Differences in Antibody Response to Streptococcal Antigens in Children with Rheumatic and Non-rheumatic Mitral Valve Disease

By Stanford T. Shulman, M.D., Elia M. Ayoub, M.D., Benjamin E. Victorica, M.D., Ira H. Gessner, M.D., Dolores F. Tamer, M.D., and Francisco A. Hernandez, M.D.

SUMMARY

The usefulness of streptococcal antibody tests — anti-streptolysin O (ASO), anti-desoxyribonuclease B (anti-DNase B), and anti-group A carbohydrate (A-antibody) — in differentiating rheumatic from non-rheumatic mitral disease was explored. Sera from 154 children with mitral disease were studied. Fifteen of 17 patients with chronic mitral insufficiency (MI) following acute rheumatic fever manifested persistence of elevated A-antibody levels following the decline of ASO and anti-DNase B titers to normal 18–36 months after their acute illness. This antibody pattern was not observed among sera from 35 patients with congenital mitral valve deformities. Serologic study of 71 children with mitral disease of obscure etiology identified three groups: subgroup A includes those 12 who demonstrated the antibody pattern associated with rheumatic MI, while subgroup B is comprised of 39 children with normal A-antibody levels. Twenty patients (subgroup C) manifested evidence of recent streptococcal infection. These data suggest that the use of the A-antibody test in conjunction with other streptococcal antibody tests is of potential value in differentiating rheumatic from non-rheumatic mitral disease.

Additional Indexing Words:
Rheumatic heart disease        Streptococcal group A carbohydrate

The fact that mitral valve disease frequently may be of non-rheumatic etiology has been emphasized in recent studies. At present no reliable means exists for the clinical differentiation of the etiology of mitral valve disease in a patient without historical data to suggest an attack of acute rheumatic fever (ARF). The correct identification of those patients with mitral disease of rheumatic origin is important because of the efficacy of anti-streptococcal antibiotic prophylaxis in the prevention of recurrent rheumatic attacks. The importance of secondary prophylaxis in patients with rheumatic carditis has been emphasized recently by the high frequency of recovery from cardiac disease of patients who adhere to this regimen.

Elevated antibody titers to various streptococcal products, such as the anti-streptolysin O (ASO) and the anti-desoxyribonuclease B (anti-DNase B), are usually found in patients with ARF. Similarly, elevated levels of antibody to the group specific carbohydrate (A-antibody) have been reported in the majority of patients with ARF. A significant observation related to the latter antibody was the finding that while the ASO and anti-DNase B levels decline to normal within 18 months following the acute disease, the A-antibody remains elevated for several years in patients with residual rheumatic valvular disease. In contrast, persistence of the A-antibody does not occur in patients with post-streptococcal glomerulonephritis or in rheumatic patients without chronic valvular disease. Based on these findings, the present study was undertaken to determine the usefulness of these antibody tests in the differentiation of rheumatic from non-rheumatic mitral valvular disease in patients lacking a history of an acute rheumatic attack.

Material and Methods

Patients

The patients included in this study are summarized in Table 1. Three groups of patients were investigated: children with mitral insufficiency (MI) during or following a well-
documented attack of ARF (group 1); patients with congenital MI, in most cases associated with an endocardial cushion defect and cleft mitral valve (group 2); and children presenting with evidence of mitral valve disease (most commonly asymptomatic MI) in the absence of history of ARF and lacking features suggestive of an endocardial cushion defect (group 3).

Each of the 47 patients in group 1 presented with an acute illness clearly fulfilling the modified Jones criteria for the diagnosis of ARF. All patients in group 1, including those studied during the acute stage of ARF (group 1a), as well as those investigated 18–36 months after ARF (group 1b), manifested MI at the time of study. Several patients also had murmurs of aortic valvular insufficiency (AI). Group 1b consisted of 13 patients included in group 1a plus four other patients who had been followed prospectively after their acute episode of ARF. Initial sera were not available from these latter four patients, although each had an elevated ASO level. All 17 patients in group 1b were selected because their ASO and anti-DNAse B titers had declined to within 0.1 log above the upper limit of normal during the follow-up period of 18–36 months after their acute attack. The remaining patients of group 1a were excluded from category 1b because their acute attacks occurred less than 18 months ago (15 patients), because follow-up sera were not available (13 patients), or because the ASO and/or anti-DNAse B titers were still 0.2 log or greater above the upper limits of normal 18–36 months after ARF (6 patients).

The patients in group 2 include 26 children with congenital MI associated with an endocardial cushion defect and cleft mitral valve. The diagnosis in these patients was based upon clinical, electrocardiographic, and cineangiographic findings and was confirmed in the 20 of 26 patients in this category who had undergone cardiac surgery. Twenty-five had residual MI at the time of study. An additional group of nine patients (group 2b) was considered to have congenital mitral valve disease on the basis of diagnosis within the first six months of life and/or the presence of mitral disease in association with complex congenital cardiac defects (table 2).

Group 3 consists of 71 children without historical evidence of ARF who were referred for the evaluation of possible rheumatic heart disease because of the auscultatory findings of mitral valve disease, most commonly isolated MI. In these patients, almost all of whom were asymptomatic, history of an illness suggestive of an attack of ARF could not be elicited, and the electrocardiographic and clinical findings characteristic of an endocardial cushion defect or other specific anomaly were not present. Several of the patients were found to have AI also, while five patients had mitral stenosis, either isolated or in conjunction with MI and/or AI, discovered as early as four years of age.

Sera

Serum specimens obtained from the patients in groups 1–3 were handled aseptically and stored at −10°C until the time of assay. Antibody assays were performed on proportionate numbers of sera from each of the study groups and from the control group (vide infra).

**Antibody Determinations**

ASO and anti-DNAse B titers were measured by the micro methods previously described. The serum dilution scheme for the ASO and anti-DNAse B titers was based on a logarithmic scale, with 0.1 log separating each of the consecutive tube dilutions. The values obtained for ASO and anti-DNAse B titers were expressed as logs of antibody titer. Antibody levels were determined by the radioimmuno precipitin assay, and were expressed as the fraction of C14-A-carbohydrate bound by 0.2 cc whole serum and precipitated at half-saturation with ammonium sulfate. The antibody scale for this test spans from 0.00 to 1.00 “units” with the antibody levels of various sera differing by multiples of 0.01 units.

**Normal Antibody Levels**

The upper limits of normal for A-antibody, ASO, and anti-DNAse B were established by the determination of these antibody titers on serum samples from 80 children, 2–17 years old, residing in Florida and lacking evidence or history of recent streptococcal infection. These sera were

---

**Table 1**

**Streptococcal Antibody Titers of Patient Groups Studied**

<table>
<thead>
<tr>
<th>Patient Groups Studied</th>
<th>No.</th>
<th>Age in years median (range)</th>
<th>ASO (median log titer)</th>
<th>Anti-DNAse B (median fraction precipitated)</th>
<th>A-Antibody (median fraction precipitated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 — Rheumatic disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) ARF with MI</td>
<td>47</td>
<td>11.0 (4–15)</td>
<td>2.8 (2.4–2.9)*</td>
<td>2.8 (2.8–3.3)*</td>
<td>0.92 (0.85–0.98)*</td>
</tr>
<tr>
<td>(b) Residual MI 18–36 months after ARF</td>
<td>17</td>
<td>12.0 (7–16)</td>
<td>2.1 (2.1–2.3)</td>
<td>2.2 (2.1–2.4)</td>
<td>0.84 (0.74–0.93)</td>
</tr>
<tr>
<td><strong>Group 2 — Congenital disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Endocardial cushion defects with cleft mitral valve</td>
<td>26</td>
<td>7.0 (3–19)</td>
<td>2.1 (1.7–2.3)</td>
<td>2.1 (1.4–2.8)</td>
<td>0.33 (0.09–0.51)</td>
</tr>
<tr>
<td>(b) Additional congenital mitral defects</td>
<td>9</td>
<td>2.5 (1/12–13)</td>
<td>1.7 (1.7–1.7)</td>
<td>1.4 (1.4–1.4)</td>
<td>0.03 (0.02–0.07)</td>
</tr>
<tr>
<td><strong>Group 3</strong> — Mitral valve disease of unknown etiology</td>
<td>71</td>
<td>11.0 (2–19)</td>
<td>2.2 (1.7–2.4)</td>
<td>2.4 (2.1–2.7)</td>
<td>0.63 (0.30–0.79)</td>
</tr>
</tbody>
</table>

Abbreviations: ASO = anti-streptolysin O; Anti-DNAse B = anti-desoxyribonuclease B; A-antibody = antibody to group A streptococcal carbohydrate; ARF = acute rheumatic fever; MI = mitral insufficiency.

*Numbers in parentheses represent first and third quartile values.
Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years</th>
<th>ASO</th>
<th>Anti-DNAase B</th>
<th>A-Antibody</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. G.</td>
<td>3</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.03</td>
<td>MI discovered at age 6 mos.</td>
</tr>
<tr>
<td>J. D.</td>
<td>1/12</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.07</td>
<td>Dysplastic mitral valve with MI; congestive failure age 1 day</td>
</tr>
<tr>
<td>P. C.</td>
<td>2 1/2</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.02</td>
<td>Ballooning mitral valve with MI, coarctation of the aorta, atrial septal defect with partial anomalous pulmonary venous return</td>
</tr>
<tr>
<td>P. F.</td>
<td>6</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.05</td>
<td>Coarctation and MI diagnosed at 3 months</td>
</tr>
<tr>
<td>S. F.</td>
<td>2 1/2</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.03</td>
<td>Congenital mitral stenosis with hypoplastic left heart, double outlet right ventricle, coarctation of aorta, and patent ductus arteriosus</td>
</tr>
<tr>
<td>J. T.</td>
<td>2 3/4</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.02</td>
<td>Deformed mitral valve with mitral stenosis, partial anomalous venous return, &amp; atrial septal defect</td>
</tr>
<tr>
<td>G. C.</td>
<td>4 1/2</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.01</td>
<td>Patent ductus and MI diagnosed at age 3 months</td>
</tr>
<tr>
<td>C. C.</td>
<td>13</td>
<td>480</td>
<td>1600</td>
<td>.89</td>
<td>Congenital rubella, severe aortic and pulmonic stenosis, abnormal mitral valve with prolapse &amp; mitral stenosis</td>
</tr>
<tr>
<td>Y. W.</td>
<td>2 2/12</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>.14</td>
<td>Endocardial fibroelastosis with severe MI</td>
</tr>
</tbody>
</table>

Abbreviations: ASO = anti-streptolysin O; anti-DNAase B = anti-desoxyribonuclease B; A-antibody = antibody to group A streptococcal carbohydrate; MI = mitral insufficiency.

Randomly obtained throughout the calendar year. The upper limit of normal was defined as that antibody titer or level exceeded by no more than 20% of the normal children.11

Results

Normal Antibody Values

As defined above, the upper limits of normal for the three streptococcal antibodies studied were found to be: 200 for ASO (log of titer = 2.3), 320 for anti-DNAase B (log of titer = 2.5), and 0.60 for the A-antibody. These values are comparable to those obtained in other geographic locations.12, 13

Antibody Titers of Patients of Groups 1–3

The median log ASO and anti-DNAase B titers and the median A-antibody levels (with first and third quartile values) for the study groups are presented in table 1.

Antibody Titers of Patients with ARF and Chronic Inactive Rheumatic Heart Disease (Group 1). As expected, the anti-streptococcal antibody levels of 47 patients with ARF in association with MI (group 1a) were markedly elevated (table 1). Each ARF patient manifested an A-antibody level greater than 0.60. With the exception of two subjects with normal ASO titers and three patients with normal anti-DNAase B titers, the ARF patients demonstrated elevated ASO and anti-DNAase B levels. Streptococcal antibody titers for serum samples obtained 18–36 months following well-documented ARF with MI are plotted in figure 1. Although each patient in this group had essentially normal ASO and anti-DNAase B titers at the time of study, 15 of the 17 patients (88%) manifested persistence of elevated levels of A-antibody. Comparison of ASO titers of groups 1a and 1b, as expected, revealed significantly higher titers among group 1a (P < 0.001). Likewise, higher anti-DNAase B titers were found among the group 1a patients (P < 0.001). In contrast, no significant difference in A-antibody level was observed between the two rheumatic groups studied during the acute stage of ARF as well as 18–36 months following ARF (P > 0.05). These prospective findings confirm the previously reported retrospective data13 and suggest that an elevated A-antibody level

Circulation, Volume 50, December 1974
in the presence of normal ASO and anti-DNase B titers represents a pattern frequently associated with chronic MI of rheumatic etiology.

**Antibody Titers of Patients with Congenital Mitral Valve Disease (Group 2).** The streptococcal antibody titers of the group 2 patients are shown in figure 2. The A-antibody levels of 81% of the patients in this group are below the upper limit of normal of 0.60, a distribution similar to that obtained for the normal population. The A-antibody levels of this group (median = 0.19, first and third quartiles = .04-.49) are significantly lower than those of the group 1b patients with persistent rheumatic MI (median = 0.84, first and third quartiles = 0.74-0.93) with \( P < 0.001 \). In addition, it is apparent that each of the seven patients in this category with an elevated A-antibody level demonstrates concomitant elevation of ASO and/or anti-DNase B titers. This finding suggests that only those patients with congenital MI who have had a recent streptococcal infection manifest elevated levels of A-antibody. The pattern of elevated A-antibody level in the presence of normal ASO and anti-DNase B, which was frequently seen in the rheumatic patient group, was not observed in the group 2 patients. Thus, the antibody pattern characteristic of this group of patients with congenital mitral disease consists of the presence of normal A-antibody level when the ASO and/or anti-DNase B titers are normal.

**Antibody Titers of Patients with Mitral Valve Disease in the Absence of History of ARF (Group 3).** The streptococcal antibody titers of all 71 patients in this group are distributed over a very wide range. An analysis of the antibody patterns obtained for this heterogeneous group allows the classification of these patients into three subgroups (table 3).

Subgroup A consists of 12 patients who manifested elevated A-antibody levels in association with normal ASO and anti-DNase titers (fig. 3), i.e., the antibody pattern characteristic of patients with chronic inactive rheumatic MI. Comparison of the antibody titers obtained for this subgroup with those of group 1b, patients with chronic rheumatic MI, yields no significant difference (\( P > 0.9 \) for each of the three anti-streptococcal antibodies studied). Among the 12 patients in subgroup A were three patients for whom subsequent studies provided evidence for a rheumatic etiology: one patient who later developed Sydenham's
Table 3

Subdivision of Group 3 Patients on the Basis of Streptococcal Antibody Titers

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Age in years (median)</th>
<th>ASO (median log titer)</th>
<th>Anti-DNAse B (median log titer)</th>
<th>A-Antibody (median fraction precipitated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12</td>
<td>12.0</td>
<td>2.1 (2.1–2.2)*</td>
<td>2.2 (2.1–2.4)*</td>
<td>0.85 (0.72–0.89)*</td>
</tr>
<tr>
<td>B</td>
<td>39</td>
<td>11.0</td>
<td>1.7 (1.7–2.2)</td>
<td>2.4 (1.7–2.4)</td>
<td>0.45 (0.22–0.47)</td>
</tr>
<tr>
<td>C</td>
<td>20</td>
<td>11.0</td>
<td>2.4 (2.4–2.6)</td>
<td>2.7 (2.6–2.9)</td>
<td>0.86 (0.79–0.92)</td>
</tr>
</tbody>
</table>

Abbreviations: ASO = anti-streptolysin O; Anti-DNAse B = anti-desoxyribonuclease B; A-antibody = antibody to group A streptococcal carbohydrate.

*Numbers in parentheses represent first and third quartile values.

chorea, one child who was found at autopsy to have a calcified rheumatic mitral valve, and a 7-year-old girl with mitral stenosis whose surgical myocardial biopsy was interpreted as healed myocarditis compatible with rheumatic carditis. None of the 12 patients in this subgroup demonstrated features suggestive of congenital heart disease.

The 39 patients with normal levels of A-antibody comprise subgroup B (fig. 4). This pattern is similar to that observed in the patients with congenital mitral valve disease (group 2). Comparison of the anti-streptococcal titers of these individuals with the titers of patients in group 2 failed to reveal significant differences (P > 0.9 for ASO, P > 0.3 for anti-DNAse B, and P > 0.6 for A-antibody). The clinical features of the 39 children in this subgroup are summarized in table 4. Twenty patients manifested asymptomatic isolated MI, while at least 14 had other associated clinical and angiocardiographic findings strongly suggesting a non-rheumatic etiology. None of the remaining patients subsequently developed other criteria compatible with a diagnosis of rheumatic fever.

The patients in subgroup C were 20 individuals with elevated A-antibody levels associated with elevated ASO and/or anti-DNAse B titers (fig. 5). Included in this subgroup were three patients with MI in association with balloon mitral valve (including one with Marfan's syndrome), one patient with MI associated with AI, one with MI and congestive failure since 1 1/2 years of age (probable myocardiopathy), two children with mitral stenosis and AI, and 13 children with isolated asymptomatic MI. The antibody values of these patients were comparable to those of patients

![Streptococcal antibody titers of patients of subgroup A of group 3. The dotted lines represent the upper limits of normal. Abbreviations as in figure 1.](chart1.png)

![Streptococcal antibody titers of patients of subgroup B of group 3. The dotted lines represent the upper limits of normal. Abbreviations as in figure 1.](chart2.png)
STREP ANTIBODIES IN MITRAL VALVE DISEASE

Table 4
Clinical and Cardiac Features of Patients in Subgroup B (Group 3)

<table>
<thead>
<tr>
<th>Feature Description</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, isolated MI</td>
<td>20</td>
</tr>
<tr>
<td>Balloon mitral valve with MI</td>
<td>5</td>
</tr>
<tr>
<td>Myocardial infarction (endocardial fibroelastosis) with MI</td>
<td>3</td>
</tr>
<tr>
<td>MI and congestive failure &lt;2 years of age</td>
<td></td>
</tr>
<tr>
<td>Marfan's syndrome, with &quot;floppy&quot; mitral valve and MI</td>
<td>1</td>
</tr>
<tr>
<td>Coarctation of the aorta, bicuspid aortic valve, mitral stenosis, and aneurysm of sinus of Valsalva</td>
<td>1</td>
</tr>
<tr>
<td>Aortic insufficiency and MI</td>
<td>1</td>
</tr>
<tr>
<td>Mitral stenosis at 8 years of age</td>
<td>1</td>
</tr>
<tr>
<td>MI, mitral stenosis, aortic insufficiency, and failure to thrive at 4 years of age</td>
<td>1</td>
</tr>
<tr>
<td>MI, coarctation of the aorta, bicuspid aortic valve, and aortic insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>MI, prolapsing mitral valve, bicuspid aortic valve</td>
<td>1</td>
</tr>
<tr>
<td>MI, with history of cardiac murmur since birth</td>
<td>1</td>
</tr>
<tr>
<td>MI, antecedent history of sudden hemiplegia (?vasculitis)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>39</td>
</tr>
</tbody>
</table>

Abbreviation: MI = mitral insufficiency.

convalescent from recent streptococcal infection, and probably reflected recent streptococcal infection.

Discussion

The difficulty in clinically differentiating rheumatic from non-rheumatic mitral valve disease has resulted in the management of children with mitral valve disease of unknown etiology in a fashion identical to that of patients with unequivocal rheumatic heart disease. While the benefits of a prophylactic regimen for patients with rheumatic heart disease have been well established, there appears to be little advantage of such a regimen to the patient with non-rheumatic heart disease. In fact, an increased hazard of both anaphylactic reactions and bacterial endocarditis with penicillin-resistant organisms, among others, may be cited. Because of this clinical dilemma and the unavailability of tests to define clearly the etiology of mitral valve disease in the absence of a definitive diagnostic history, we have explored the possible use of streptococcal antibody tests as a means for differentiating rheumatic from non-rheumatic valvular heart disease. The present data suggest that the A-antibody test, in conjunction with other streptococcal antibody titers, may provide such a tool.

The finding of elevated A-antibody levels 18–36 months following well-documented ARF and residual MI in 15 of 17 (88%) patients in whom the ASO and anti-DNase B titers have declined to normal levels confirms earlier retrospective data on the persistence of elevated A-antibody among patients with chronic rheumatic valvular heart disease. Of the 47 ARF patients included in group 1a, 19 patients were studied during the acute state as well as 18–36 months following ARF. While the ASO and anti-DNase B levels had declined to normal levels in 13 of these 19 patients, six still had elevated ASO and/or anti-DNase B titers when last studied. The median log ASO and anti-DNase B titers of these six patients 18–36 months after ARF were 2.50 and 2.75 respectively. These values represent a significant fall in titer from the ASO and anti-DNase B titers of these six patients during the acute stage of ARF (median values = 2.95, with range = 2.70–3.00, and 3.30, with range = 3.00–3.50, respectively), with P < 0.01. In contrast, the median A-antibody level of these six patients showed no decline from the acute stage (median A-antibody = 0.90) to 18–36 months later (median A-antibody = 0.91). To allow a valid comparison with patients of other categories, the 13 patients of group 1a with ASO and anti-DNase B levels which had declined to normal during the period of observation and four patients who were studied prospectively but who had only ASO titers performed during the acute attacks of ARF, were selected to comprise group 1b. Of note is the fact that of the two group 1b patients whose A-antibody levels declined to normal, one had MI which was mild initially and which...
became progressively less apparent, being detected at 18 months only after vigorous exercise; while the second patient was a child with severe AI and only very mild MI as evidenced by clinical and angiocardiographic criteria.

The antibody pattern observed in the rheumatic patients contrasts with that of patients with proven congenital mitral valve disease. None of the patients in the latter group manifested the pattern of streptococcal antibodies characteristic of the rheumatic group of patients, viz., elevated A-antibody levels in association with normal ASO and anti-DNase B titers. Each of the patients with congenital disease with elevated A-antibody levels had concomitant elevation of ASO and/or anti-DNase B titers, i.e., evidence of recent streptococcal infection.

The finding of these two contrasting antibody patterns, obtained on sera of patients with rheumatic and congenital MI, allowed the differentiation of patients with MI of undetermined etiology into three distinct subgroups. Twelve of the 71 patients (17%) demonstrated the streptococcal antibody pattern characteristic of patients with well-documented residual rheumatic MI, i.e., elevated A-antibody in the presence of normal ASO and anti-DNase B titers, and were designated as subgroup A. These patients may represent individuals whose episode of ARF was subclinical. As noted above, subsequent clinical and pathologic data in three of the 12 patients in this “presumptive rheumatic” category confirmed that these individuals did indeed have rheumatic heart disease. None of the 12 patients manifested clinical or laboratory findings suggestive of congenital heart disease. Thus, rheumatic prophylaxis for the prevention of streptococcal infection and recurrent rheumatic fever appears to be indicated in this subgroup of patients with mitral valve disease who demonstrate the pattern of streptococcal antibody titers characteristic of patients with chronic rheumatic valvular disease.

Normal levels of A-antibody were found in the sera of 39 of the 71 (55%) patients in group 3 (subgroup B). The antibody titers of these 39 patients were very similar to those of the patients with congenital mitral disease. At least fourteen of these patients had associated clinical or laboratory evidence to support a non-rheumatic etiology, including balloon mitral valve, myocardiopathy, or an association with Marfan’s syndrome, bicuspid aortic valve, coarctation of the aorta, or a variety of associated congenital cardiac lesions (table 4). The patients in this subgroup may represent “presumptive non-rheumatics,” for whom long-term rheumatic prophylaxis could be discontinued. At the present time, it would appear that any such recommendation should be individualized, depending upon the associated clinical and laboratory data.

The remaining 20 of the 71 (28%) patients (subgroup C), who manifested elevation of A-antibody in conjunction with high ASO and/or anti-DNase B titers, can only be considered as having evidence of recent streptococcal infection. It is likely that these patients may include some who have recently suffered a subclinical attack of ARF. A rational approach for the management of this category of patients appears to be the maintenance of rheumatic prophylaxis with follow-up streptococcal antibody studies to be performed during the ensuing 12–24 months. The subsequent antibody pattern may then allow re-assignment of patients to either the presumptive rheumatic or the presumptive non-rheumatic group, depending upon the presence or absence of persistently elevated A-antibody levels.

The predictive accuracy of the streptococcal antibody pattern characterized by elevated A-antibody with normal ASO and anti-DNase B in the diagnosis of chronic rheumatic mitral disease may be assessed by an examination of the false positive and false negative rates encountered in this study. None of the 35 patients with congenital mitral valve disease (group 2) manifested this antibody pattern. In contrast, 88% (15/17) of children studied with rheumatic MI demonstrated the above antibody pattern 18–36 months following ARF. These findings suggest that the use of the above criterion yielded no “false positives” and only a rate of 12% “false negatives” in the differentiation of rheumatic from non-rheumatic chronic mitral disease. Previous retrospective studies of adult patients with chronic inactive rheumatic heart disease have demonstrated elevated A-antibody levels in 58% of patients studied as long as 10 to 25 years after their presumed last attack of ARF. This study had certain limitations including its retrospective nature, the documentation of the acute attacks of ARF in many of the patients only by history, and the fact that some of the patients included had pure aortic regurgitation, a finding now recognized to be infrequently due to rheumatic heart disease. These factors could result in the inclusion of some non-rheumatic individuals which, with the small number of patients studied, could produce an apparent lower frequency of elevated A-antibody in patients with chronic inactive rheumatic mitral disease. Although the present data do not allow for conclusions regarding the applicability of the A-antibody test for differentiating rheumatic from non-rheumatic mitral valve disease beyond 36 months after ARF, prospective studies now being carried out should provide data regarding the usefulness of this test at longer intervals after ARF.
STREP ANTIBODIES IN MITRAL VALVE DISEASE

Recent studies by Burch and Giles provide data suggesting that infectious agents other than the group A streptococcus may be etiologically related to the pathogenesis of acquired valvular heart disease. Convincing evidence exists that Coxsackie viruses in particular are capable experimentally of producing chronic valvular lesions resembling rheumatic heart disease among cynomolgus monkeys, although the significance of such agents with respect to acquired valvular heart disease in humans is unclear. 20

The finding that a large percentage of patients with mitral disease of unknown etiology may have non-rheumatic disease agrees with the experience of other investigators who have assessed the frequency of non-rheumatic mitral disease by other parameters. Using cineangiocardiographic criteria, Wexler et al. found that 43% of a series of adult patients with MI had non-rheumatic heart disease, with subsequent confirmation by surgical and pathologic examination. Several pathologic studies have confirmed the frequency of non-rheumatic valvular heart disease. In a large autopsy series of adults with chronic valvular disease, Roberts concluded that 24% of patients with isolated mitral valve disease had non-rheumatic heart disease, based upon pathologic examination. Likewise, the fact that congenital mitral valve disease is not exceptionally uncommon was emphasized in the recent report by Davachi et al. summarizing the pathologic findings of mitral valve lesions in 55 infants with congenital disease. Other clinical studies also have noted that non-rheumatic mitral disease is frequently encountered. In their review article Selzer and Cohn refer to the fact that pure mitral regurgitation is most often non-rheumatic in origin. The frequency of solitary congenital MI, including the ballooning mitral valve syndrome, was commented upon in a recent editorial by Vlad, who noted that in children it ranks second in frequency only to rheumatic mitral valve disease.

The findings in the present study are in agreement with the above studies and tend to support the concept advanced in these reports that many patients may have mitral disease of non-rheumatic etiology. The streptococcal antibody tests used in this study, together with electrocardiographic, roentgenographic and clinical data, may be useful in distinguishing between rheumatic and non-rheumatic mitral valve disease in the majority of patients whose disease is of obscure etiology.

Acknowledgment

The authors wish to acknowledge the technical assistance of Mrs. E. Harden and Mrs. P. McCormick. The invaluable aid of the following physicians in obtaining serum samples is also kindly acknowledged: Drs. John Whitcomb, Ben C. Storey, Joel McCall, Edgar Hitchcock, Robert Miller, Thomas J. Philpot, George Brodsky, Charles Ozaki, Donald Frazer, Edward Kaplan, John G. Lane, Jr., Gordon Heath, Michael L. Steiner, James R. Boulware III, and B. Lynn Miller.

References

Differences in Antibody Response to Streptococcal Antigens in Children with Rheumatic and Non-rheumatic Mitral Valve Disease
STANFORD T. SHULMAN, ELIA M. AYOUB, BENJAMIN E. VICTORICA, IRA H. GESSNER, DOLORES F. TAMER and FRANCISCO A. HERNANDEZ

*Circulation*. 1974;50:1244-1251
doi: 10.1161/01.CIR.50.6.1244
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/50/6/1244

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/