Congenital Malformations of the Heart Associated with Splenic Agenesis

With a Report of Five Cases

By Enid F. Gilbert, M.B.B.S., Kinsuke Nishimura, M.B., and Bernice G. Wedum, M.D.

This paper presents a theory for the cause of congenital malformations of the heart and other structures associated with absence of the spleen. A complete review of the literature and the data of the authors' 5 cases lead to this proposal: a lethal factor, possibly the product of a faulty ovulation, specifically affects the germinal bed of the mesoblastic surface of the coelom at an ovulatory age of 24 to 28 days.

IT WOULD appear that congenital absence of the spleen is almost invariably associated with severe cardiac malformations. The purpose of this paper is to review the literature on this subject, to present 5 additional cases, and to postulate a theory of etiology based on embryologic development. The first detailed description of splenic agenesis was recorded by Pohlius1 in 1740. The description of the heart, however, left some doubt whether a structural defect was present. Six reports2-7 had appeared earlier, the first being those of Schenkius2 and Holleriuss. Ø Martin8 and Breschet9 described the first 2 cases of the association of splenic agenesis and defects of the heart and great vessels. A total of 81 cases of this combination has thus far been reported. Splenic agenesis is associated with anatomic malformations of the heart that include variations in systemic and pulmonary venous return, defects in the atrial and ventricular septa, anomalies of the truncus, pulmonary artery and valve, and atrioventricular orifice. Dextrocardia and anomalies of the abdominal viscera and lungs, resulting in bilateral symmetry or partial situs inversus, are frequently present.

Review of the Literature

Twenty-seven instances of absence of the spleen that were unassociated with intracardiac defects have been recorded in the literature.1, 4, 6, 10-13, 14-35 In an additional 16 cases no specific mention of the heart was made in the autopsy findings,2, 3, 5, 7, 34-45 making a total of 43. Partial situs inversus occurred in 811, 13, 14, 19, 26, 28, 29, 35 (including 111 in which there was separate drainage of the hepatic veins into the right atrium), and multiple congenital anomalies in 5 patients.4, 6, 10, 12, 34 Prolonged chronic infection or neoplasia was the cause of death in 14 instances.3, 7, 13, 15, 17, 18, 26-28, 27, 28 It would seem most probable in the latter that destruction of splenic tissue rather than agenesis accounted for the absence of the spleen.

Millar and Garrow31 reported a 6-week-old infant with cyanosis since birth who was found at autopsy to have an enlarged heart, a right aortic arch, and an absent spleen. However, no intracardiac defect was present. This infant also showed a high percentage of normoblasts in the peripheral blood and bone marrow. An infant who died shortly after birth and who was found at postmortem examination to have a patent foramen ovale, symmetrical liver, and absence of the spleen was reported by Birch-Hirschfeld.16 One instance of congenitally absent spleen in a 9-month-old white female infant, dying as a result of purulent meningitis and showing no other anomalies at autopsy, was mentioned by Ivemark.46

Congenital absence of the spleen in association with congenital cardiac malformations has been reported in 81 cases9, 19, 33, 40-92 (table 1). The details of sex, age of patient, and character of lesions appear in this table. A marked
<table>
<thead>
<tr>
<th>Year of publication and reference number</th>
<th>Age</th>
<th>Sex</th>
<th>Position of the heart</th>
<th>Congenital defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1826</td>
<td>6 wk.</td>
<td>?</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PDA, TS, SL</td>
</tr>
<tr>
<td>1829</td>
<td>8 da.</td>
<td>M</td>
<td>D</td>
<td>ASD, VSD, SV, TGV, TS, TL</td>
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<tr>
<td>1847</td>
<td>20 da.</td>
<td>?</td>
<td>L</td>
<td>ASD, VSD, CB, TGV</td>
</tr>
<tr>
<td>1868</td>
<td>15 wk.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, CT, TGV, PA, PDA, APVR, SL, TS</td>
</tr>
<tr>
<td>1875</td>
<td>2 da.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, PA, APVR</td>
</tr>
<tr>
<td>1886</td>
<td>5 wk.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, TGV, APVR, SL, TS, TL</td>
</tr>
<tr>
<td>1887</td>
<td>1 mo.</td>
<td>?</td>
<td>D</td>
<td>ASD, VSD, SV, SL, TS</td>
</tr>
<tr>
<td>1888</td>
<td>2 mo.</td>
<td>L</td>
<td>TGV, PS, PDA, SL</td>
<td></td>
</tr>
<tr>
<td>1888</td>
<td>6 mo.</td>
<td>M</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PA, PDA, APVR, SL, TS, TL</td>
</tr>
<tr>
<td>1890</td>
<td>20 da.</td>
<td>?</td>
<td>L</td>
<td>ASD, ASVR, TGV</td>
</tr>
<tr>
<td>1901</td>
<td>14 wk.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, VSD, SV, TGV, PDA, TS</td>
</tr>
<tr>
<td>1905</td>
<td>1½ yr.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, PA, SL</td>
</tr>
<tr>
<td>1907</td>
<td>9 da.</td>
<td>M</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, SV, TA, APVR, SL, SL</td>
</tr>
<tr>
<td>1908</td>
<td>2½ mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, TGV, PS, SL</td>
</tr>
<tr>
<td>1915</td>
<td>4½ mo.</td>
<td>M</td>
<td>D</td>
<td>ASD, ASVR, SV, TGV, APVR, SL, TL</td>
</tr>
<tr>
<td>1920</td>
<td>9 mo.</td>
<td>?</td>
<td>L</td>
<td>ASD, VSD, SV, TS, SL</td>
</tr>
<tr>
<td>1922</td>
<td>3 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, VSD, APVR, SL, TL</td>
</tr>
<tr>
<td>1926</td>
<td>Newborn</td>
<td>?</td>
<td>L</td>
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</tr>
<tr>
<td>1962</td>
<td>6 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, VSD, TGV, SL, TS, TL</td>
</tr>
<tr>
<td>1927</td>
<td>?</td>
<td>D</td>
<td>ASD, ASVR, VSD, SV, TA, APVR</td>
<td></td>
</tr>
<tr>
<td>1929</td>
<td>3 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, PS, APVR, SL, TS, SL</td>
</tr>
<tr>
<td>1930</td>
<td>1 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PS, SL, SL, SL</td>
</tr>
<tr>
<td>1930</td>
<td>3 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, VSD, TA, APVR, SL</td>
</tr>
<tr>
<td>1937</td>
<td>14 mo.</td>
<td>M</td>
<td>D</td>
<td>ASD, CAVV, VSD, SY, TA</td>
</tr>
<tr>
<td>1938</td>
<td>2½ yr.</td>
<td>F</td>
<td>D</td>
<td>ASD, CAVV, VSD, TGV, PS, PDA</td>
</tr>
<tr>
<td>1939</td>
<td>4 mo.</td>
<td>M</td>
<td>D</td>
<td>ASD, CAVV, VSD, PA, PDA, TS</td>
</tr>
<tr>
<td>1939</td>
<td>6 mo.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PA, PDA, APVR, TS, SL</td>
</tr>
<tr>
<td>1939</td>
<td>1 da.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PDA, SL, TS, SL</td>
</tr>
<tr>
<td>1939</td>
<td>2 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, SV, TGV</td>
</tr>
<tr>
<td>1940</td>
<td>6 mo.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, CB, PA, PDA, APVR, SL</td>
</tr>
<tr>
<td>1942</td>
<td>4½ hr.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PA, PDA, APVR</td>
</tr>
<tr>
<td>1942</td>
<td>1 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PDA</td>
</tr>
<tr>
<td>1942</td>
<td>9½ mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, TGV, PA, PDA, SL, TS, TL</td>
</tr>
<tr>
<td>1947</td>
<td>Stillborn</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PA, PDA, APVR, SL, TS</td>
</tr>
<tr>
<td>1947</td>
<td>6 da.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, TGV, PDA, APVR, SL, TS, SL</td>
</tr>
<tr>
<td>1950</td>
<td>3 yr.</td>
<td>M</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PS, TS, SL</td>
</tr>
<tr>
<td>1951</td>
<td>4 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PA, PDA, APVR, SL, TS, SL</td>
</tr>
<tr>
<td>1951</td>
<td>10 wk.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, VSD, SV, TGV, PDA, APVR, SL</td>
</tr>
<tr>
<td>1952</td>
<td>11 wk.</td>
<td>F</td>
<td>L</td>
<td>ASD, VSD, SV, TA</td>
</tr>
<tr>
<td>1952</td>
<td>10 wk.</td>
<td>M</td>
<td>L</td>
<td>ASD, VSD, SV, TGV, PA, PDA, APVR, SL, TS, SL</td>
</tr>
<tr>
<td>1952</td>
<td>15 wk.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PS, PDA, APVR, SL, SL</td>
</tr>
<tr>
<td>1952</td>
<td>23 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, PS, SL, TL</td>
</tr>
<tr>
<td>1952</td>
<td>1 yr.</td>
<td>M</td>
<td>D</td>
<td>ASD, CAVV, VSD, SV, PS, SL</td>
</tr>
<tr>
<td>1953</td>
<td>6 wk.</td>
<td>F</td>
<td>L</td>
<td>ASD, CAVV, VSD, SV, TGV, PS, PDA, SL, SL</td>
</tr>
<tr>
<td>1953</td>
<td>10 da.</td>
<td>F</td>
<td>L</td>
<td>ASD, CAVV, VSD, PA, PDA, SL, SL, TS, TL</td>
</tr>
<tr>
<td>1953</td>
<td>4 mo.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, VSD, TGV, PS, PDA, APVR, SL</td>
</tr>
<tr>
<td>1953</td>
<td>4 yr.</td>
<td>F</td>
<td>L</td>
<td>ASD, VSD, SV, TGV, PS, SL, SL, TS, TL</td>
</tr>
<tr>
<td>1953</td>
<td>8 yr.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, SV, TGV, PS, SL, SL, TS, SL</td>
</tr>
</tbody>
</table>
TABLE 1.—Continued

<table>
<thead>
<tr>
<th>Year of publication and reference number</th>
<th>Age</th>
<th>Sex</th>
<th>Position of the heart</th>
<th>Congenital defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>19539</td>
<td>5 yr.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PS, APVR, SLL, TS, SL</td>
</tr>
<tr>
<td>19548</td>
<td>3 da.</td>
<td>M</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, CB, TA, PDA, APVR, SLL, TS, TL</td>
</tr>
<tr>
<td>19548</td>
<td>1½ hr.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, CB, TA, PA, PDA, APVR, SLL, TS, SL</td>
</tr>
<tr>
<td>19549</td>
<td>Stillborn</td>
<td>M</td>
<td>L</td>
<td>VSD, SL</td>
</tr>
<tr>
<td>19549</td>
<td>3 mo.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PA, PDA, SLL</td>
</tr>
<tr>
<td>19553</td>
<td>7½ mo.</td>
<td>M</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, CB, TGV, PA, PDA, APVR, SLL, TL</td>
</tr>
<tr>
<td>19559</td>
<td>7 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, VSD, TGV, PA, PDA, APVR, SLL, TS, TL</td>
</tr>
<tr>
<td>19559</td>
<td>7 da.</td>
<td>F</td>
<td>D</td>
<td>CAVV, VSD, SV, PA, PDA, APVR, SLL</td>
</tr>
<tr>
<td>19554</td>
<td>Stillborn</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, SV, TA, APVR, SL, SL</td>
</tr>
<tr>
<td>19554</td>
<td>3 da.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TA, SLL, TS, TL</td>
</tr>
<tr>
<td>19554</td>
<td>4 wk.</td>
<td>F</td>
<td>L</td>
<td>VSD, SV, TA, APVR, SL</td>
</tr>
<tr>
<td>19554</td>
<td>1 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PS, APVR, SLL, TS, SL</td>
</tr>
<tr>
<td>19554</td>
<td>2 mo.</td>
<td>F</td>
<td>L</td>
<td>ASD, CAVV, VSD, TGV, PDA, TS, SL</td>
</tr>
<tr>
<td>19554</td>
<td>15 wk.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PA, PDA, APVR, SLL, TS, SL</td>
</tr>
<tr>
<td>19554</td>
<td>4 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, SV, PS, TS, SL</td>
</tr>
<tr>
<td>19554</td>
<td>4 mo.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, APVR, SLL, SL</td>
</tr>
<tr>
<td>19554</td>
<td>4 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, TGV, PA, PDA, SLL, TS, SL</td>
</tr>
<tr>
<td>19554</td>
<td>5 mo.</td>
<td>M</td>
<td>D</td>
<td>ASD, CAVV, VSD, SV, TA, APVR, SLL, TS, TL</td>
</tr>
<tr>
<td>19554</td>
<td>6 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, APVR, SLL, SL</td>
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<tr>
<td>19554</td>
<td>9 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PA, APVR, SLL, TS, TL</td>
</tr>
<tr>
<td>19554</td>
<td>10 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PS, APVR, TS, SL</td>
</tr>
<tr>
<td>19554</td>
<td>2½ yr.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, VSD, TGV, PS, APVR, TS, SL</td>
</tr>
<tr>
<td>19562</td>
<td>2 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, CAVV, VSD, CT, TGV, PDA, SLL, TS, TL</td>
</tr>
<tr>
<td>19562</td>
<td>18 da.</td>
<td>M</td>
<td>L</td>
<td>CAVV, VSD, CT, PA, PDA, SLL, SL</td>
</tr>
<tr>
<td>19562</td>
<td>7½ mo.</td>
<td>M</td>
<td>L</td>
<td>ASVR, VSD, CT, TGV, PA, APVR, SLL, TS, TL</td>
</tr>
<tr>
<td>19562</td>
<td>15 hr.</td>
<td>F</td>
<td>D</td>
<td>ASD, TS</td>
</tr>
<tr>
<td>19562</td>
<td>Prem.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, VSD, PDA, APVR, TS, TL</td>
</tr>
<tr>
<td>19562</td>
<td>5 mo.</td>
<td>M</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, CB, TGV, PS, SLL</td>
</tr>
<tr>
<td>19562</td>
<td>36 hr.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, CB, TA, APVR</td>
</tr>
<tr>
<td>1957⁺</td>
<td>2½ yr.</td>
<td>F</td>
<td>D</td>
<td>ASD, ASVR, CAVV, VSD, TGV, PS, APVR, SLL, TL</td>
</tr>
<tr>
<td>1957⁺</td>
<td>6 da.</td>
<td>F</td>
<td>L</td>
<td>ASD, CAVV, TGV, PA, PDA, SLL, SL</td>
</tr>
<tr>
<td>1957⁺</td>
<td>8 mo.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TGV, PDA, APVR, SLL, TS, SL</td>
</tr>
<tr>
<td>1957⁺</td>
<td>20 da.</td>
<td>F</td>
<td>L</td>
<td>ASD, ASVR, CAVV, VSD, SV, TA, APVR, SLL, TS, SL</td>
</tr>
</tbody>
</table>

*A more detailed form of this table has been deposited as Document number 5328 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $2.50 for photocopies or $1.75 for 35 mm. microfilm. Advance payment is required. Make checks payable to: Chief, Photoduplication Service, Library of Congress.

† Refers to case 1 of the authors' series.
‡ Refers to cases 2, 3, 4, and 5, of the authors' series.

ASD = atrial septal defect; ASVR = anomalous systemic venous return; CAVV = common atrioventricular valve; VSD = ventricular septal defect; SV = single ventricle; CB = cor biloculare; CT = cor triloculare; TA = truncus arteriosus; TGV = transposition of great vessels; PA = pulmonary atresia; PS = pulmonary stenosis; PDA = patent ductus arteriosus; APVR = anomalous pulmonary venous return; SLL = supernumerary lobulation of the lungs; TS = transposition of the stomach; TL = transposition of the liver; SL = symmetrical liver.

The defects not listed were either not present or not mentioned in the report.

Tendency toward a symmetrical disposition of the abdominal viscera was strikingly frequent. The liver was transposed in 22 cases, the left lobe was equal in size to the right lobe in 32 cases, larger than the right lobe in 1, and had abnormal lobes in 1. Dextroposition of the stomach occurred in 41 instances and a common mesentery was present in 35 cases. Minor degrees of displacement of the duodenum or pancreas were mentioned infrequently. The presence of a primitive dorsal mesogastrium and absence of the greater omentum was em-
Table 2.—Developmental Horizons with Corresponding Length and Age of the Human Embryo (from Streeter)\(^6\)

<table>
<thead>
<tr>
<th>Horizon</th>
<th>Length of embryo (mm.)</th>
<th>Age of embryo (days)</th>
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<tbody>
<tr>
<td>XI</td>
<td>2.5-3.0</td>
<td>24±1</td>
</tr>
<tr>
<td>XII</td>
<td>3.5</td>
<td>26±1</td>
</tr>
<tr>
<td>XIII</td>
<td>4-5</td>
<td>28±1</td>
</tr>
<tr>
<td>XIV</td>
<td>6-7</td>
<td>28-30</td>
</tr>
<tr>
<td>XV</td>
<td>7-8</td>
<td>31-32</td>
</tr>
<tr>
<td>XVI</td>
<td>9-10</td>
<td>33±1</td>
</tr>
<tr>
<td>XVII</td>
<td>11-13.6</td>
<td>35±1</td>
</tr>
<tr>
<td>XVIII</td>
<td>14-16</td>
<td>37±1</td>
</tr>
</tbody>
</table>

Phenomena in the 2 cases reported by Durie and Wyndham,\(^7\)

There were, in addition, 6 cases of spina bifida or maldevelopment of the vertebral,\(^5\) 52, 75, 84, 86, 87 case 3, case 92 case 100,748 7 cases of anomalies of the branches of the abdominal aorta,\(^8\) 51, 57, 62 cases 4 and 5, 64, 71 7 cases of anomalies of the urogenital system,\(^6\) 46 case 7, 57, 58, 59 case 2, 90, 92 case 24,638, our case 4 3 cases of dextrospinal esophagus,\(^4\) 46 case 7, 52, 69 2 cases of anal atresia,\(^6\) 66, 88 and 1 each of hydrocephalus,\(^7\) barelip,\(^4\) Meckel’s diverticulum,\(^8\) case 3 torticollis,\(^5\) absence of the tail of the pancreas,\(^8\) case 2 absence of the gallbladder and clubbing of the phalanges,\(^6\) case 7 aplasia of the left diaphragm,\(^9\) case 100,748 and stenosis of the rectum.\(^5\)

Recently 4 cases have been reported in which an antemortem diagnosis, confirmed later at autopsy, was made on the basis of the hematologic morphology.\(^33,90\) The presence of Heinz-Ehrlich bodies, Howell-Jolly bodies, target cells, and nucleated red cells in the peripheral blood and siderocytosis as well as erythrocyte hyperplasia in the bone marrow appeared to be a constant feature. Two other cases reported by Willi and Gasser\(^33\) (cases 3 and 5) were diagnosed during life by hematologic studies as well as by angiocardiography and cardiac catheterization.

**Embryology**

The developmental horizons with the corresponding length and age of the human embryo are presented in Table 2.

Early splenic primordia, consisting of a mesenchymal thickening in the dorsal mesogastrium are present when the developing embryo has an ovulatory age of 31 to 35 days (horizons XV-XVII; 9-12 mm.).\(^6\) During the same period, fusion of the anterior and posterior endocardial cushions with the margin of the septum primum causes obliteration of the foramen primum and partitioning of the atrioventricular canal.\(^83,94\) Complete division of the truncus is accomplished at 35 days (horizon XVII; 11-13.6 mm.).\(^95\)

The septum primum can be identified at 26 days (horizon XII; 3.5 mm.). The cephalic portion shortly thereafter undergoes resorption with the formation of the foramen secundum, with the septum secundum making its appearance at 35 days. Division of the ventricle begins at 31 days (horizon XV; 7-8 mm.) as an anteroposterior muscular ridge in the floor of the bulboventricular cavity. Aortic and pulmonary semilunar valves are formed at 35 days. Venous drainage from the cephalic portion of the embryo is via the right and left anterior cardinal veins; these veins join into the common cardinal veins and drain into the sinus venosus.\(^96\) At 33 days (horizon XVI; 9-10 mm.) the left common cardinal vein courses down posteriorly and eventually becomes absorbed to form the coronary sinus.\(^94\) A persistent left superior vena cava results from persistence of the left anterior cardinal vein.

Venous drainage from the caudal portion of the embryo is through 3 groups of veins: the postcardinal, the vitelline, and the omphalomesenteric. The posterior cardinal veins undergo several modifications and are eventually completely replaced in their abdominal course by the subcardial veins. The upper portion contributes to the formation of the inferior vena cava, the lower to the formation of the common iliac veins. The right and left vitelline veins are connected both ventrally and dorsally to the duodenum. When the stomach and duodenum rotate from their mid-sagittal position, which occurs between 31 and 35 days\(^67\) (horizons XV-XVII; 7-13.6 mm.), the blood in the right vitelline vein tends to flow across the ventral anastomotic plexus to the left vitelline vein. The left vitelline vein in turn sends its blood directly to the liver by
way of a dorsal anastomosis with the hepatic end of the persistent part of the right vitelline
vein. Failure of rotation of the stomach and duodenum may account for the persistence of both vitelline veins and their independent drainage into the right atrium. The umbilical veins pass into the liver where they form sinusoids and freely communicate with the vitelline system at 31 days (horizon XV; 7-8 mm.). At 34 days the right umbilical vein atrophies and disappears. The left umbilical vein becomes incorporated into the ductus venosus.

Early pulmonary venous channels are derived from the splanchnic plexus, which drains into the precardinal and postcardinal veins as well as the umbilicovitelline system. At this stage the primordia of the lungs have no direct connection with the heart. To the left of the septum primum an outpouching occurs that extends toward the developing lungs and makes connection with that portion of the splanchnic plexus related to the lungs. As the pulmonary veins are incorporated into the developing left atrium, the main anastomosis of the pulmonary vessels with the cardiac and umbilicovitelline venous systems is interrupted. This development of the pulmonary venous system has been observed in embryos between 21 and 30 days (horizons X-XIV; 2-7 mm.). Abnormal positioning of the atrial septum with displacement of the septum primum to the left may account for anomalous connections of the pulmonary veins with the right atrium.

CASE REPORTS

Case 1

A. L. This 4-month-old Negro male infant was first admitted at 5 days of age because of cyanosis of lips and circumoral region. The family history was noncontributory. The pregnancy and labor were uneventful. The birth weight was 7 pounds, 2 ounces.

The physical findings of significance on admission were limited to the cardiovascular system. There was circumoral cyanosis. The heart rhythm was regular. The first heart sound was of normal intensity and the second sound was markedly accentuated and extraordinarily pure. No murmurs were heard. The blood pressure in the upper extremities was 72/48. The femoral pulsations were present bilaterally.

A hemogram showed a red blood count of 4.9 million per mm. with 20 Gm. of hemoglobin. The white blood count was 14,000 per mm. with 48 per cent neutrophils, 1 per cent eosinophils, and 51 per cent lymphocytes. There were 34 nucleated red blood cells per 100 white blood cells. The urinalysis was negative. An antero-posterior roentgenogram of the chest revealed a heart of normal size. The contour was abnormal with a tipped-up apex and a widening of the great vessel shadow, making a rather sharp angle at its junction with the heart. The vascularity of the lung fields was markedly decreased and the gas bubble in the stomach was on the right side. A barium swallow verified the dextroposition of the stomach without dextrocardia or displacement of the esophagus. An electrocardiogram showed normal sinus rhythm at 150 per minute, P-R interval of 0.12 second, QRS duration of 0.06 second, and right axis deviation. The R wave in V, measured 16 mm., and in V, 8 mm. There was right ventricular preponderance.

The infant's course was characterized by progressive increase in cyanosis terminating in congestive failure and death at 9 months of age.

Pertinent Autopsy Findings. The major portion of the heart lay to the left of the midline. Both lungs had 3 lobes. The right and left lobes of the liver were of approximately equal size, but the inferior vena cava had an abnormal position to the left of the quadrate lobe. The gallbladder lay beneath the right lobe of the liver in a normal position. The stomach was dextroposed, the duodenum passing to the left. The majority of the pancreas lay to the right of the midline with the tail extending to the right and the head lodged in the curve of the duodenum. The ileocecal junction was in the right lower quadrant. A careful search for the spleen failed to reveal any splenic tissue. The splenic artery and vein were also absent.

Description of the Heart. The major portion of the heart (fig. 1) lay in the left chest. The right atrium was somewhat dilated and hypertrophied. There was a right-sided superior vena cava that drained into the right atrium and the right hepatic veins arose from the posterior surface of the liver and entered the right atrium in the position usually occupied by the inferior vena cava. The coronary sinus was not present, but numerous openings of small coronary veins were seen in both atria.

There was a defect in the atrial septum measuring 0.5 cm. in diameter and a large defect existed among all 4 chambers that measured 2 cm. in diameter. The common orifice between the atria and ventricles was guarded by a single large valve.
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Fig. 1. Case 1. Schematic illustration of the heart.

consisting of 3 cusps; a large anterior, a large posterior, and a small lateral cusp.

A rudimentary ventricular septum was present somewhat to the left of its usual position.

Both ventricular walls were hypertrophied, measuring 1 cm. in thickness. There was complete atresia of the pulmonary valve and the pulmonary artery was a fibrous cord, measuring 0.2 mm. in diameter, originating posterior to its normal position and to the left of the aorta. The lumina of the major branches of the pulmonary artery were patent at its bifurcation, and measured 3 mm. in diameter. The ductus arteriosus was patent and united with the left pulmonary artery. The aorta arose anterior and to the right of its usual position, receiving blood from both ventricles. Three semilunar valves were present. The ostia of the coronary arteries were in their usual position. The innominate, left carotid, and left subclavian arteries arose in this order from the arch of the aorta, which descended on the left. All 4 of the pulmonary veins drained into the right atrium. A persistent left superior vena cava and a left-sided inferior vena cava, which received the left hepatic veins, entered a small left atrium.

Microscopic examination showed extramedullary hematopoesis of the liver.

The pathologic diagnoses are summarized in table 1.

Case 2

J. L. This white female infant was first admitted at the age of 10 months because of fever and cough for 3 days. The infant was the product of a first uncomplicated pregnancy and was born at term, weighing 6 pounds, 4 ounces. Cyanosis became apparent at about 4 weeks of age. There had been frequent episodes of fever, respiratory infection, and difficulty in breathing. Both parents were living and well and there was no family history of any serious illnesses.

The physical findings of significance were limited to the cardiovascular system. Cyanosis and clubbing of the fingers and toes were present. There was a slight right precordial bulge, the point of maximum intensity was in the fifth right intercostal space and the rhythm was regular. The blood pressure was not recorded. There was a harsh systolic murmur heard best over the apex and that extended throughout systole. The murmur was transmitted to both axillae, the back, and the entire precordium. Diastole was clear. There were good femoral pulses.

Urinalysis was negative. The hemoglobin was 14.0 Gm. per 100 ml., the leukocyte count was 26,000 per mm.² with 38 per cent polymorphonuclear cells and 62 per cent lymphocytes. An anteroposterior roentgenogram of the chest revealed a heart to be on the right and not enlarged. There was straightening of the left border in the position usually occupied by the right atrium in a dextrocardia, and the great vessel shadow at the base was narrowed. There was slight decrease in the vascularity of the lung fields. The liver was on the left side of the abdomen. An electrocardiogram revealed regular sinus rhythm with a rate of 155 per minute and a P-R interval of 0.15 second. The P waves in lead I were inverted. In aV₃ the main deflection was upright and the T waves were diphasic. The QRS complex was diphasic in aV₃ with inverted T waves. The infant's condition progressively deteriorated and she died at 2½ years of age.

Pertinent Autopsy Findings. The major portion of the heart lay on the right side of the thorax. The left lung was divided into 3 lobes with an additional small accessory lobe. The right lung was normally lobulated. The larger lobe of the liver was on the left side of the abdomen as was the gallbladder. The stomach was on the left side. The cecum and appendix were
located in the left iliac fossa. No spleen or splenic vessels were identified.

Description of the Heart. The heart (fig. 2) and lungs together weighed 375 Gm. The apex of the heart was on the right side of the thorax. There was a functional single atrium, the atrial septum being formed by the septum primum, which was 1 cm. in length. No septum secundum was present. The superior vena cava drained into the inferior portion of the right side of the atrium. Two left hepatic veins drained separately into the inferior portion and left side of the atrium. The coronary sinus was absent. There was a common atrioventricular orifice guarded by a single valve having 3 cusps consisting of a large anterior, a posterior, and a small lateral cusp. A rudimentary ventricular septum divided the heart into a diminutive right ventricle from which the aorta arose, and a larger left ventricle from which the pulmonary artery arose. The pulmonary valve was bicuspid with marked pulmonary stenosis. The aortic valve was formed by 3 cusps and both coronary arteries were present. The vessels of the right-sided aortic arch were normally situated for a dextrocardia, the right subclavian, right common carotid, and the innominate arteries arising in that order from right to left. The ductus arteriosus was closed. Two pulmonary veins drained the right lung and entered the right side of the atrium separately. Only 1 small pulmonary vein drained the left lung and this vessel entered the right side of the atrium posteriorly.

Microscopic examination revealed extramedullary hematopoiesis of the liver and lymphoid hyperplasia of the lymphatic tissues.

The details of the pathologic findings are summarized in table 1.

Case 3

M.H. This Negro female infant was the product of a normal full-term pregnancy and normal delivery. The birth weight was 6 pounds, 10 ounces. Cyanosis was first noticed 6 hours after delivery; it gradually became more intense and on the second day of life the infant was admitted to the hospital. The family history was noncontributory.

The relevant physical findings included moderate cyanosis, heart sounds of normal quality and intensity without murmurs, and a liver palpable 2 cm. below the right costal margin. The hemoglobin was 20.2 Gm. per 100 ml.; hematocrit reading 68 per cent; the leukocyte count 5,200 per mm.²; polymorphonuclear cells 38 per cent, lymphocytes 55 per cent, and monocytes 7 per cent. The platelets were adequate. There were 244 nucleated red cells per 100 white cells. The sickling preparation was negative. An electrocardiogram revealed regular sinus rhythm, rate 150 per minute, P-R interval 0.13 second, QRS duration 0.05 second. There were prominent P waves in the right-sided chest leads and low T waves in the limb leads. Four days after admission she became more cyanotic, developed respiratory distress, and died.

Pertinent Autopsy Findings. The heart was in the midline being partially displaced to the right side with the apex directed to the left. The left lung consisted of 2 large and 2 smaller accessory lobes. The liver occupied a central position beneath the diaphragm, the left lobe being almost as large as the right lobe. The gallbladder was in its normal location on the right side. The stomach and entire gastrointestinal tract were normally located. Careful search for the spleen revealed no trace of splenic tissue or splenic vessels.

Description of the Heart. The heart (fig. 3) weighed 20 Gm. There was a functional single atrium. The septum primum was well formed but there was only a lacy vestige of the margin of the septum secundum leaving a large atrial septal defect measuring 1.4 by 1.1 cm. Both superior and inferior venae cavae were large and drained into the right side of the atrium. The coronary sinus was present. A common atrioventricular valve measured 4.6 cm. and consisted of 3 cusps: a large anterior cusp, a smaller posterior cusp over the crest of the ventricular septum, and a small lateral cusp. The ventricular septum was normally formed. The great vessels were transposed, the aorta arising from the right ventricle. The coronary artery orifices were normally situated. The pulmonary artery was represented by a thin fibrous strand of tissue that terminated in the ductus arteriosus. There was complete atresia of the pulmonary valve. A large patent ductus arteriosus bearing a normal relationship to the vessels of the left-sided aortic arch communicated with the right and left pulmonary arteries. All the pulmonary veins were extraordinarily small and drained into
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the left side of the atrium. The pulmonary vein orifices were atrietic.

Microscopic examination showed extramedullary hematopoiesis of the liver and the bone marrow contained an increased number of nucleated red cells. There was a moderate degree of lymphoid hyperplasia.

Table 1 summarizes the autopsy findings.

Case 4

M.C. This 7 1/2-month-old Negro female infant was first admitted at 6 months of age, because of a respiratory infection of 1 week's duration. The family history was nonecontributory.

Physical findings of significance were related to the cardiovascular system. The pulse rate was 160 and the respiratory rate was 56 per minute. There were circumoral cyanosis and clubbing of the fingers. The point of maximal impulse of the heart was in the fourth intercostal space in the left midclavicular line. The rhythm was regular, the heart sounds were of normal intensity, and a systolic murmur was heard in the left precordial, apical, and third intercostal regions. The blood pressure in the upper extremities was 90/65 and there were good femoral pulsations.

A hemogram revealed a hemoglobin of 8.7 Gm. per 100 ml., a hematocrit of 35 per cent, a leukocyte count of 11,700, with 32 per cent segmented cells, 2 per cent band forms, 62 per cent lymphocytes, and 2 per cent eosinophils. The platelet count was normal. The erythrocytes showed a moderate hypochromia, marked anisocytosis, poikilocytosis, many target cells, moderate polychromasia, and 119 nucleated erythrocytes per 100 leukocytes. No sickling was seen. An anteroposterior roentgenogram of the chest revealed the heart to be somewhat enlarged, especially to the left, with a globular contour and relative narrowing of the great vessel shadow at the base. In

Fig. 4. Case 4. Schematic illustration of the heart.

the left anterior oblique position there was a slight bulge in the anterior contour in the position usually occupied by the right atrium and definite enlargement of the left ventricle posteriorly. A clear aortic window was not seen. The vascular markings of the lungs were moderately increased. On fluoroscopic examination the pulmonary markings appeared decreased, with right ventricular and possibly right atrial enlargement. Dextroposition of the stomach was demonstrated by an upper gastrointestinal series. An electrocardiogram showed regular sinus rhythm, a pulse rate of 150 per minute, P-R interval of 0.12 second, and QRS duration of 0.05 second. There were fairly equal R and S waves in V, and upright T waves. The infant's condition deteriorated and she died at 7 months of age.

Pertinent Autopsy Findings. The heart together with the lungs weighed 276 Gm. The right lung was normally lobulated but the left lung had 3 lobes. The liver was markedly enlarged and overlaid the major portion of the dextroposed stomach. The left lobe was larger than the right lobe. The vermiform appendix was located in the right iliac fossa and the cecum was elongated and mobile. No spleen or splenic vessels were identified. There were 2 ureters arising from the left kidney.

Description of the Heart. The heart (fig. 4) was on the left side. There was a functional single atrium, the only evidence of an atrial septum being a septum primum, which was markedly displaced to the left. It was broad on the posterior aspect and narrow on the anterior aspect. There was no septum secundum. The superior vena cava was in its usual position and drained into the right side of the single atrium; the inferior vena cava drained into its left side. The coronary sinus was absent. There was a common atrioventricular orifice measuring 8.6 cm. consisting of 5 cusps, 1 very large anterior cusp, 1 smaller posterior cusp, and 3 additional diminutive cusps, all of which appeared to be displaced to the right in a clockwise direction. The endocardial cushions were displaced to the right and were represented by the 2 larger cusps. Both great vessels lay side by side, the aorta arising from the right side and the pulmonary artery from the left side of the single ventricle. The aortic and pulmonary valves measured 2.9 cm. and 3.3 cm. respectively, each consisting of 3 cusps and having 3 semilunar valves. There was no division of the ventricles except by a small muscular ridge that arched anteriorly between the orifices of the great vessels; no rudimentary outlet chamber was present. The ductus arteriosus was patent and measured 0.2 cm. in diameter at its pulmonary orifice. The vessels of the left-sided aortic arch were normally situated. All the pulmonary veins converged into
a single vessel that drained into the left side of the atrium.

Microscopic examination showed extramedullary hematopoiesis of the liver and an increased number of nucleated red cells in the sections of the bone marrow. There was a moderate degree of lymphoid hyperplasia.

The pathologic diagnoses are summarized in table 1.

Case 5
K.W. This white female infant was admitted to the hospital at 3 weeks of age because of cyanosis since birth. There was no relevant family history. The birth weight was 9 pounds and the delivery was uneventful. Respiratory difficulty and cyanosis became progressively worse until admission.

The relevant physical findings were as follows: The heart was regular, there was cardiac enlargement to the left, and a harsh systolic murmur was heard over the entire precordium, loudest over the left lower sternum. There was a questionable systolic thrill in the fourth left intercostal space. The peripheral pulses were weak. The blood pressure was not recorded. There was 2 plus pitting edema of the lower extremities and puffiness of the eyes and face. The liver was palpable 5 cm. below the right costal margin. The hemoglobin was 14.4 Gm. per 100 ml., red blood cell count 4.88 million per mm.³, white blood cell count 16,678 per mm.³ with a differential count of 66 per cent polymorphonuclear cells, 32 per cent lymphocytes, and 2 per cent monocytes. There were 62 nucleated red cells per 100 white blood cells. An anteroposterior roentgenogram of the chest revealed the heart to be enlarged both to the left and to the right with a tipped-up apex and a widened great vessel shadow, which made an abrupt angle at its junction with the heart. The vascularity of the lung fields was moderately decreased. An electrocardiogram revealed a regular sinus rhythm of 150 per minute and a P-R interval of 0.12 second. The P waves were flat in lead I and upright in leads II and III. There was marked left axis deviation. The T waves were flat in lead I and slightly upright in leads II and III. The precordial leads were normal. The patient was digitalized and operation was planned for the morning following admission, but during the night the patient died.

Pertinent Autopsy Findings. The heart lay on the left side and each lung had 3 lobes. The liver was central in position, the largest lobe being on the right. The gallbladder was in a central position. The stomach was on the right side under the liver. The duodenum consisted of 1 small loop that was short, joining quickly with the jejunum. The head of the pancreas was on the left side and the tail extended to the right. The small bowel appeared normal but was on the right side of the abdomen with the ascending colon being completely mobile and to the left of the small bowel. No spleen or splenic vessels were found in the abdominal cavity.

Description of the Heart. The heart (fig. 5) and lungs together weighed 210 Gm. There was a functional single atrium with no septum secundum. The only evidence of an atrial septum was a triangular-shaped septum primum, which was normal in position with its base inserted dorsally and the apex ventrally in the midline of the common cavity formed by the 2 atria. The superior vena cava was in its usual position and the inferior vena cava in addition to a persistent left superior vena cava drained into the left side of the septum primum. The coronary sinus was absent. There was a common atroventricular valve consisting of 3 cusps, a large anterior, a large posterior, and a small lateral cusp. The single atrium communicated by way of the common atroventricular orifice with a single ventricle that in turn communicated with a rudimentary outlet chamber from which a persistent truncus arteriosus arose. The valve was formed by 3 cusps; both coronary arteries were present. There was no main pulmonary artery; the right and left pulmonary arteries arose directly from the common trunk and the ductus arteriosus was absent. The vessels of the left-sided arch were normally situated. All pulmonary veins converged into 1 large vessel that drained into the atrium to the right of the septum primum.

Microscopic examination of the liver showed a slight degree of extramedullary hematopoiesis.

A summary of the autopsy findings is in table 1.

Discussion of Cases Reported
These 5 cases are remarkable in their similarity both to each other and to those previously reported...
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in the literature.

Levoaerdia was present in 4 and dextrocardia in 1. A functional single atrium was present in all cases and was associated with a single ventricle in 1. A common atrioventricular valve as well as anomalies of the cono-truncus region were features common to all cases, a truncus arteriosus occurring in 1 and transposition of the great vessels in 4. Of the latter, 2 were associated with pulmonary atresia, 1 with pulmonary stenosis, and 1 with a normal pulmonary artery. Total anomalous pulmonary venous return was present in 3 instances; in 1, the orifices of the pulmonary veins were atretic; and in 1, a single common pulmonary vein drained into the left side of the common atrium. The systemic venous return was anomalous in 4 cases; in case 1 a persistent left superior vena cava as well as a left inferior vena cava, which received 2 hepatic veins, drained into the left side of the atrium; in case 2 the superior vena cava as well as 2 hepatic veins drained separately into the left atrium while the inferior vena cava joined the right atrium; in case 4 the inferior vena cava drained into the left atrium, while in case 5 a persistent left superior vena cava as well as the inferior vena cava drained into the left atrium. The coronary sinus was absent in cases 1 and 4.

Supernumerary lobulation of the left lung as well as partial situs inversus with a marked tendency toward bilateral symmetry was common to all cases. Extramedullary hematopoiesis in the liver as well as erythroid hyperplasia of the bone marrow were also constant findings. A normoblastemia of the peripheral blood was seen in cases 1, 3, 4, and 5.

Four cases occurred at Children's Hospital, Washington, D. C., between 1951 and 1955 in an autopsy series of 676. One incompletely documented case of levocardia and partial situs inversus associated with splenic agenesis came to autopsy in 1948, making a total of 5 cases in an autopsy series of 3,526 during the period 1932 to 1955.

Electrocardiography. Vector analyses were done on the electrocardiograms by Dr. Robert Grant. Although electric forces from the atria were directed downward in cases 2, 3, and 5 and apparently also in case 1 rather than obliquely as when the atria are entirely normal, there was no evidence of atrial inversion. The electric forces reflected instead the anatomic symmetry that was present. The QRS forces were directed upward and to the right in case 2 suggesting abnormality of the crista supraventricularis, which was in this case hypertrophied. They were directed to the left in case 5, but the absence of the crista supraventricularis and presence of a single ventricle in this case could not be discerned from the contour of the vector loop.

DISCUSSION

Examples of splenic agenesis with malformations of the heart and great vessels together with partial situs inversus fall into a fairly uniform anatomic pattern.

Agenesis of the spleen was considered by Putschar28 to be the result of arrested development. Studies of the cardiac malformations that occur in association with splenic agenesis reveal anomalies of structures that would be developing during early splenic organogenesis. Ivemark46 in an extensive study drew the general conclusion that a teratogenic action on the heart takes place simultaneously with resulting developmental arrest.

Gasser and Willi81 considered the underlying causative mechanism to be an endogenous lethal factor.

The problem of partial or total situs inversus with a constant tendency toward visceral symmetry has been discussed by Toldt,19 Geipel,5 Geipel,100 and Tondriy101 and was extensively studied by Törgersen.102-104

Forgacs105 postulated a theory for the cardiac malformations associated with abdominal situs inversus. He made the observation that when either the abdominal viscera or the heart is transposed there is usually inversion of the atria. The right horn of the sinus venosus grows rapidly in early embryonic life, eventually forming part of the right atrium. Abdominal venous channels shunt blood from the left side of the abdomen to the opposite side, so that the venous drainage is to the right horn of the sinus venosus via the vena hepatis communis. Reversal of the normal relationship between the heart and liver would cause a reversal of the process with the left horn of the sinus venosus receiving the venous return from the abdomen, and the inferior vena cava eventually terminating in the left atrium. Forgacs therefore postulated that the associated malformations result as a faulty development of the cardiac septa or of an incomplete torsion of the aortopulmonary septum in an attempt to divert the venous return into the correct outflow channel.

Several investigators have stressed the importance of spiralling blood currents as being
responsible for the septation of the cono-truncus; Doerr postulated a "conflict zone" or intimate relationship between the cono-truncus and the atrioventricular canal in an attempt to explain simultaneous developmental errors occurring at both sites. Atrioventricular anomalies are always associated with malformation of the cono-truncus region in the series under discussion.

From a study of monographs, models, sections, and serial photomicrographs at the Carnegie Institute of Washington, Department of Embryology, the most probable explanation for this combination of lesions appears to be a factor with a wide lethal range operating at about an ovulatory age of 24 days (horizon XI; 2.5-3.0 mm.). This factor in its mildest form causes only a suppression of the development of the spleen, as in Ivemark's case A-25-167 from the Boston Children's Hospital but in its most severe form an arrest in the development of the entire germinal bed of the mesoblastic surface of the coelomic cavity (Streeter, fig. 3 XI, p. 29). As a result there is suppression of the development of the spleen and omental bursa, arrest in the development of the primitive heart tube, and, in particular, arrest in the development of the dorsal and ventral mesenteries so that the structures derived from the gut develop in situ in a symmetrical manner instead of early evidencing the asymmetry that appears to be initiated by a break in the ventral mesentery. A common mesentery and varying degrees of malrotation of the viscera ensue. A simple persistence of symmetry rather than a suppression of leftness as suggested by Putschar and Manion would seem to be the basic disturbance, since the omental bursa that develops in the right dorsal mesogastrium opposite the primordium of the spleen has been reported absent in several of the more carefully documented cases; it seems possible that its absence has been overlooked in other instances.

It seems unlikely that resulting abnormal blood currents influence the development of the heart (Forgacs), since symmetry and partial situs inversus of the abdominal viscera can occur with a normal heart, and a malformed heart, in the absence of anomalies of the abdominal viscera other than agenesis of the spleen. In such instances the lethal factor would seem to be of only moderate severity. The heart may be profoundly affected, resulting in a primitive structure consisting of a single atrium, single ventricle, and truncus arteriosus as in the authors' case 5; not affected at all, as in the case cited by Ivemark; or affected so that portions of it proceed to develop normally while other portions are arrested, as in case 3. It seems most likely that it is the initial degree of severity of the lethal factor that determines the outcome rather than an arrest of the atrioventricular region resulting in trunco-conal abnormalities as suggested by Ivemark, since an atrioventricularis communis without splenic agenesis occurs more often without than with an anomaly of the trunco-conal region.

This factor would seem to affect specifically the germinal bed of the mesoblastic surface of the coelom. The structures derived from the gut, although symmetrical and malposed, including instances where the dorsal pancreas develops separately from the ventral pancreas, rarely show arrest in their development.

The timing of the operation of this factor at 24 to 28 days raises the question whether it is a by-product of a faulty or abortive ovulation released into the blood stream at the time ovulation would have taken place had a pregnancy not occurred. From a practical standpoint, a study of pregnant women 2 weeks after their first missed menstrual period might result in a discovery of this factor and ultimately lead to preventive measures.

**Summary**

The literature on splenic agenesis associated with congenital malformations of the heart has been reviewed and 5 additional cases have been reported. The current theories of etiology have been discussed. Certain postulations concerning the probable explanation for the combination of lesions found in this syndrome, have been advanced.
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ADDENDUM

Since the preparation of this paper 18 additional cases of congenital malformations of the heart associated with splenic agenesis have been reported and 1 additional case of splenic agenesis in an infant without a cardiac malformation.

SUMMARIO IN INTERLINGUA

Es presentate un revista del litteratura relative a agenese splenic occurrente in association con congenite malformaciones del corde. Es reportate 5 casos additional. Le currente theorias etiologic es discutite. Certe postulationes es facite concernente le explication probabile del occurrentia combinata del lesiones que es incontrate in iste syndrome.

REFERENCES


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GILBERT, NISHIMURA, AND WEDUM


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