever[23].

The degree of severity of mitral regurgitation can be assessed from the cardiothoracic ratio, as well as from electrocardiographic voltage-dependent criteria of left ventricular enlargement[24]. Simultaneous use of both methods reduces fallacies of either system, but still has the following drawbacks which have been corrected accordingly:

The cardiothoracic ratio is very highly correlated with the respiratory phase[22]. A right diaphragmatic level of one intercostal space higher in the same individual leads to a mean increase of 7% in the cardiothoracic ratio. In comparison with the values in the same subject and also the classification of cardiac enlargement values, a correction was made according to Onat[22], which was designed to standardize all cardiothoracic ratio values to a right diaphragmatic arc's level of under the fifth anterior rib. This was referred to as the corrected cardiothoracic ratio.

In the acute phase of carditis about 13% of our cases manifested pericarditis clinically but in another 16% pericarditis was diagnosed by a significant increase in the voltage of various standard as well as unipolar chest leads with a

simultaneous decrease in the corrected cardiothoracic ratio within one or two weeks. In order to correct the false positive heart enlargement on the chest X-ray due to pericarditis, the values used were those which had been obtained after a serial clinical detection of pericarditis and not those which had been taken at the inital examination. In later years of the study, where echocardiography was used, the above-mentioned serial clinical detection and echocardiographic findings of pericarditis were in conformity.

With these above-mentioned points in mind, the grading of mitral regurgitation was considered IA if the diaphragm-dependent corrected cardiothroracic ratio on the postero-anterior chest teleradiography was $\leqslant$ 0.50, R-wave in V5 was less than 2.5 mV, R in V5 + S in V1 was less than 3.5 mV, and if no third heart sound could be heard at the apex. It was subgrouped as IB, if S3 was audible but the above-mentioned criteria for left ventricular enlargement were absent. A grade II was designated, if the cardiothoracic ratio was between 0.51-0.55 and either RV5 + SVI was 3.5 mV or RV5 was >2.5 mV, or if the corrected cardiothoracic ratio was near 0.50 but RV5 + SVI was over 4.5 mV. Grade III regurgitation was designated if the corrected cardiothoracic ratio was $\geqslant$ 0.56 and electrocardiographic signs of left ventricular enlargement accompanied it. A distribution of patients in the specified subgroups of this classification system according to age and sex is presented in Table I.

Sixty-eight patients from the initial 117 with MR were followed-up for 10 years or longer. MR was the only valvular involvement in 86 patients; aortic regurgitation accompanied the mitral regurgitation in the remaining 31 patients. In this study, prognosis was based on the traced 730 patient-years of the 86 initally isolated MR patients. The mean follow-up of these subjects was 8.49 years, while the median value was over ten years.

The patients were examined daily in the first three or four weeks, weekly in the second month and in the tenth week, which usually corresponded to a week after the completion of the corticosteroid treatment. The examinations continued at three monthly intervals in the first year, and at six monthly intervals later on, where all pertinent data were checked within a prospective plan.

The distribution of the missing data of the patients lost to study in a longitudinal study can lead to biased results if significantly different from the remaining subjects. Therefore, a Chi square test was used to assess the evaluations of these patients in different years in relation to the following factors: degree of severity of MR ($X^2 = 1.236$; $p > 0.30$), percentage of patients with congestive heart failure ($X^2 = 0.401$; $p > 0.50$), pretreatment interval ($X^2 = 0.108$; $p > 0.70$); percentage of those with regular penicillin prophylaxis ($X^2 = 0.037$; $p > 0.80$). The values of those lost to study were not statistically significantly different from the

TABLE I: Distribution of Patients in the Classification System According to Age and Sex

MR°	Prophylaxis	Onset of Therapy Early	Late	CHF *	Sex Male	Female	Age (Yrs) Mean ± SD
IA	P ±	2	5	0	1	6	9.65 ± 2.81
	P +	9	3	0	6	6	
IB	P ±	5	2	0	4	3	9.43 ± 2.67
	P +	10	4	0	6	8	
II	P ±	7	7	6	5	9	9.57 ± 2.64
	P +	13	9	2	10	12	
III	P ±	2	3	5	1	4	9.42 ± 3.19
	P +	2	3	4	3	2	
Total	P ±	16	17	11	11	22	9.54 ± 2.71
	P +	34	19	6	25	28	range 4-14
		50	36	17	36	50	

* MR° = grade of severity of mitral regurgitation

CHF = congestive heart failure

P ± = irregular penicillin prophylaxis

P + = regular penicillin prophylaxis

distribution of the total initial material. Thus, the yearly percentage of patients with disappearance of MR was accepted to represent unbiased data.

The yearly linear regressions of the disappearance rate of MR were calculated from the yearly percentage of patients without regurgitation/total MR present for that follow-up year. The two patients who died from carditis were considered persistent carditis in the following years. The results pertaining to multiple factors influencing the disappearance of regurgitation represent the basis for the study.

The MR was considered cured, if the apical systolic murmur had disappeared and was also undetectable after exercise on subsequent visits, and if there were no electrocardiographic or radiologic signs of left ventricular enlargement.

Results

The age at onset of MR was 9.54 years with a range from 4.4 to 14.0 years. This did not differ significantly in groups of severity of MR. Female preponderance in general (58.1%) as well as in relation to groups of grade of severity of regurgitation was not significant ($p > 0.20$) nor were sex differences in relation to regularity of penicillin prophylaxis ($X^2 = 1.802$; $p > 0.20$).

Obtaining treatment late was not significantly associated with regularity in prophylaxis. The incidence of patients with continuous penicillin prophylaxis was

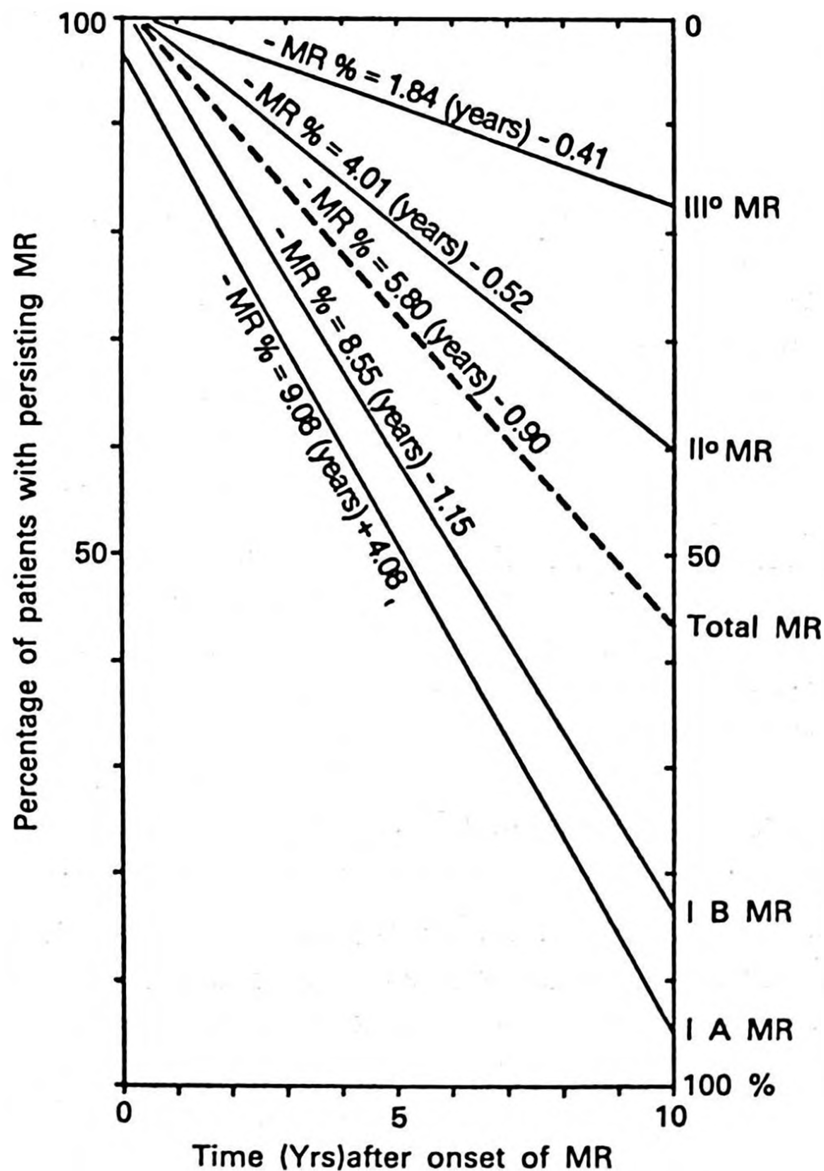

Fig. 1: Percentage of patients with persisting mitral regurgitation (MR) in relation to time (yrs) after onset of MR. The regression equations are presented in percentage of disappearance of MR (−MR%), and their slopes represent the yearly probability (%) of disappearance of MR, which increases with decreasing grade of severity of MR. Note that the patients without cardiac enlargement but with a third heart sound at onset (IB) have practically the same slope as IA, but are a year late to recover.

TABLE II: Linear Regressions of Percentage of Yearly Disappearance of Mitral Regurgitation (MR) in Relation to Its Grade of Severity and to Subgroups of Penicillin Prophylaxis and Time of Onset of Treatment

Grade of Severity of MR	n	Regressions of Yearly % Disappearance of MR
Grade I	40	9.06 (years) − 3.15
PP irregular	14	6.57 (years) − 9.55
PP regular	26	10.26 (years) + 0.54
PP regular + Early*	19	13.29 (years) + 1.58
Grade II	36	4.01 (years) − 0.52
PP irregular	14	1.46 (years) + 0.67
PP regular	22	5.60 (years) − 1.10
PP regular + Early	13	7.01 (years) − 3.89
PP regular + Late*	9	3.94 (years) + 2.10
Grade III	10	1.84 (years) − 0.41
Congestive HF*	17	3.12 (years) − 2.11
Congestive HF + Early	9	3.55 (years) − 6.56
MR (Total)	86	5.80 (years) − 0.90
MR + Early	50	7.11 (years) + 2.69
MR + Late	36	4.26 (years) − 5.85
MR + regular PP*	53	7.31 (years) + 0.36
MR + irregular PP	33	3.18 (years) − 3.18
MR + reg. PP + Early	34	8.92 (years) + 3.27
MR + irreg. PP + Late	17	3.54 (years) − 7.74
MR + irreg. PP + Early	16	2.78 (years) + 2.13
MR + reg. PP + Late	19	4.87 (years) − 4.18

*Early = pretreatment interval less than three weeks
Late = pretreatment interval more than three weeks
PP = penicillin prophylaxis, HF = heart failure

68% in those with a pretreatment interval of less than three weeks in contrast to 53% in those with a pretreatment interval of more than three weeks (X^2 = 1.458; $p > 0.20$). However, there was a significant tendency for those patients with congestive heart failure at onset to continue prophylaxis irregularly (X^2 = 4.903; $p < 0.05$).

The mean severity grade of MR was 1.59 in those with a short pretreatment interval as compared to 1.79 (grades I-III) in the group with a pretreatment interval

exceeding three weeks. Likewise, 65% of those without cardiomegaly and 52% of those with cardiomegaly (groups II-III) were in the early treated group. The difference was not statistically significant ($X^2 = 0.967$; $p > 0.30$). The incidence of regularity in prophylaxis was not significantly different in the three groups of severity of MR ($X^2 = 1.252$; $p < 0.20$).

Linear regressions estimating the percentage of the yearly disappearance of MR in relation to its grade of severity, subgroups of penicillin prophylaxis and time of onset of treatment are presented in Table II. Of the 86 patients with pure MR, the yearly probability of disappearance of regurgitation was 5.8% (Table II; Fig. 1). The expected median time of disappearance was 8.8 years. This general tendency to recover is modified very significantly in relation to grade of severity of MR. It decreased to 1.84% per year in grade III regurgitation, and to 4.01% per year in grade II regurgitation, but increased to 9.06% per year in grade I regurgitation (Table II). A 50% chance of recovery is expected within 5.8 years in group I (A+B), while it is only 18% and 40% in 10 years in groups III and II, respectively. The estimated chance of recovery in 10 years, according to the regression is 87% in group I. The real value was 85%.

The effect of strict compliance with penicillin prophylaxis and the pretreatment interval are seen by the differences in the slopes of the regressions in which the grade of severity of regurgitation is being held constant (Table II; Figs. 2, 3). In patients with grade I regurgitation, the yearly chance of recovery was 10.26% vs. 6.57% in those with regular and irregular prophylaxis, respectively (Table II; Fig. 2). The same tendency of differences are observed, but with smaller slopes in patients with grade II regurgitation (Table II; Fig. 3). The yearly probabilities for those with or without prophylaxis are 5.60% vs. 1.46%, respectively; the slope is three times steeper. The differences of 31% vs. 9% in five years, and 46% vs. 13% in ten years were not statistically significant at the 0.05 level because there were few patients in the subgroups. However, this was consistent in all years when grade of severity of regurgitation was held constant in the grade I and grade II groups. The higher rate of disappearance of MR in the regular vs. irregular penicillin prophylaxis in group I was significant in five years and on the borderline in ten years (Fig. 2). The median expected recovery time of MR was 4.9 years vs. 9.06 years in the patients receiving regular or irregular prophylaxis, respectively.

The probability of the disappearance of MR increased with a pretreatment interval of less than three weeks. If prophylaxis was continuous and therapy was started within three weeks, the yearly chance of recovery was 13.3% in grade I and 7% in grade II regurgitation (Table II; Figs 2, 3).

If grade of severity as well as regularity of prophylaxis are held constant, the differences between early and late onset of therapy are still conspicuous, that is,

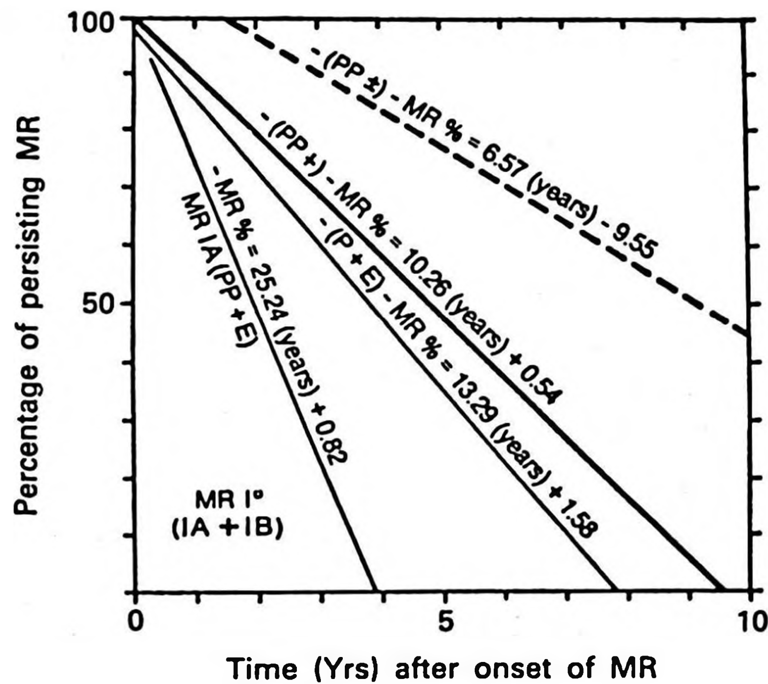

Fig. 2: The regression equations present the yearly probability (%) of disappearance of mitral regurgitation (–MR%) in grade I. The yearly rate of disappearance of MR was 6.57% in patients with irregular penicillin prophylaxis; it increased to 10.26% with regular penicillin prophylaxis to 13.29% if also treated early (E), and to 25.24% if no third sound was heard (IA). Note that all MR I patients with continuous prophylaxis recover, and that it occurs earlier in those patients with a shorter pretreatment interval (E) and in those without an audible third heart sound.

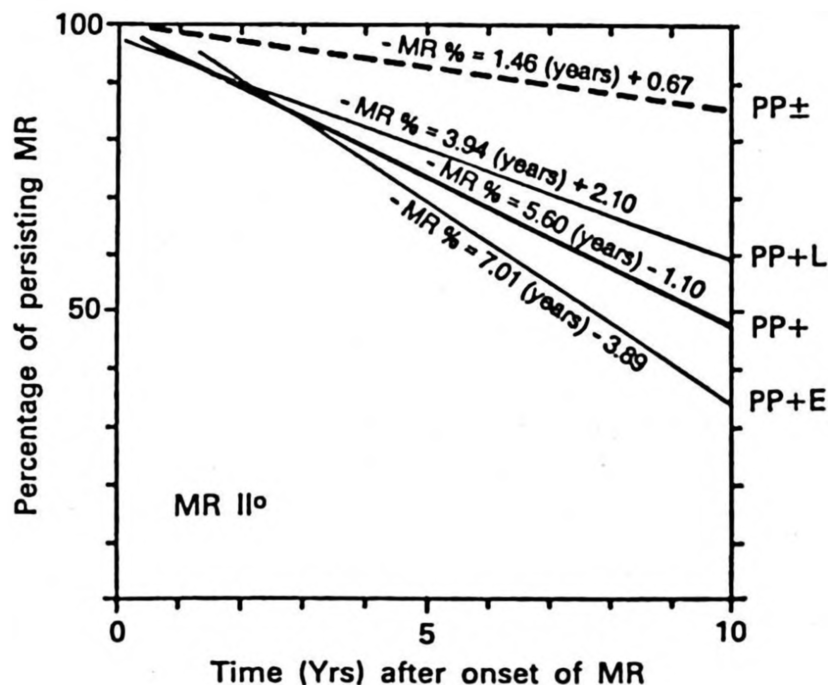

Fig. 3: Same coordinates and abbreviations as in Figs. 1-2, in MR grade II. Note that the rate of disappearance of MR is much lower if penicillin prophylaxis is irregular, and that in the same grade of severity and in continuous penicillin prophylaxis the slope is steeper in earlier onset of therapy (E) as compared to onset of therapy later than three weeks (L).

7% per year as compared to 3.9% per year in grade II. Thus, according to the regressions presented in Table II and Fig. 3, the estimated chance of recovery in group II regurgitation with continuous penicillin prophylaxis is 66% in ten years if the pretreatment interval is less than three weeks while the estimate is reduced to 41% for a longer interval. The actual values were 57% vs. 33%, respectively. The same tendency was observed in group I. The yearly rate increased to 25.2% in group IA, if the patients were treated earlier than three weeks and continued with prophylaxis (Fig. 2). In contrast, the chances were three times less (7.3%), even in group IA, if penicillin prophylaxis was continued irregularly. The same rules were valid for the total group I A+B (Table II).

Table II also presents regressions of yearly chances of recovery of MR in relation to duration of pretreatment interval and to regularity of prophylaxis, but disregards the grade of severity of regurgitation. The yearly chances of recovery from MR were 7.3% vs. 3.2% in patients with regular or irregular penicillin prophylaxis, respectively. The rate of disappearance of MR in five years was 41% vs. 8% with regular vs. irregular prophylaxis, respectively ($X^2 = 7.080$; $p < 0.01$). In ten years the same rate was 67% vs. 28%, respectively ($X^2 = 5.348$; $p < 0.025$).

Congestive heart failure was present in 17 patients (20%). This incidence was 14% in those with a short pretreatment interval in contrast to 28% in those with an interval of more than three weeks. The difference, however, was not significant ($X^2 = 1.712$; $p > 0.10$). Likewise, of the 17 patients with congestive heart failure, seven were treated before and ten after three weeks ($p > 0.30$). The yearly probability of recovery from MR was 3.1% in those with congestive heart failure, but in nine, in which therapy was instituted early, it was 5.55%, with a median recovery time of ten years (Table II).

The course of patients in which, at the last examination, MR had not yet disappeared, but who were followed up for less than ten years was as follows: All seven of group IA remained in group IA, 12 of group IB became group IA; of the 28 patients in group II, 16 regressed to grade I, 10 remained in grade II and two deteriorated to grade III; of the nine patients in group III, two regressed to grade I and two to grade II, while two remained in group III and two died. Thus, of the total 86, there were only four patients in whom the course deteriorated, resulting in the death of two.

Mitral stenosis was observed in four female patients and in one male patient (5.8%), who were in grade III with congestive heart failure and irregular prophylaxis. In the two patients with continuous prophylaxis, the mitral regurgitation had disappeared but mitral stenosis developed at age 20, 6-8 years after the discontinuation of prophylaxis. This led us to change our policy of discontinuing prophylaxis in the third decade even if the mitral regurgitation was seen to have completely disappeared.

The mortality rate in our study was 2.3% (2/86). The two patients who died, one aged 17 and the other aged 15, were both females and displayed all the unfavorable factors in common. They had manifestations of congestive heart failure at onset, were in group III, the pretreatment interval was long, and they did not continue prophylaxis.

Discussion

Our study demonstrates that persisting mitral regurgitation depends on its grade of severity, provided of course that penicillin prophylaxis is continued on a regular basis and on the duration of the pretreatment interval. These points are discussed below comparatively with the findings in published reports. Studied have shown that residual heart disease has increased with recurrences[2-6,11,13,17,25,26], and that it is the continuation of antistreptococcal prophylaxis that has reduced these recurrences, resulting in a higher rate of recovery and also a lower death rate. Tompkins et al[14], have reported that of 79 isolated or combined MR patients, no deaths occurred after the initial attack, provided that penicillin prophylaxis was continuous. This was also observed in our patients.

The recurrence rate/year in our study was 1.25% if penicillin prophylaxis was continuous, while it was 27.2% if it was irregular. Our incidence of recurrence, inspite of the regular use of penicillin was a little higher than the reports of Tompkins et al[14] and Sanyal et al[16], but much lower than other published studies[2,15,17,27].

The favorable results of continuous prophylaxis could substantially be shown in our study by keeping the grade of severity constant (Table II, Figs. 2, 3).

Besides the above-mentioned role of the regularity in penicillin prophylaxis, the incidence of the disappearance of MR was found to be a function of time, as well as grade of severity. Studies reporting the incidence of the disappearance of mitral regurgitation are few-they can be grouped as those presenting yearly results[14], those reporting final results, without specifying the time of disappearance[4,5,13,16], and those presenting results recorded after one, five or ten years[1-3]. Their systems of classification into subgroups, and total time of observation differ, and different criteria have been utilized to estimate the grade of severity of mitral regurgitation.

Tompkins et al[14], were the first, and only investigators, to present yearly incidences of persisting MR, but they did not give yearly results of subgroups, i.e., in grades of severity of regurgitation. They reported the results of their nine-year follow-up study of 79 patients with an initial attack of MR who were kept on continuous penicillin prophylaxis and observed that regurgitation had disappeared in 74% of the cases. This incidence was 36% (5/14) in those with, and 84%

(43/51) in those without cardiomegaly. The same incidence computed from our regressions for nine years of the comparable group with regular prophylaxis would be 93% for grade I, 49% for grade II and 16% for grade III. An average of our grade II and III, i.e., of those with cardiomegaly for nine years is 39%, versus 36% as reported by Tompkins et al[14]. Thus, the regressions presented herein are consistent with the final-results of Tompkins et al[14].

Bland and Jones[13], have reported their results of 87 patients with MR over a twenty-year period. The grade of severity of regurgitation was not mentioned and they represent only a small fraction (87/806) of the original 1000 patients who revealed rheumatic heart disease, 653 at onset and 806 throughout the 20 years. Nevertheless, they represent a time prior to antistreptococcal prophylaxis and show that the regurgitation murmur disappeared in 33%. This natural favorable incidence of disappearance was balanced by the development of mitral stenosis in 27%. The disappearance of MR in ten years in our group with irregular penicillin prophylaxis was 28% which is consistent with the value reported by Bland and Jones[13].

There was a 33% incidence of disappearance of MR in 45 patients in the five-year follow-up study of Sanyal et al[16]. This value decreased to 14% in patients with congestive heart failure. These figures are consistent with our findings and can be predicted from our corresponding subgroup regressions.

The Irvington-on-the-Hudson Study give quite different values in their two reports on the results of patients with MR, although their study population was the same 441 patients with acute rheumatic fever seen from 1950-57. They present an overall disappearance rate of 38% in 61 isolated MR patients for a mean follow-up time of 7.8 years[5], while the rate was 75% in their 59 patients in Table VI[4]. The disappearance of MR in both reports depended on the size of the heart, and on whether there had been previous attacks or not, which are consistent with our findings.

According to the results of a joint report from the United Kingdom and the United States[3], the incidence of disappearance of MR in the same 97 patients studied with no previous heart disease and without "failure and/or pericarditis" was 48%, 67% and 72%, respectively, in one, five and ten years. The differences in the rates of disappearance in ten years in their subgroups of MR were not significant (81%, 73% and 67%, respectively, with increasing severity). This might be due to the method of estimation of the severity of MR which was based on a system graded in relation to the intensity of the apical systolic murmur[1], which is not a good index of severity of MR. It showed great overlapping in our material with the grades of severity of regurgitation presented herein, although differences between both ends were significant at the 0.05 level. Our results in five and ten years correspond to the values given above[3], but the rate of disappearance of

MR in the first year was never that high in any of our groups. Their recovery rate of 11% within ten years, if previous heart disease and congestive heart failure were present, is consistent with our findings in the group with failure in which the onset of therapy started late.

Results of earlier studies regarding the relationship between the pretreatment interval of the initial attack and the incidence of residual heart disease in rheumatic carditis, but disregarding its severity, have shown a higher incidence of disappearance of heart disease in the group with onset of therapy earlier than two weeks. In certain studies the difference was not significant[4,8]. Other workers [3,6,7,9,10,28] have shown a significantly higher incidence of residual heart disease in their groups with a pretreatment interval of more than two weeks. Our compilation of the incidence of residual heart disease in the above-mentioned 856 carditis cases, regardless of their severity and very varied follow-up time (three months to ten years) has, however, revealed a very high X^2 value equal to 37.38, which is in favor of early onset of treatment. The discrepancies in the incidence of residual heart disease were probably due to the differences in the follow-up time, severity of carditis and their criteria for defining the grade of severity.

It is debatable as to whether the above-mentioned beneficial effect on residual heart disease is due to prompt treatment or to a selective association of milder cases in the early treated groups. It is anticipated, but not proven, that with prolongation of the pretreatment interval in carditis, damage to the heart would become more severe. Therefore, we studied this in our material and found no significant relationship between the pretreatment interval and the grade of severity of MR at onset, if three weeks are taken as the criterion ($p > 0.30$). The incidence of congestive heart failure in our series was present in 14% of those with a shorter pretreatment interval in contrast to 27.8% of those with a longer interval. This difference, however, was not significant at the 0.05 level ($X^2 = 1.712$, $p > 0.10$). Thus, it is debatable, whether the pretreatment interval determines the severity of carditis, although there is a tendency towards milder carditis if the pretreatment interval is short.

For a direct solution to the problem, one has to compare the results in the same grade of severity and in the same observation time. Our results in this respect revealed that when severity of MR, which was more strictly defined, was held constant, the disappearance rate/time function was higher in the early treated group (Figs. 2, 3). The same tendency persisted in all the groups, despite the fact that severity of regurgitation was not significantly less in the earlier treated patients. Thus, we can conclude that the beneficial effect of early treatment must be responsible, per se, for lowering the incidence of residual heart disease, provided that penicillin prophylaxis is continued, and the carditis is not very severe, because the tendency of severe carditis disappearing is low (Table II, Fig. I).

It is, however, mainly those patients with a mild to moderate form of carditis, who with early onset of therapy have more favorable short-term results as compared to late onset of therapy. A comparison of only long-term results in mild carditis may obscure the difference in the two pretreatment interval groups, because as it was demonstrated in our patients without cardiac enlargement (grade IA+B), the MR will disappear earlier, if the pretreatment interval is less than three weeks.

Summary

Acute rheumatic isolated mitral regurgitation was followed up in 86 children for 730 patient-years. The grade of severity of regurgitation was classified according to degree of left ventricular enlargement, which was based on an original method of correction of cardiothoracic ratio on the chest x-ray, taking into consideration the diaphragmatic level, and electrocardiographic criteria for age. A combination of both quantitative estimations, after the regression of a detectable pericardial effusion reduced false-positive radiologic and false-negative electrocardiographic results. Linear regressions of percentage of yearly disappearance of MR were presented in relation to the grades of severity; the mean yearly rate of disappearance of 5.8% increased to 9.08% in mild, and decreased to 1.84% in severe regurgitation. The effect of other beneficial factors such as the shortness of the pretreatment interval and regularity of prophylaxis could be demonstrated by keeping the grade of severity of regurgitation constant. Thus, chances for recovery in reported years after onset, up to ten years, can readily be calculated from the presented regressions with regard to the appropriate subgroups.

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