Natural History and Prognosis of Atrial Septal Defect


SUMMARY
A series of 128 consecutive cases of atrial septal defect in adult patients was analyzed from the standpoint of the course and prognosis. The ages of the patients ranged from 18 to 67 years and the ratio of men to women was 1 to 2. Age distribution when compared with life expectancy tables indicated reduced life expectancy. Clinical analysis revealed that three quarters of the patients were symptomatic, but symptoms were mild to moderate and usually nonprogressive. Hemodynamic analysis revealed significant pulmonary hypertension in 22% of the series, of which 15% had high pulmonary vascular resistance, and significant arterial hypoxemia in 14%. The most serious risk factor in atrial septal defect is severe pulmonary hypertension. This complication, which develops in about 14% of patients with atrial septal defect when they are between 20 and 40 years of age, may be rapidly progressive, leading to shunt reversal, disability, and death. Once established, pulmonary hypertension may progress even when the defect is surgically closed. Heart failure occurs usually in older individuals and is associated mostly with chronic atrial arrhythmias rather than pulmonary hypertension.

DEFECTS OF THE ATRIAL septum represent a congenital malformation of the heart which is amenable to a curative surgical treatment. The low risk of such surgical treatment in properly equipped institutions has made it customary to recommend routine closure of such defects, preferably in childhood. Yet it is well known that even large atrial septal defects can take a benign course and permit longevity. The course and natural history of septal defects in adults is not clearly known. It is obvious that, with routine surgical closure of atrial septal defects in childhood, prospective studies can no longer be organized. In retrospective studies thus far available, the largest series deal with children. Many questions regarding the course of this defect in adults have not been answered or are subject to conflicting and controversial views. This investigation was undertaken in the hope of answering some of these questions by a retrospective analysis of a large, unselected series of atrial septal defects and to establish the risk factors in patients who survived childhood.

Methods
The study is based on 128 consecutive patients with atrial septal defect over the age of 18 years who underwent diagnostic study in this institution. This number represents all adult cases of atrial septal defect in over 3,500 diagnostic cardiac catheterizations performed in this laboratory. Inasmuch as the great majority of cases were referred to this institution for diagnosis and the decision regarding operability was made after the diagnostic procedure by us, it is unlikely that the series is seriously biased toward surgically correctable cases. Each patient underwent a clinical evaluation, including a complete history, physical examination, and electrocardiographic,
vectorcardiographic, phonocardiographic, and roentgenographic studies prior to the diagnostic cardiac catheterization. Surgical repair of the atrial septal defect was performed in all patients in whom such treatment was recommended, namely 116 patients. Operative records were used for surgical description of the defect. All important findings and measurements were tabulated and those considered pertinent to the profile and natural history of this defect were scrutinized with special reference to relationship between them. Patients with atrial septal defects associated with other congenital lesions (except anomalous drainage of right pulmonary veins) were excluded from the series. However, those combined with acquired forms of cardiac disease (for example, mitral stenosis) were included.

Results

The age and sex distribution of the patients in the series is shown in table 1. To analyze the significance of the distribution of this material arranged by decades, these figures have been compared with the distribution of 128 normal individuals, older than 18 years, according to vital statistics reported by the U.S. Public Health Service. This comparison is shown in table 2. It is seen that the drop-off of the figures for patients older than 50 years in this series is not shared by normal individuals, the statistical significance of this difference being of the order of less than 1 in 1,000. In order to reinforce these figures by a larger number of cases, three other reported series have been added to ours1-3 with a total of 655 adult cases of atrial septal defect. A significant difference between the age distribution of the larger sample and the normal population can be demonstrated at a level slightly lower than that for our series alone.

Anatomic Types

Anatomic types of atrial septal defects were noted in 112 cases in which surgical description of the defects were made available: A simple secundum type of a defect was present

<p>| Table 1 |
| Age at the Time of Study and Sex of Patients in This Series |</p>
<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>18-20</th>
<th>21-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>Over 60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>8</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>Females</td>
<td>9</td>
<td>22</td>
<td>23</td>
<td>19</td>
<td>10</td>
<td>4</td>
<td>87</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>33</td>
<td>32</td>
<td>27</td>
<td>15</td>
<td>4</td>
<td>128</td>
</tr>
</tbody>
</table>

<p>| Table 2 |
| Comparison of Distribution of Cases of Atrial Septal Defects According to Age with the Predicted Distribution of a Sample of Identical Ages of the Normal Population* |</p>
<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>20-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>Over 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>33</td>
<td>32</td>
<td>27</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Predicted normals</td>
<td>24</td>
<td>24</td>
<td>23</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Combined figures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>This series</td>
<td>33</td>
<td>32</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Bedford1</td>
<td>82</td>
<td>69</td>
<td>81</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Himbert et al.2</td>
<td>68</td>
<td>39</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Zaver and Nadas3</td>
<td>28</td>
<td>35</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Total ASD</td>
<td>211</td>
<td>175</td>
<td>157</td>
<td>89</td>
<td>23</td>
</tr>
<tr>
<td>Predicted normals</td>
<td>141</td>
<td>140</td>
<td>135</td>
<td>129</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistical analysis done using the χ² method.

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ATRIAL SEPTAL DEFECT

in 95 patients (85%), sinus venosus type in nine patients (8%), primum type in seven cases (6%), and total absence of septum (single atrium) in one case. In line with the stated policy patients with endocardial cushion defects were included in the series only if the atrial septal defect was the sole significant lesion (minor valve clefts were overlooked).

**Associated Lesions**

Among associated, unrelated lesions, mitral stenosis due to rheumatic fever was the only significant one, having been found in five cases. The diagnosis in each case was confirmed by surgical inspection, the valve being described as a typical rheumatic, stenotic mitral valve. These patients* represent the syndrome described by Lutembacher. In addition, three patients were found to have significant arterial hypertension (systemic). One patient had severe kyphoscoliosis, and one had diabetes.

**Hemodynamic Data**

Cardiac catheterization revealed the following. Cardiac output (systemic flow) tended to be low in the entire series; however, 56 patients (47%) still had a cardiac output within the accepted normal range (2.5 L/min/m² or greater), 55 patients had cardiac output between 2.0 and 2.4 L/min/m², and nine patients, cardiac output smaller than 2.0 L/min/m². Table 3 indicates that normally low cardiac output was the rule in patients older than 40 years of age.

The magnitude of left-to-right shunt through the atrial defect, expressed as a ratio of the pulmonary to systemic flow, is presented in table 4. Large and moderate shunts were

**Table 3**

Systemic Cardiac Output (per Square Meter of BSA) in Age Groups

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-20</td>
<td>2.6 ± 0.45</td>
<td>2.9 ± 0.82</td>
<td>2.8 ± 0.65</td>
</tr>
<tr>
<td>21-30</td>
<td>2.9 ± 0.91</td>
<td>2.7 ± 0.64</td>
<td>2.9 ± 0.71</td>
</tr>
<tr>
<td>31-40</td>
<td>2.8 ± 1.05</td>
<td>2.7 ± 0.80</td>
<td>2.7 ± 0.88</td>
</tr>
<tr>
<td>41-50</td>
<td>2.2 ± 0.20</td>
<td>2.6 ± 0.87</td>
<td>2.4 ± 0.69</td>
</tr>
<tr>
<td>51-60</td>
<td>2.2 ± 0.31</td>
<td>2.4 ± 0.60</td>
<td>2.3 ± 0.45</td>
</tr>
<tr>
<td>60+</td>
<td>—</td>
<td>2.0 ± 0.82</td>
<td>2.0 ± 0.82</td>
</tr>
</tbody>
</table>

*Hemodynamic data of patients with atrial septal defect and mitral stenosis will be reported in a separate communication.

**Table 4**

Magnitude of Shunts

<table>
<thead>
<tr>
<th>Pulmonary to systemic flow ratio</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 3:1</td>
<td>50</td>
</tr>
<tr>
<td>Between 2:1 and 3:1</td>
<td>45</td>
</tr>
<tr>
<td>Smaller than 2:1, net left-to-right shunt</td>
<td>24</td>
</tr>
<tr>
<td>Balanced, bidirectional, or reversed shunt</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 5**

Range of Systolic Pressure in the Pulmonary Artery in This Series

<table>
<thead>
<tr>
<th>Systolic pressure</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 25 mm Hg</td>
<td>45</td>
</tr>
<tr>
<td>25 to 50 mm Hg</td>
<td>55</td>
</tr>
<tr>
<td>51 to 75 mm Hg</td>
<td>12</td>
</tr>
<tr>
<td>Greater than 75 mm Hg</td>
<td>16</td>
</tr>
</tbody>
</table>

**Table 6**

Measurements of Total Pulmonary Resistance in This Series

<table>
<thead>
<tr>
<th>Total pulmonary resistance (dynes sec cm⁻²)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 100</td>
<td>51</td>
</tr>
<tr>
<td>100 to 200</td>
<td>39</td>
</tr>
<tr>
<td>201 to 450</td>
<td>18</td>
</tr>
<tr>
<td>Greater than 450</td>
<td>18</td>
</tr>
</tbody>
</table>

**Table 7**

Levels of Resting Arterial Oxygen Saturation in This Series

<table>
<thead>
<tr>
<th>Arterial O₂ saturation</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher than 94%</td>
<td>50</td>
</tr>
<tr>
<td>90 to 94%</td>
<td>51</td>
</tr>
<tr>
<td>85 to 89%</td>
<td>13</td>
</tr>
<tr>
<td>Lower than 85%</td>
<td>4</td>
</tr>
</tbody>
</table>

*Circulation, Volume XXXVII, May 1968*
found in 95 patients (74%). A possible relationship between patient’s ages and magnitude of shunts was evaluated. Such a relationship was not demonstrated.

The range of systolic pressure in the pulmonary artery is shown in table 5. Normal pressures were present in 35% of cases. However, the majority of those with elevation of pulmonary arterial pressure had only modest degrees of pulmonary hypertension, inasmuch as only 22% of the series had pressures higher than 50 mm Hg. The differentiation between hyperkinetic and obstructive pulmonary hypertension is dealt with in table 6, in which calculated values of total pulmonary resistance are presented. It is generally recognized that the diagnosis of obstructive pulmonary hypertension should only be made if a significant elevation of pulmonary vascular resistance is present, well outside the border-line range. Arbitrary lower limits for obstructive pulmonary hypertension have been accepted at 400 dynes sec cm⁻⁵ (expressed in “units”—5 mm Hg/L/min). Thus obstructive pulmonary hypertension was present in only 15% of the patients. Table 7 presents a summary of the range of distribution of arterial oxygen saturation in the series. With a normal level for our laboratory of 95 to 97%, reduced oxygen saturation was present in 58% of the patients; however, arterial hypoxia was mostly mild, as only 14% of the patients had arterial oxygen saturation under 90%. A relationship between the calculated total pulmonary resistance and arterial oxygen saturation is presented in figure 1. This scatter graph indicates that arterial hypoxia is most commonly associated with high resistance type of pulmonary hypertension, but may also develop in patients with normal pulmonary arterial resistance.

### Symptoms

Symptoms of patients were evaluated and tabulated (table 8). It was seen that three quarters of the patients were symptomatic at the time of the study, the commonest symptom being effort dyspnea. However, symptoms were, as a rule, reported as mild or moderate. The great majority of patients did not consider themselves disabled and engaged easily in ordinary activities. Relationship between symptoms and shunt size, between symptoms and patients’ ages, and between symptoms and pulmonary resistance were searched for and revealed no statistical significance. It was noted that, in patients with elevated pulmonary resistance, however, symptoms were most often of shorter duration than in the remainder of the series and their severity tended to be progressive.

### Pulmonary Hypertension

Pulmonary hypertension is the most important single factor influencing the course of atrial septal defect. It has been shown that 15% of patients had significantly elevated total pulmonary resistance indicating an obstructive process. Inasmuch as the left atrial pressure in this condition is low, being equal to right atrial pressure, elevated total pulmonary resistance is tantamount to high pulmonary vascular resistance. Figure 2 shows the relationship between the age of patients

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**Table 8**

The Presence and Nature of Symptoms in This Series

<table>
<thead>
<tr>
<th>Nature of symptoms</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>79</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26</td>
</tr>
<tr>
<td>Palpitations</td>
<td>27</td>
</tr>
<tr>
<td>Chest pain</td>
<td>6</td>
</tr>
</tbody>
</table>

*Circulation, Volume XXXVII, May 1968*
and the pulmonary resistance. The scatter indicates clearly that obstructive high-resistance pulmonary hypertension is most commonly seen in younger individuals. Because of the importance of pulmonary hypertension, a brief summary of findings in the 18 patients with high pulmonary vascular resistance is presented in table 9. The table shows the wide range of clinical and hemodynamic findings in this group of patients. Three patients fell into the border-line group in which surgical treatment was debatable, but the operation was performed in hope of providing even a small benefit to the patient. Eight patients had shunt ratios greater than 1.6 and constituted fair to good material for surgical treatment. It is noteworthy that the preponderance of women in this group is slightly higher than in the entire series (78% versus 66%). Cardiac failure was observed in only four patients in this group, in two of whom it was complicated by mitral stenosis. No evidence of cardiac failure was found in the ten patients under the age of 40 years.

In three patients it was possible to perform serial hemodynamic studies, as presented in table 10. In the patient L. J. a threefold increase in pulmonary arterial pressure was caused by a rise in pulmonary vascular resistance—still in the normal range—with a period of 2½ years. The other two patients underwent surgical closure of the atrial septal defect in spite of high pulmonary vascular resistance. In one, the follow-up study performed 1 year after the operation revealed no change in pulmonary vascular resistance and only a minor fall in pulmonary arterial pressure. This patient, reinvestigated 2 years later, showed a severe progression of the obstructive pulmonary hypertension which led to his death a year after the last study. The third patient when seen 4 years after operation showed considerable increase in pulmonary

<table>
<thead>
<tr>
<th>MS</th>
<th>H</th>
<th>AF</th>
<th>PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>DG</td>
<td>MB</td>
<td>MH</td>
<td>NY</td>
</tr>
<tr>
<td>19</td>
<td>20</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>JK</td>
<td>KW</td>
<td>MB</td>
<td>AO</td>
</tr>
<tr>
<td>30</td>
<td>31</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>AD</td>
<td>VE</td>
<td>RD</td>
<td>CW</td>
</tr>
<tr>
<td>42</td>
<td>42</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>RU</td>
<td>JC</td>
<td>WA</td>
<td>TD</td>
</tr>
<tr>
<td>48</td>
<td>49</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>DS</td>
<td>VA</td>
<td>GE</td>
<td>ES</td>
</tr>
<tr>
<td>61</td>
<td>62</td>
<td>65</td>
<td>65</td>
</tr>
</tbody>
</table>

Figure 3

Graphic presentation of patients, arranged by age, who had pulmonary hypertension (PH), atrial flutter or fibrillation (AF), cardiac failure (HF), and mitral stenosis (MS), to show coexistence of these factors in the patients.
### Table 9

**Summary of Clinical and Hemodynamic Findings in Patients with Elevated Pulmonary Resistance***

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age (yr) &amp; sex</th>
<th>Symptoms</th>
<th>Age at onset of symptoms (yr)</th>
<th>Arrhythmia</th>
<th>Congestive heart failure</th>
<th>Type of defect</th>
<th>RA (mm Hg)</th>
<th>RV (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.G.</td>
<td>19F</td>
<td>Dyspnea</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>Sec. type</td>
<td>6</td>
<td>8/6</td>
</tr>
<tr>
<td>M.B.</td>
<td>20M</td>
<td>Dyspnea, severe</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>109/3</td>
</tr>
<tr>
<td>M.H.</td>
<td>24F</td>
<td>Dyspnea</td>
<td>23</td>
<td>—</td>
<td>—</td>
<td>Sec. type</td>
<td>3</td>
<td>98/6</td>
</tr>
<tr>
<td>N.Y.</td>
<td>25F</td>
<td>Dyspnea, severe</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>100/4</td>
</tr>
<tr>
<td>W.V.</td>
<td>27M</td>
<td>Dyspnea, fatigue</td>
<td>15</td>
<td>Paroxysmal nodal tachycardia</td>
<td>—</td>
<td>Sec. type</td>
<td>4</td>
<td>90/3</td>
</tr>
<tr>
<td>J.K.</td>
<td>30F</td>
<td>Dyspnea, fatigue, palpitation</td>
<td>28</td>
<td>—</td>
<td>—</td>
<td>Sec. type</td>
<td>2</td>
<td>70/4</td>
</tr>
<tr>
<td>K.W.</td>
<td>31F</td>
<td>Dyspnea, severe</td>
<td>27</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>100/4</td>
</tr>
<tr>
<td>M.B.</td>
<td>32F</td>
<td>Dyspnea, chest pain</td>
<td>Childhood</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4</td>
<td>90/5</td>
</tr>
<tr>
<td>A.O.</td>
<td>34F</td>
<td>Dyspnea, fatigue</td>
<td>30</td>
<td>—</td>
<td>—</td>
<td>Sec. type</td>
<td>1</td>
<td>82/2</td>
</tr>
<tr>
<td>J.M.</td>
<td>34F</td>
<td>Dyspnea</td>
<td>30</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>89/4</td>
</tr>
<tr>
<td>A.D.</td>
<td>42F</td>
<td>Dyspnea</td>
<td>39</td>
<td>—</td>
<td>—</td>
<td>Sec. type</td>
<td>5</td>
<td>73/6</td>
</tr>
<tr>
<td>V.E.</td>
<td>42F</td>
<td>Dyspnea</td>
<td>10</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>10</td>
<td>142/12</td>
</tr>
<tr>
<td>R.U.</td>
<td>46M</td>
<td>Dyspnea</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>Primum</td>
<td>8</td>
<td>62/8</td>
</tr>
<tr>
<td>C.R.</td>
<td>46F</td>
<td>Dyspnea</td>
<td>40</td>
<td>A. fib., paroxysmal</td>
<td>—</td>
<td>Secundum</td>
<td>14</td>
<td>73/15</td>
</tr>
<tr>
<td>W.A.</td>
<td>48M</td>
<td>Dyspnea, palpitations</td>
<td>45</td>
<td>—</td>
<td>—</td>
<td>Sinus venosus</td>
<td>3</td>
<td>91/6</td>
</tr>
<tr>
<td>D.S.</td>
<td>54F</td>
<td>Dyspnea</td>
<td>48</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12</td>
<td>118/16</td>
</tr>
<tr>
<td>V.A.</td>
<td>57F</td>
<td>Dyspnea, palpitations</td>
<td>47</td>
<td>A. fib.</td>
<td>—</td>
<td>Sec. type</td>
<td>10</td>
<td>60/6</td>
</tr>
<tr>
<td>P.C.</td>
<td>66F</td>
<td>Dyspnea</td>
<td>63</td>
<td>Paroxysmal a. flutter</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>32/2</td>
</tr>
</tbody>
</table>

*TPR greater than 450 dynes sec cm⁻⁵.

Abbreviations: PA = pulmonary artery; BA = brachial artery; TPR and TSR = total pulmonary and systemic resistance.

This summary includes findings in patients with elevated pulmonary resistance since the preoperative study.

**Cardiac Failure**

This is relatively uncommon in the course of atrial septal defect. Overt heart failure was present in 10 patients of the series. The youngest patient in failure was 43 years old. Among these 10 patients, the five with atrial septal defect combined with rheumatic mitral stenosis were included. Eight of the 10 patients had chronic atrial arrhythmia, either flutter or fibrillation.

**Cardiac Arrhythmias**

Cardiac arrhythmias of chronic nature, namely atrial flutter or fibrillation, were observed in 10 patients, all of whom were older than 40 years of age. Atrial fibrillation was present in four of the five patients with co-
existing mitral stenosis. As a rule atrial flutter or fibrillation was associated with cardiac failure, for in only one patient was atrial fibrillation present without signs of cardiac failure.

A composite graphic presentation of the four principal factors influencing the course of atrial septal defect is presented in figure 3. Here, arranged by age, all patients are presented who showed pulmonary hypertension, chronic atrial arrhythmias, cardiac failure, and mitral stenosis, singly or in combination. It is seen that pulmonary hypertension is found most often in younger patients, while the other three factors occur only in older patients. It is noteworthy that the incidence of these complications increase with age: 14% of patients who were between 20 and 40 years

<table>
<thead>
<tr>
<th>PA (mm Hg)</th>
<th>BA (mm Hg)</th>
<th>P:S flow ratio</th>
<th>Systemic cardiac index (L/min/m²)</th>
<th>TPR (dynes sec cm⁻⁵)</th>
<th>TSR (dynes sec cm⁻⁵)</th>
<th>Art. O₂ sat. (%)</th>
<th>Remarks</th>
</tr>
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tance; a. fib. = atrial fibrillation; a. flutter = atrial flutter.
of age; 24% of patients between 40 and 60 years; 100% over 60 years of age.

**Discussion**

The natural history of atrial septal defect is approached in this study by reviewing three points: (1) symptoms leading to clinical disability, (2) heart failure and death directly related to the dynamic effects of this lesion, and (3) complications related to atrial septal defect.

**Symptoms**

It has been demonstrated that 74% of adult patients with atrial septal defect are symptomatic with dyspnea being the prevailing symptom in most. While the range of disability varied considerably, the great majority of patients were capable of performing most ordinary activities, being thus in functional class I or early class II. It is seen from this series that clinical disability increases with age, and that all patients over the age of 60 were in serious difficulties. Yet patients with atrial septal defect have been occasionally reported doing well into their seventies, showing that a normal span of life is possible even in the presence of large intracardiac shunts.5, 6

**Cyanosis**

Chronic hypoxia leading to cyanosis is known to occur occasionally in atrial septal defect as a delayed feature ("cyanosis tardive"), although it may have been present since childhood.7 In our series significant hypoxia was rare. The principal cause of it is shunt reversal due to pulmonary hypertension. However, it is shown here that right-to-left shunting may occur in the absence of pulmonary hypertension, confirming earlier expressed views.7

**Heart Failure**

Heart failure, manifesting itself as systemic venous hypertension with systemic congestive phenomena, is found to be uncommon in atrial septal defect. Eliminating the five patients who had significant mitral stenosis in addition to atrial septal defect, only five others
in this series developed cardiac failure as a direct effect of this congenital lesion. Of these, four had atrial fibrillation and one, pulmonary hypertension. It is noteworthy that none of the younger patients with pulmonary hypertension had heart failure at the time of the study, although one is known later to have died in cardiac failure (K.W.). It is therefore concluded that pulmonary hypertension is not the principal cause of cardiac failure.

**Cause of Death**

This series provides little information regarding causes of death in atrial septal defect because of the type of clinical material upon which it is based. Surgical death occurred in four high-risk patients in the series; one unoperated patient with severe pulmonary hypertension was known to have died; another patient (W.V.) died 4 years after the surgical procedure from progressive pulmonary hypertension. Causes of death in other series vary widely and are obviously dependent upon the mode of collection of material. In Zaver and Nadas' series, the majority of deaths were surgical and only four patients out of 298 died of natural causes related directly to atrial septal defect. On the other hand, in a series weighted with autopsy material such as Campbell and associates, the death rate was high (13 of 47 adult patients). A review of causes of death in the various reports revealed that congestive cardiac failure, pulmonary arterial thrombosis or embolism, and bronchopulmonary infections appear to be the predominant causes of death.

**Atrial Arrhythmias**

Atrial flutter and fibrillation are relatively common in atrial septal defect and their incidence increases steeply with age. The proneness to these arrhythmias is demonstrated by their common occurrence in patients undergoing surgical repair of the defect, in which postoperative, reversible atrial arrhythmias occur in the majority of patients older than 35 years of age. Spontaneous chronic arrhythmias are less common than those in the postoperative period, but constitute the most important complication of the aging patient, leading to disability and cardiac failure.

**Pulmonary Hypertension**

Pulmonary hypertension is the single most important risk factor in atrial septal defect, because it often renders a curable disease inoperable. The pathogenesis of pulmonary hypertension in atrial septal defect is not well understood. The oft considered hypothesis of an end-result of wear and tear of the pulmonary vasculature from the high pulmonary flow is not borne out by this series, as well as others, because increased pulmonary blood flow may persist for years, even a normal life span, without leading to obstructive pulmonary hypertension. It should be emphasized that only a fraction of cases of atrial septal defect develop obstructive pulmonary hypertension, in this series 13% (a total incidence of 15% is corrected by eliminating cases with mitral stenosis). This figure is lower than Dexter’s, but is comparable to those of Besterman and Wood. It is also noteworthy that, while during childhood obstructive pulmonary hypertension complicating atrial septal defect is very rare, early adults show relatively high proneness to this complication (14% in this series in the 18 to 40 year age-range). The possibility of a rapidly progressive, irreversible process is suggested by cases presented in table 10. Furthermore, the graph in figure 2 implies that pulmonary hypertension may be separated into two populations: pulmonary hypertension in the younger group tending to be more severe than that in the older group with the dividing line being the age of 40 years.

The pathological changes in the pulmonary vasculature of patients with atrial septal defects and pulmonary hypertension have been studied by Edwards and shown to be primarily intimal—the degree of intimal abnormalities reflecting the severity of pulmonary hypertension. This is in contrast to pulmonary hypertension occurring in association with ventricular septal defect, where medial hypertrophy predominates as an expression of obligatory pulmonary hypertension present...
since birth. The cause for the development of late intimal reaction is not known. The suggestion that it is caused by wear and tear of excessive pulmonary flow has already been dismissed above. The proposal that it is due to a congenital disorder of the pulmonary vasculature is equally unlikely in view of its late appearance and rapidly progressive nature. The possibility of an unrelated process—such as pulmonary embolization—is improbable, because the incidence is too high. Perhaps the most appealing is the possibility that pulmonary hypertension develops in individuals with a hyperreactive pulmonary vasculature in response to the prolonged hypercirculatory state within the pulmonary circulation. Such hyperreactivity could then be responsible also for the obstructive pulmonary vascular reaction that occurs in 15% of patients with mitral stenosis, when such reaction is secondary to a different stimulus—elevation of left atrial pressure. It is implied that such reactive pulmonary hypertension is reversible in mitral stenosis but unlikely to regress in atrial septal defects.

Mitral Stenosis

The occurrence of mitral stenosis in association with atrial septal defect has been known since the observation of Lutembacher. In this series, the incidence of mitral stenosis is 4%, and all five patients were shown at operation to have classical features of rheumatic mitral valve deformity. This incidence is considerably higher than a chance coexistence of two diseases. This is further supported by the fact that the five patients represented atrial septal defects found among some 800 cases of mitral stenosis; yet, not a single instance of mitral stenosis was found in association with other equally common congenital lesions (ventricular septal defect and pulmonary stenosis). The cause of the preferential acquisition of rheumatic mitral stenosis by patients with congenital atrial septal defect is not known.

Life Span and Course of Disease

A comparison between patients with atrial septal defect arranged by decades and a similarly arranged sample of the normal population shows a highly significant difference in the older age groups suggesting reduced life span in this condition. This is supported by the radiographic study of Seldon and associates, who surveyed 500,000 people and found no one with a roentgenogram suggestive of atrial septal defect over the age of 65 years. On the basis of this study and information obtained from other studies, one can now attempt to reconstruct the natural history of atrial septal defect. The young adult with this form of heart disease is, as a rule, well. Symptoms, if present, are seldom disabling and are usually nonprogressive. Many patients afflicted with a serious cardiac disorder since birth lead intuitively an inactive life and may even be unaware of their limitations. However, a young adult with an atrial septal defect stands about a 14% chance of developing abruptly progressive pulmonary hypertension. This complication gradually reduces the left-to-right shunt and eventually may lead to shunt reversal and cyanosis. Such patients may still survive for several years, though severely disabled. They die eventually of cardiac failure or thrombosis of the pulmonary arteries.

The remaining 86% of patients usually pass the third and fourth decades, without change in their condition. Among those, there is the 4% of patients who have acquired rheumatic heart disease and who in their late forties or fifties may develop serious consequences of mitral stenosis, namely atrial fibrillation, pulmonary hypertension, and heart failure. In older patients, progressive disability and heart failure develop most frequently coincidentally with the onset of chronic atrial arrhythmias (flutter or fibrillation). This occurs most commonly in the late fifties and early sixties, although occasional survival and persistence in relatively good condition into the seventies has been observed.

It is clear from this discussion that atrial septal defect is a relatively benign form of cardiac disease and is the one with the best prognosis among congenital cardiac lesions. It should be pointed out that small interatrial
shunts cannot be clinically recognized so that all patients in this and other series have hemodynamically significant lesions. However, in spite of the benign nature of this condition, routine closure of atrial septal defects in childhood is fully justified by the availability of a very low risk, curative operation.

References
Natural History and Prognosis of Atrial Septal Defect
ROBERT J. CRAIG and ARTHUR SELZER

Circulation. 1968;37:805-815
doi: 10.1161/01.CIR.37.5.805

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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