The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life

I. Prognosis with Special Reference to Survivorship

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The object of this study is to provide information on the natural course of rheumatic heart disease in the third, fourth, and fifth decades of life. It is concerned with 757 out of 1,042 children under observation during the years 1916 to 1956 who reached the age of 20 or more years. The major manifestations of rheumatic fever experienced by these patients from the onset of the disease is related to the degree of residual cardiac damage. Survival to successive ages was analyzed with respect to sex, type of valvular lesion, and degree of cardiac enlargement.

Basic data on the natural course of a chronic disease are essential for evaluation of the effect of therapeutic procedures. In 1947 we presented the mortality experience of a group of 1,042 children who had been under medical supervision during the years 1916 to 1947. Another 10 years have elapsed, providing information on the natural course of rheumatic heart disease in the third, fourth, and fifth decades of life. This report is concerned with 757 of those patients who have reached the age of 20 years or more. Prognosis will be considered in terms of the major manifestations of rheumatic fever experienced during the course of the disease and the degree of residual cardiac damage. Survivorship will be analyzed to successive ages, specific for sex, type of valvular lesion, and degree of cardiac enlargement.

In order to assess survivorship or mortality risks for any of these groups, due account must be taken of the duration of follow-up for the different individuals entering the study. This has been done by the actuarial methods used by life insurance companies, which are applicable to studies on prognosis. The data thus give a partial description of the natural history of the disease, and have relevance to the selection of patients for cardiac surgery or other therapeutic procedures.

In interpreting the data it must be remembered that our patients represent a group that sought medical care in childhood and have been followed without further selection into adult life. They are not therefore comparable to a group of adults in whom cardiovascular disease is discovered on examination or to those seeking medical care for cardiopulmonary symptoms.

Sufficient data have accumulated in the past 8 years to indicate that immediate surgical mortality has decreased with experience, both in surgical technics and in selection of patients, and the majority of published studies indicate an improvement in functional cardiac status but beyond this we have no real assessment of results. The difficulty in judging the surgical experience as reported in the literature is that survivorship is usually given in terms of the direct calculation of the proportion of patients in any series who survived, without any account being taken of the variable length of follow-up. This index cannot be interpreted even in a descriptive sense.

It is hoped that the present study will give further perspective on the disease and furnish some guides in the selection of patients for surgical intervention as well as for evaluating its effect on longevity.

Material

From an original total of 1,042 children with rheumatic heart disease who came under observa-
tion since 1916, the records of 757 patients who reached the age of 20 or more years were reviewed.\textsuperscript{1} Of these, 73, or 10 per cent, were lost at various points in the follow-up; 90 per cent were observed until death or the end of the study on January 1, 1956.

The character of the sample and type of medical supervision have been described in our 1947 study, and characterize the entire 40-year period of study from 1916 to 1956. A diagnosis of rheumatic fever was only made on the following major manifestations: carditis, polyarthritis, chorea, or subcutaneous nodules. It needs to be emphasized that all of the patients demonstrated cardiac involvement. Patients with symptoms suggestive of rheumatic fever, without carditis, are not included in this study. Subacute carditis was characterized by poor heart sounds, tachycardia or gallop, increasing cardiac chamber enlargement demonstrable on fluoroscopic examination with or without new and changing murmurs, and electrocardiographic evidence of myocardial involvement. Acute carditis was characterized by the above findings and pericardial rub, diminishing cardiac reserve, dyspnea, and symptoms and signs of congestive failure.

The sex distribution and the age at last observation or death are presented in table 1. It will be noted that there are about 100 more females than males. About three fifths of the total of 757 patients have been followed beyond 30 years of age, about one third beyond 35 years, and one seventh beyond 40 years of age.

The number of deaths according to causes and age groups are summarized in table 2. During the period of observation, 78 patients died who had reached the age of 20 or more years. Of these, 53, or 68 per cent, of the deaths were attributed to rheumatic heart disease; 8 or 10 per cent, to bacterial endocarditis; and 17, or 22 per cent, to other diseases or accidents. Verification of the cause of death was obtained by postmortem examination in 25 patients, or 33 per cent.

Criteria for diagnosis followed the nomenclature and criteria of the New York Heart Association.\textsuperscript{9} The cardiac diagnosis at the last observation is presented in table 3. The diagnosis of mitral insufficiency, mitral stenosis, and aortic insufficiency was made on the basis of characteristic constant murmurs and cardiac chamber enlargement that persisted at least 6 months to 1 year after termination of active carditis. Murmurs were considered to have regressed if they became inconstant or uncharacteristic for a period of 1 year or more. The diagnosis was not changed when murmurs regressed and enlargement of cardiac chambers and characteristic heart sounds remained. Patients with auscultatory murmurs of valvular lesions were separated into those whose murmur was "constant" or "regressed," i.e., MP or MP, etc. during the period of observation.

\begin{table}
\centering
\caption{Distribution of Patients Who Were Followed to Age 20 or Beyond, by Sex and Age at Last Observation}
\begin{tabular}{cccc}
\hline
Age (years) & Female & Male & Total patients \\
\hline
20-25 & 66 & 42 & 108 & 14 \\
25-30 & 104 & 83 & 187 & 25 \\
30-35 & 104 & 113 & 217 & 29 \\
35-40 & 80 & 55 & 135 & 18 \\
40-45 & 51 & 25 & 76 & 10 \\
45-52 & 25 & 9 & 34 & 4 \\
\hline
Total & 430 & 327 & 757 & 100 \\
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Age Distribution of Patients at Last Observation and of Deaths, by Cause}
\begin{tabular}{cccc}
\hline
Age at last observation (years) & Number of patients & Total deaths & Number of deaths \\
\hline
20-25 & 108 & 28 & 16 & 4 & 3 & 5 \\
25-30 & 187 & 17 & 10 & 3 & 2 & 2 \\
30-35 & 217 & 16 & 13 & 0 & 1 & 2 \\
35-40 & 135 & 13 & 10 & 1 & 1 & 1 \\
40-45 & 76 & 1 & 1 & 0 & 0 & 0 \\
45-52 & 34 & 3 & 3 & 0 & 0 & 0 \\
\hline
Total & 757 & 78 & 53 & 8 & 7 & 10 \\
\end{tabular}
\end{table}

Cardiac chamber enlargement was determined by serial fluoroscopic examination in the posteroanterior and right anterior oblique positions with contrast medium, and in the left anterior oblique position at standard degrees of rotation on a turntable.\textsuperscript{10-12} Patients were classified as having "moderately" enlarged hearts (1 + or 2 +) who usually showed no abnormality of cardiac silhouette or increased cardiothoracic ratios in the posteroanterior view. In the left anterior oblique position the normal angle of clearance of the left ventricle of 45 or 50 degrees was increased to 55 or 60 degrees, and in the right anterior oblique position there was 1 + displacement of the esophagus by an enlarged left atrium. Patients were considered to have "markedly" enlarged hearts (3 + or 4 +) whose abnormal cardiac silhouette was usually discernible in the posteroanterior view, frequently showing an increase in cardiothoracic ratio. In the left anterior oblique position the angle of clearance of the left ventricle was increased to 65 to 90 degrees, and in the right anterior oblique position retrodisplacement of the barium-filled esophagus by the
left atrium was 2+ to 4+. Abnormalities of the cardiac silhouette in all positions were duly noted.

Vital capacity measurements were recorded at each clinic visit. Serial electrocardiographic tracings, including precordial leads, were obtained on all patients during the latter years of the observation period.

**Methodology**

Analysis of long-term follow-up observations is best expressed in terms of a life table or its equivalent. The requisites for deriving a life table include a specified starting point and the distribution according to time from the starting point of the number of individuals alive and under study, the number lost from observation, and the number of individuals who died. In this study, patients had as their starting point 20 years of age. In analyzing survivorship, the information furnished by each individual in the study must be included for the entire period of observation. The assumption in handling the “lost” patients is that subsequent to their last observation they are dying off at the same rate as those remaining under follow-up. It is important to note that the 73 patients who were lost from observation at various points in our follow-up were slightly more favorable in their diagnostic classification than those remaining under follow-up. It seems unlikely, therefore, that any appreciable number were lost because they died or that the assumption as to subsequent mortality is seriously in error.

As in our previous analysis, we have presented both the average annual death rate for 5-year age groups and the probability of dying between the birthdays that mark the beginning and close of each 5-year period for all cases. The latter description permits the calculation of a survivorship table from the age of 20 years to the latest age to which the patients have been followed. We have presented this survivorship only to the age of 45 years, since, up to the present time, only a small number have attained later ages and the sampling errors therefore became substantial.

The survivorship figures were obtained through a conventional life table method, computed for each year of life. A comprehensive description and discussion of such methods has been presented by Merrell. 13

**Clinical Course and Degree of Residual Cardiac Damage**

During the 40-year period of observation for the total of 757 patients, acute carditis with or without subacute carditis occurred in one or more attacks in one third of the group, while one or more attacks of subacute carditis occurred in two thirds. Of the associated major manifestations polyarthritis occurred in one or more attacks in one third of the patients, chorea in another third, and polyarthritis and chorea in about one sixth. Carditis was associated with only minor manifestations in about one fifth of the patients. Only 3 per cent experienced an attack of rheumatic fever after the age of 20 years.

A comparison of the relative incidence of the major manifestations of rheumatic fever experienced by 757 patients during the course of the disease, according to cardiac diagnosis at last observation, is presented graphically in figure 1. It will be noted that for 392 patients...
with mitral insufficiency, acute carditis occurred in one or more attacks with or without subacute carditis in 14 per cent, and subacute carditis in 86 per cent. Only 1 patient experienced a recurrent attack of carditis during adult life. Subcutaneous nodules were observed in 3 per cent. Polyarthritis or chorea, or both, occurred one or more times in about three fourths of the patients; in one fifth, only minor manifestations were associated with the carditis.

There were 269 patients with physical signs of mitral stenosis and insufficiency. The clinical course was characterized in slightly less than one half of the patients by one or more attacks of acute carditis in addition to the frequent occurrence of subacute carditis. In slightly more than one half, the attacks of carditis were subacute. Subcutaneous nodules were observed in 9 per cent of these patients. Polyarthritis occurred in one or more attacks in about one third, and chorea in slightly less than one third. Polyarthritis and chorea occurred in about one fifth of the patients. In only 18 per cent was carditis associated with only minor manifestations. It is of some interest that the incidence of chorea in this group was not significantly different from that observed in the group with mitral insufficiency. After the age of 20 years, recurrent active carditis was observed clinically or pathologically in 7 patients.

Of the 96 patients who had combined aortic and mitral lesions, one or more attacks of acute carditis with or without subacute carditis was experienced by about three fourths; in only one fourth was the course characterized by one or more attacks of subacute carditis. Subcutaneous nodules occurred in 30 per cent. One or more attacks of polyarthritis occurred in about

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**Fig. 1.** Comparison of the relative incidence of the major manifestations of rheumatic fever experienced by 757 patients during the course of the disease, according to cardiac diagnosis at last observation.
one third, and chorea in about one sixth; polyarthritis and chorea occurred in slightly less than one half. In about one tenth the associated manifestations were minor. Active carditis was demonstrated clinically or pathologically after the twentieth year in 13 patients.

In figure 2 there is presented a graphic description of the complete cardiac diagnosis at the last observation. The precordial systolic murmur remained constant and characteristic in about one third of the 392 patients with mitral insufficiency (MI1); in two thirds it regressed over the years (MI3). Before the age of 20, the murmur was constant and characteristic in about 50 per cent of the patients for 2 to 5 years, and in the remainder for 6 to 20 years. Of the murmurs that regressed, regression occurred after the age of 20 in 21 per cent, persisting in two thirds for 2 to 5 years and in one third for 6 to 20 years. Whether the murmur remained constant or regressed, cardiac chamber enlargement did not change. All but 1 patient had "moderate" cardiac chamber enlargement. It should be emphasized that increase in cardiac chamber enlargement with advancing age, or the appearance of new murmurs, was rarely noted. At last observation all of these patients were considered to be class I according to the New York Heart Association classification. One hundred sixteen patients had experienced 1 to 5 pregnancies, and 113 men served in the Armed Forces. Of 12 deaths, 11 were due to noncardiac causes, and 1 to bacterial endocarditis.

Of the 269 patients with mitral stenosis, the diagnosis had been established in 79 per cent within 1 to 2 years of an observed attack of active carditis. The ages at which the diagnosis was recorded in one fifth of the patients ranged from 5 to 10 years, in less than one half between 10 to 15 years, and in about one fourth, from 15 to 20 years of age. The murmur of mitral stenosis was constant and characteristic in over one third (MS¹), remaining constant for a period of 5 to 30 years or more. In less than two thirds of the patients the murmur regressed (MS²) after being constant and characteristic for a period of 2 to 5 years in one third, and 6 to 20 years or more in two thirds. The murmur of mitral insufficiency was con-
stant in about two thirds of these patients, and regressed in about one third. The regression of murmurs probably accounts for the reported incidence of isolated aortic insufficiency, and presumably for "pure mitral stenosis." In the majority of these patients there was cardiac chamber enlargement of "moderate" degree and in only one fifth was there "marked" enlargement. In the absence of recurrent carditis, cardiac chamber enlargement did not increase or change with age, whether auscultatory murmurs were constant or inconstant. Atrial fibrillation of 1 to 20 years' duration was present in 5 per cent. At last observation, in only 11 per cent was the functional classification II to IV. One hundred twelve patients had experienced 1 to 5 pregnancies, and 31 men served in the Armed Forces. Systemic emboli occurred in 4 patients. Of 29 deaths, 18 were due to cardiac causes, and 5 to bacterial endocarditis. Four of these patients died from 1 to 5 years following mitral valvulotomy.

Of the 96 patients with aortic lesions, the murmur of aortic insufficiency was constant in the majority, and in 14 (15 per cent) of the patients there was regression within 1 to 15 years. Twenty three patients also had aortic stenosis; in 2 there was tricuspid insufficiency. The murmur of mitral insufficiency was constant in 95 per cent; the murmur of mitral stenosis, in three fourths. Cardiac chamber enlargement was "marked" in three fourths of the patients. Atrial fibrillation was present in 24 per cent for a duration of 3 to 27 years. At last observation one half of this group was considered class II to IV. Fourteen patients experienced 1 to 3 pregnancies, and 6 men served in the Armed Forces. Five patients experienced systemic emboli. There were 37 deaths, 35 of which were attributed to cardiac causes. Active carditis occurred in 9, bacterial endocarditis in 2.

Comment

In this representative group of rheumatic children who reached the age of 20 years, about one half had a minimal degree of cardiac damage. In practically all of the patients the anatomic diagnosis was established by the age of 20 years. Furthermore, less than 3 per cent experienced a recurrent attack of carditis after the age of 20.

The frequency of the observed regression of systolic and diastolic murmurs during the clinical course needs emphasis. That absence of murmurs does not exclude persistence of valvular pathology has been demonstrated at postmortem and more recently during surgical exploration. The degree of residual cardiac damage and the constancy of murmurs paralleled the incidence of acute carditis. It is noteworthy that there was no significant difference in the incidence of attacks of polyarthritis or chorea in patients with mitral insufficiency or mitral stenosis. New murmurs or increasing cardiac chamber enlargement was rarely observed in the absence of rheumatic activity. Cardiac chamber enlargement did not appear to increase with time.

In 9 of the 53 patients whose death was attributed to cardiac causes, active carditis was demonstrated clinically or pathologically. The majority of the 8 deaths due to bacterial endocarditis occurred before the era of antibiotic therapy. Six patients who developed bacterial endocarditis during the past 6 years and were treated, are alive and asymptomatic. A more critical analysis of the morbidity of the majority of these patients, as well as consideration of factors contributing to the terminal event, will be presented in a subsequent report.16

Prognosis in Terms of Survivorship

Survivorship Subsequent to the Age of 20 (all cases)

The average annual mortality rate and probability of survival for 757 patients with rheumatic heart disease is presented in 5-year age groups in table 4, together with figures derived from the general United States population for the years 1939 to 1941,14 which were corrected for sex ratio in our series. The over-all average annual mortality rate, based on a total of 9,347.5 person-years, is 8.3 per 1,000 (column 7). This may be compared with an average annual death rate of 3.1 per 1,000 in the United States general population as calculated for the same age distribution. The average annual
TABLE 4.—Risk of Death at Five-Year Intervals, All Cases

<table>
<thead>
<tr>
<th>Age X to X + N</th>
<th>No. under observation at X years of age</th>
<th>No. living whose latest observation was X to X + N</th>
<th>Deaths between X and X + N</th>
<th>Person-years of observation between X and X + N</th>
<th>Average annual death rate per 1000</th>
<th>Probability of death from X to X + 5 XqX</th>
<th>Probability of surviving from X to X + 5 XpX</th>
<th>Percentage surviving from age 20 to X</th>
<th>Percentage of U.S. population surviving from age 20 to X (1939-1941)</th>
<th>Age X</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25</td>
<td>757</td>
<td>54</td>
<td>28</td>
<td>3519.0</td>
<td>7.9</td>
<td>0.039</td>
<td>0.961</td>
<td>100</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>25-30</td>
<td>649</td>
<td>137</td>
<td>17</td>
<td>2801.5</td>
<td>6.0</td>
<td>0.030</td>
<td>0.970</td>
<td>96</td>
<td>99</td>
<td>25</td>
</tr>
<tr>
<td>30-35</td>
<td>462</td>
<td>192</td>
<td>9</td>
<td>1738.5</td>
<td>9.2</td>
<td>0.044</td>
<td>0.956</td>
<td>93</td>
<td>98</td>
<td>30</td>
</tr>
<tr>
<td>35-40</td>
<td>245</td>
<td>119</td>
<td>3</td>
<td>859.5</td>
<td>15.2</td>
<td>0.071</td>
<td>0.929</td>
<td>89</td>
<td>97</td>
<td>35</td>
</tr>
<tr>
<td>40-52</td>
<td>110</td>
<td>104</td>
<td>2</td>
<td>431.0</td>
<td>9.3</td>
<td>0.013</td>
<td>0.987</td>
<td>83</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>606</td>
<td>73</td>
<td>78</td>
<td>9347.5</td>
<td>8.3</td>
<td></td>
<td></td>
<td>82</td>
<td>93</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Survivorship in cardiac series compared to that of the United States general population from 1939-1941. The horizontal scale gives the age, and the vertical scale the percentage estimated to survive to each age. A. All cases (757). B. 392 patients with mitral insufficiency. C. 269 patients with mitral stenosis and insufficiency. D. 96 patients with combined aortic and mitral lesions.

dearth rate appears to increase slightly with age as would be expected.

Survival to specific ages for patients reaching the age of 20 years (column 10) shows that 96 per cent survived to the age of 25, 93 per cent to the age of 30, 89 per cent to 35, and 82 per cent to the age of 45 years. Figure 3A shows graphically the percentage surviving to specific ages for the total group and for each sex. The horizontal scale gives the age, and the vertical
scale the percentage estimated to survive to each age. For comparison there is presented the survivorship for the general population of the United States from 1939 to 1941. There is no evidence of a sex difference in survivorship. Both the cardiac series and the general population show a gradual downward trend with advancing age but at about 33 years of age there is a sharper decline in survivorship in the cardiac series. Of those surviving to the age of 20, 82 per cent of the cardiac group survive to age 45, compared to 93 per cent for the general population.

Survivorship in Relation to Anatomic Diagnosis

To compare prognosis in terms of the type of valvular lesion and degree of cardiac chamber enlargement, life tables were constructed for each group (table 5). The over-all average annual mortality rate, over the ages 20 to 52, for 392 patients with mitral insufficiency was found to be 2.76 per 1,000 based on a total of 4,349 person-years. It is important to recall that the majority of deaths in this group were due to noncardiac causes. The death rate is not significantly different from that of the United States death rates previously quoted. Figure 3B shows that the survival curve for these patients is significantly better than that which obtained for patients with mitral stenosis and insufficiency (fig. 3C), and for combined aortic and mitral lesions (fig. 3D). In the group with mitral insufficiency the survival was 97 per cent at the age of 30, 96 per cent at 35, and 95 per cent at 40 years, which is essentially the same as that of the general population of the United States.14

For 269 patients with mitral stenosis and insufficiency the over-all average annual mortality rate is found to be 7.8 per 1,000, based on a total of 3,725.5 person-years, and is nearly 3 times greater than for mitral insufficiency alone. Comparison of the survivorship at specific ages revealed that 93 per cent survived to the age of 30 years, 90 per cent to 35, and 86 per cent to the age of 40 years. The survival curve for these patients shows a decline after about the age of 33, which is greater than for patients with mitral insufficiency alone but

significantly less than for patients with combined aortic and mitral lesions (fig. 3B–D).

For the 96 patients with combined aortic and mitral lesions the over-all average annual mortality rate is 29 per 1,000, based on a total of 1,273 person-years. Figure 3D indicates that the survival curve drops precipitously after 30 years of age; 78 per cent of these patients survived to age 30, 65 per cent to 35, and 49 per cent to the age of 40 years.

A comparison of mortality according to heart size (table 5) reveals an over-all average annual mortality rate of 3.5 per 1,000 for a total of 7,736 person-years for 632 patients having moderate enlargement of the heart, compared to 31.6 per 1,000 for a total of 1,612 person-years in 125 patients with marked enlargement. Survival rates are significantly lower for patients with marked cardiac enlargement than for those with moderate enlargement, as shown in figure 4A. In the group with moderate enlargement of the heart, 97 per cent survived to the age of 30 compared to 78 per cent for patients with marked enlargement, and 93 per cent still survived at 40 years compared to 48 per cent for those with marked enlargement.

Further comparison of mortality in patients with mitral stenosis according to degree of cardiac enlargement (table 5) shows an over-all

<table>
<thead>
<tr>
<th>Valvular lesion and cardiac size</th>
<th>Total cases</th>
<th>Total deaths</th>
<th>Total per-son-years of obser-vation</th>
<th>Average over-all death rate/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral insufficiency with moderate EH</td>
<td>392*</td>
<td>12</td>
<td>4349.0</td>
<td>2.76</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>269</td>
<td>29</td>
<td>3725.5</td>
<td>7.78</td>
</tr>
<tr>
<td>with marked EH</td>
<td>48</td>
<td>16</td>
<td>555.5</td>
<td>28.80</td>
</tr>
<tr>
<td>Aortic insufficiency with moderate EH</td>
<td>20</td>
<td>2</td>
<td>263.0</td>
<td>7.60</td>
</tr>
<tr>
<td>with marked EH</td>
<td>76</td>
<td>35</td>
<td>1010.0</td>
<td>34.60</td>
</tr>
<tr>
<td>Cardiac Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate EH (1–2+)</td>
<td>632</td>
<td>27</td>
<td>7735.5</td>
<td>3.49</td>
</tr>
<tr>
<td>marked EH (3–4+)</td>
<td>125</td>
<td>51</td>
<td>1612.0</td>
<td>31.60</td>
</tr>
</tbody>
</table>

EH = enlargement of heart.

* includes one case of marked EH.
average annual mortality rate of 4.1 per 1,000 for moderate enlargement compared to 28.8 per 1,000 for patients with marked cardiac enlargement.

For patients with combined aortic lesions and moderate enlargement of the heart, the over-all average annual mortality rate was 7.6 per 1,000 compared to 34.6 for patients with marked enlargement.

Although the total person-years of observation for some of the subgroups is rather small, the consistency of the comparisons and the trend in survival curves appear to indicate that degree of cardiac enlargement is an important factor in influencing survivorship (fig. 4B, C, D). It is of interest that insurance mortality investigations of physical impairment also concluded that the degree of cardiac enlargement affected survivorship adversely.\textsuperscript{15}

Comment

Interpretation of the data presented on mortality and survivorship for patients with rheumatic heart disease must take into account the representativeness of the sample subject to analysis.

Unlike the previous study on longevity in rheumatic fever\textsuperscript{1} where children were included at onset of the disease at various ages, this analysis concerns only those children who reached the age of 20 years. All the patients were kept under continuous medical supervision as part of a long-term study of the natural history of rheumatic heart disease. As stated earlier, they are not comparable to a series of
patients seeking medical attention because of cardiopulmonary symptoms, and any estimate of mortality risk based on such a symptomatic group would greatly exaggerate the true mortality for persons having a history of rheumatic fever.

When the results of this study are compared with those of the previous one, it is seen that the over-all average mortality rate in the third, fourth, and fifth decades is 8.3 per 1,000 per year, about half that obtained during the first 2 decades of life (16.0 per 1,000 per year).

It is significant that for the 391 patients with mitral insufficiency and moderate cardiac enlargement the survival curve, after 20 years of age, followed closely that of the general population.

The importance of degree of cardiac chamber enlargement is indicated by the low survival rates among patients with marked cardiac enlargement. The morbidity experienced by a majority of these patients will be considered in a subsequent study.  

DISCUSSION

Prognosis for patients with rheumatic heart disease who reached the age of 20 years is obviously dependent on the degree of residual cardiac damage sustained during the earlier years. It is significant that in about 50 per cent of the patients, residual cardiac damage was characterized by mitral insufficiency and moderate cardiac enlargement. In two thirds of these patients the auscultatory murmurs regressed and cardiac chamber enlargement would not have been recognized on physical examination or by the usual radiographic examination limited to the posteroanterior view. These patients are probably representative of those individuals who have had rheumatic fever and are considered to be without clinical evidence of heart disease. It is important to note that when patients in this study were noted to have regression of characteristic murmurs with persistent cardiac chamber enlargement, the valvular diagnosis was not changed. It is probable that patients who are considered to have "pure" mitral stenosis or isolated aortic insufficiency may have had regression of the characteristic murmurs of mitral lesions.

The significance of the relation of the extent of residual cardiac damage to the severity of carditis is illustrated by the relative increased incidence of acute carditis among patients with mitral stenosis and combined aortic lesions and markedly enlarged hearts. It is perhaps of some significance that among these patients, so-called "delayed" appearance of mitral stenosis was rarely observed in the absence of clinical evidence of rheumatic carditis. The diagnosis of mitral stenosis was recorded in the majority of patients within 1 to 2 years of an observed attack of carditis.

In practically all of the patients the anatomic diagnosis was established by the age of 20 years. It is apparent therefore that it is during childhood that cardiac damage must be prevented. Our recent observations, demonstrating that early adequate short-term hormone therapy in active carditis will result in diminished residual cardiac damage, offer justification for the prediction that the survival rate for patients so treated, reaching the age of 20, will approximate that which is observed for the 50 per cent of patients with minimal cardiac damage.

At the present time it is not possible, from published data, to assess the effect of surgical intervention on longevity. However, if it were found that survival rates were favorably affected, particularly among patients with marked cardiac enlargement and combined valvular lesions, earlier surgical intervention may be indicated as suggested by many surgeons. Whether an even more favorable survivorship would result for patients with valvular lesions and moderate cardiac enlargement following surgical intervention must await controlled studies.

It must again be emphasized that the survival rates for patients with rheumatic heart disease as presented refers to a series of patients with rheumatic heart disease who were kept under supervision from childhood. Of significance is the fact that for those who had mitral insufficiency with moderate cardiac enlargement, comprising about one half of the
total group, the survival rate followed closely that of the general population. In a series of adult patients who seek medical attention because of cardiopulmonary symptoms, survivorship would not be expected to be as favorable.

**Summary**

The observed natural history of rheumatic heart disease is presented for the 757 out of 1,042 rheumatic children who reached the age of 20 years and have been followed subsequently to various ages up to 52 years. During the 40-year period of observation, of the 757 patients who reached 20 years of age, about three fifths have been followed beyond 30 years of age, one third beyond 35 years, and one seventh beyond 40.

During the clinical course, acute carditis with or without subacute carditis occurred in one or more attacks in one third, and subacute carditis in two thirds. Of the associated major manifestations polyarthritis occurred in one or more attacks in one third, chorea in another third, and polyarthritis and chorea in about one sixth of the patients. Carditis was associated with only minor manifestations in about one fifth.

The degree of residual cardiac damage and the constancy of murmurs was found to be closely related to the relative incidence of acute carditis during childhood. Increasing cardiac involvement in the absence of recurrent carditis was not noted with the passage of time. Recurrent carditis occurred in less than 3 per cent of the patients after the age of 20 years.

The anatomic diagnosis was established by the age of 20 years in practically all of the patients. In four fifths, cardiac chamber enlargement was "moderate" and in one fifth it was "marked." In more than one half of the patients there was mitral insufficiency, in one third mitral stenosis and insufficiency, and in one eighth there were combined aortic and mitral lesions. The diagnosis of mitral stenosis was established in 79 per cent within 1 to 2 years of an observed attack.

Of the 78 deaths, 68 per cent were due to cardiac causes, 10 per cent to bacterial endo-carditis, and 22 per cent to noncardiac causes. The over-all average mortality rate was 8.3 per 1,000 per year for patients 20 to 52 years of age compared to 16 per 1,000 per year for those under 20. The comparable United States mortality rate for 1940, for the ages 20 to 52 years (adjusted to the cardiac age distribution) was 3.1 per 1,000 per year. The average annual mortality rate for 392 patients with mitral insufficiency was 2.8 per 1,000; for 269 patients with mitral stenosis and insufficiency, 7.8 per 1,000; and for 96 patients with combined mitral and aortic lesions, 29 per 1,000.

The survival curve for the entire group of patients who reached the age of 20 showed that an estimated 82 per cent of them would reach the age of 45 as compared with 95 per cent in the general population. There was no evidence of a sex difference in survivorship. The survival curve for patients with mitral insufficiency followed closely that of the general population, while for patients with mitral stenosis and insufficiency there was a decline after about 33 years of age, which is greater than for mitral insufficiency alone but less than for combined aortic and mitral lesions. Only about one half of this latter group who reached the age of 20 survived to the age of 40.

The over-all average mortality rate for moderate enlargement was 3.5 per 1,000 compared to 31 per 1,000 for marked enlargement. The survival curves according to degree of heart enlargement are markedly different. Of the persons who survived to the age of 20, 93 per cent survived to the age of 40 when the heart enlargement was "moderate" while only 40 per cent survived to 40 when the heart enlargement at age 20 was "marked." When valvular lesions and heart enlargement are considered simultaneously, heart size appears to be the more important factor in relation to survivorship.

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**SUMMARIO IN INTERLINGUA**

Es presentate le observate historia natural de rheumatic morbo cardiace in 757 ex 1,042 juveniles rheumatic, qui attingeva le etate de 20 annos e eseva observeate subsequente usque a variato etate infra le maximus de 52 annos. In le curso del periodo de 40 annos de observation, circa tres quintos del 757 patientes passante le etate de 20 annos eseva observeate usque a ultra le etate de 30 annos, un tertio usque a ultra le etate de 35 annos, e un septimo usque a ultra le etate de 40 annos.

Durante le curso clinic del morbo, carditis acute con o sin carditis subacute occurreva in un o plura attaccos in un tertio del patientes; carditis subacute in duo tertios. Quanto al associate manifestaciones major, polyarthritis occurreva in un o plura attaccos in un tertio del patientes; chorea in un altere tertio; e polyarthritis e chorea insimul in circa un sexto. Carditis eseva associate solmente con manifestaciones minor, con un incidentia de circa un quinto.

Esseva trovate que le grado de residue lesions cardiaque e le constantia de murmures eseva nettemente relationate al incidentia relative de carditis acute durante le etate juvenil del patientes. Un augmento del affections cardiac in le absentia de recurrente carditis eseva noteate con le passage de tempore. Recurrente carditis occurreva in minus que 3 pro cento del patientes post le etate de 20 annos.

Le diagnosie anatomic eseva establite ante le etate de 20 annos in practicamente omne casos. In quatro quintos, le allargamento del cameras cardiac eseva “moderate,” e in un quinto illo eseva “marcate.” Insufficientia mitral eseva presente in plus que un medietate del patientes; stenosis mitral con insufficientia in un tertio; e combineate lesions aortica e mitral in un octavo. Le diagnose de stenosis mitral eseva establite in 79 pro cento del casos intra 1 a 2 annos post le observation de un attacco.

Inter le 78 mortes, 68 pro cento resultava de causas cardiac, 10 pro cento de endocarditis bacterial, e 22 pro cento de causas noncardiac. Le magnitude medie del mortalitate general eseva 8,3 pro mille per anno pro patientes de inter 20 e 52 annos de etate e 16 pro mille per anno pro patientes infra 20 annos de etate. Le comparabile mortalitate in le Statos Unite pro le anno 1940 (corrigeate secundo le distribution de etate in le gruppo cardiac) eseva 3,1 pro mille per anno pro individuos de inter 20 e 52 annos de etate. Le magnitude medie del mortalitate annual inter le 392 patientes con insufficientia mitral eseva 2,8 pro mille; inter le 269 patientes con stenosis e insufficientia mitral 7,8 pro mille; e inter le 96 patientes con combineate lesions mitral e aortic 29 pro mille.

Le curva de supervivientia pro le gruppo total de patientes passante le etate de 20 annos monstrava que un estimate proportion de 82 pro cento de illes attingerea le etate de 45 annos, in comparation con 95 pro cento in le population general. Le supervivientia manifestava nulle evidentia differentias secundo le sexo del patientes. Le curva de supervivientia pro patientes con insufficientia mitral sequence strictemente le correspondente curva pro le population general, durante que le curvas pro le altere sub-gruppos monstrava que in patientes con stenosis e insufficientia mitral il occurre post le etate de circa 33 annos un declino que es plus marcate que in le caso de patientes con insufficientia mitral sol sed minus marcate que pro patientes con combineate lesions aortica e mitral. In iste ultime gruppo, non plus que circa un medietate del individuos passante le etate de 20 annos superviveva usque al etate de 40 annos.

Le magnitude medie del mortalitate general in casos de moderate allargamento cardiac eseva 3,5 pro mille. In casos de marcate allargamento illo eseva 31 pro mille. Le curvas de supervivientia secundo le grado del allargamento cardiac eseva multo differente. Inter le individuos qui passava le etate de 20 annos, 93 pro cento superviveva usque al etate de 40 annos si lor allargamento cardiac eseva “moderate.” Solmente 40 pro cento de illes superviveva usque a ille etate si lor allargamento cardiac al etate de 20 annos eseva “marcate.” Quando on considera le lesions valvular juxta le allargamento cardiac, il pare
que le dimensiones cardiac representa un factor plus importante al le puncto de vista del superviventia.

REFERENCES

The Foxglove when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death.—William Withering. An Account of the Foxglove, and Some of Its Medical Uses. Birmingham, 1785.
The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life: I. Prognosis with Special Reference to Survivorship

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