A PATHOLOGICAL STUDY OF 32 AUTOPSY CASES OF
THE SO-CALLED SPLENIC AGENESIS SYNDROME

BY

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ABSTRACT

A total of thirty-two autopsy cases of the so-called splenic agenesis syndrome
(or Ivemark's syndrome) were collected and studied pathomorphologically. The
splenic agenesis syndrome is composed of three main elements; namely, congenital
splenic agenesis, characteristic anomalies of the cardiovascular system, and
abdominal heterotaxy with right-sidedness of the visceral organs. The cases were
classified into three types according to severity of these anomalies; complete
(having all these three components), incomplete (asplenia and one of the other two),
and simple (only congenital absence of the spleen). Anomalous pulmonary venous
return and abnormality of the efferent hepatic veins, both of which were occa-
sionally seen associated in this syndrome, seem to give some influence on the
survival period of patients.

As for the secondary changes caused by these cardiovascular anomalies, mild
hypoplasia of the media, fibrous thickening of the intima, and thrombus formation
in the lumen due to stenosis or atresia of the pulmonary trunk were frequently
found in the small pulmonary arteries. Various changes of the so-called morbus
cæruleus were observed in the liver, kidney, etc.

As a possible, compensatory reaction to congenital absence of the spleen, the
lymph follicles were found appearing in the bone marrow about one year after
birth. Infectious changes were observed, as the direct cause of death, in five cases,
all of which were below one year of age.

INTRODUCTION

It is known that congenital agenesis of the spleen is frequently associated
with cardiovascular anomalies1). According to Ivemark's review2), this fact
was first described independently by Martín and by Breschet, in 1826. After
that, many reports or reviews have been made; for example, by Kugel (1932)
and Bähr (1932) about localization abnormality of organs, by Putschar (1934)
on atresia or stenosis of pulmonary trunk, etc.3) Since Ivemark studied and
reported in detail various cardiovascular anomalies with asplenia in 1955,
using 14 autopsy cases, these syndrome complexes have been summed up as
one entity and become to be called splenic agenesis syndrome or Ivemark's

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syndrome\textsuperscript{4–7}). However, detailed definition of this syndrome, as well as its characteristic histological changes occurring secondarily, have not been investigated nor reported yet as far as is known to me. In the present series of work, 32 autopsy cases of congenital agenesis of the spleen have been collected and studied, the result of which is reported here in this paper with emphasis on its definition and histological changes of various organs. Classification of this syndrome, secondary changes to its cardiovascular anomalies, and some influence of congenital absence of the spleen to the host are also discussed.

\textbf{Materials and Methods}

Thirty-two autopsy cases of congenital agenesis of the spleen were studied among which 27 were the ones reported previously\textsuperscript{5). Thirty were associated with cardiovascular anomalies and the other two were not. As for their sources, 26 cases were collected at the Department of Pathology, Tokyo Women's Medical College (with WMC number in this paper), three were from the Department of Pathology, Tokyo Medical and Dental University (with SN number), and one from the Department of Pathology, Japan Red Cross Center Hospital (with RSN number). Two asplenia cases without other anomaly were WMC-4253 and WMC-1338. Many cases of congenital cardiovascular anomalies were studied as controls, including one particular case (WMC-5719) with characteristic cardiovascular anomalies and visceral heterotaxia, which were quite similar to those of splenic agenesis but with definite formation of the spleen.

Both macro- and microscopic examinations were made on each case with careful reference to the autopsy record. Histological examination was made with as many important organs or tissues as possible, mainly using Masson's trichrome staining technique. Hematoxylin-Eosin, periodic acid-Schiff, Elastica-Van Gieson, Berlin Blue, Giemsa, and silver impregnation for reticulin staining were also used in cases of necessity. In histological examination, various tissues of reticuloendothelial system were particularly studied, including the bone marrow, lymph node, palatine tonsil, esophageal wall, mucosal lymph apparatus of gastro-intestinal tract, appendix vermiformis, intrapulmonary lymph apparatus, and thymus.

Since the pathomorphological findings seemed to be closely related to the age of each patient, the cases were classified into two major groups: one consisting of infants of less than one year of age (21 cases) and the other of children of one year or more in age (9 cases), and comparison between them was made as a method of analysis.
Table 1. Cardiovascular anomalies in the child group (one year or more of age)

<table>
<thead>
<tr>
<th>Autopsy No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>A-V region</th>
<th>C-T region</th>
<th>Pulmonary trunk</th>
<th>Anomalous pulmonary venous return</th>
<th>Patent ductus arteriosus</th>
<th>Abnormal efferent hepatic veins</th>
<th>Abdominal heterotaxy</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMC-5378</td>
<td>1</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td>T (R. atria)</td>
<td>0</td>
<td>-</td>
<td>+</td>
<td>Blalock's operation</td>
</tr>
<tr>
<td>WMC-1051</td>
<td>3</td>
<td>m</td>
<td>T</td>
<td>S</td>
<td>-</td>
<td></td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>Blalock's operation, tricuspid atresia</td>
</tr>
<tr>
<td>WMC-5449</td>
<td>3</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td></td>
<td>0</td>
<td>-</td>
<td>+</td>
<td>Waterston's operation, accessory liver</td>
</tr>
<tr>
<td>WMC-4913</td>
<td>4</td>
<td>f</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>WMC-4976</td>
<td>4</td>
<td>f</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td></td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>WMC-1788</td>
<td>4</td>
<td>f</td>
<td>T</td>
<td>S</td>
<td>T (Sup. V.C.)</td>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Blalock's operation, mitral atresia, coronary arteries arisen from the same cusp</td>
</tr>
<tr>
<td>WMC-3077</td>
<td>5</td>
<td>f</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td></td>
<td>0</td>
<td>-</td>
<td>+</td>
<td>Softening of the brain</td>
</tr>
<tr>
<td>WMC-763</td>
<td>6</td>
<td>f</td>
<td>C</td>
<td>?</td>
<td>A</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>WMC-1216</td>
<td>9</td>
<td>f</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td></td>
<td>0</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A-V region = atrio-ventricular region, C = common atrioventricular canal, C-T region = cono-truncus region, T = transposition of the great vessels, S = stenosis, A = atresia, T (anomalous pulmonary venous return) = total, P = partial, Sup. V.C. = superior vena cava, Inf. V.C. = inferior vena cava, Portal V. = portal vein, O = obstruction. Abdominal heterotaxy includes partial or complete heterotaxy.
<table>
<thead>
<tr>
<th>Autopsy No.</th>
<th>Age</th>
<th>Sex</th>
<th>A-V region</th>
<th>C-T region</th>
<th>Pulmonary trunk</th>
<th>Anomalous pulmonary venous return</th>
<th>Patent ductus arteriosus</th>
<th>Abnormal efferent hepatic veins</th>
<th>Abdominal heterotaxy</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SN -4097</td>
<td>3 days</td>
<td>f</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>T (Inf. V.C.)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>WMC-1780</td>
<td>9 days</td>
<td>f</td>
<td>C</td>
<td>T</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Aortic stenosis, defect of the right coronary artery, hemorrhagic pneumonia</td>
</tr>
<tr>
<td>RSN- 2182</td>
<td>11 days</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td>T (R. atra)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Annular pancreas forming duodenal stenosis</td>
</tr>
<tr>
<td>WMC-2999</td>
<td>21 days</td>
<td>f</td>
<td>C</td>
<td>?</td>
<td>A</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Horse-shoe like adrenal</td>
</tr>
<tr>
<td>WMC-1836</td>
<td>27 days</td>
<td>m</td>
<td>T</td>
<td>S</td>
<td>T (Sup, V.C. Portal V.)</td>
<td>None</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Mitral atresia</td>
</tr>
<tr>
<td>WMC-2928</td>
<td>1 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>T (Sup. V.C.)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Septicemia</td>
</tr>
<tr>
<td>WMC-5333</td>
<td>1.5 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>P (Sup. V.C.)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Esophageal hiatal hernia, aspiration pneumonia</td>
</tr>
<tr>
<td>SN- 3277</td>
<td>1.5 mo</td>
<td>m</td>
<td>C</td>
<td>?</td>
<td>S</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>WMC-5397</td>
<td>2 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Esophageal hiatal hernia, postoperative infection</td>
</tr>
<tr>
<td>WMC-2804</td>
<td>2 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>T (Sup. V.C.)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>SN- 2989</td>
<td>3 mo</td>
<td>m</td>
<td>C</td>
<td>?</td>
<td>A</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Blalock's operation</td>
</tr>
<tr>
<td>WMC-2337</td>
<td>3 mo</td>
<td>f</td>
<td>C</td>
<td>?</td>
<td>S</td>
<td>T (Sup. V.C.)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Coronary arteries arisen from the same cusp</td>
</tr>
<tr>
<td>WMC-3345</td>
<td>4 mo</td>
<td>m</td>
<td>C</td>
<td>?</td>
<td>A</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>WMC-2306</td>
<td>4 mo</td>
<td>m</td>
<td>C</td>
<td>Truncus arteriosus</td>
<td>S</td>
<td>T (Inf. V.C.)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Esophageal hiatal hernia, purulent meningitis</td>
</tr>
<tr>
<td>WMC-5847</td>
<td>4 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td>T (Sup. V.C.)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>WMC-1725</td>
<td>3 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Tricuspid atresia, massive softening of the brain</td>
</tr>
<tr>
<td>WMC-2778</td>
<td>5 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>T (Portal V.)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>WMC-1255</td>
<td>6 mo</td>
<td>f</td>
<td>?</td>
<td>S</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>WMC-5739</td>
<td>8 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td>T (R. atra)</td>
<td>None</td>
<td>-</td>
<td>+</td>
<td>Blalock's operation</td>
</tr>
<tr>
<td>WMC- 953</td>
<td>9 mo</td>
<td>m</td>
<td>C</td>
<td>T</td>
<td>S</td>
<td>T (R. atra)</td>
<td>?</td>
<td>-</td>
<td>+</td>
<td>Single hepatic vein pouring into the r. atra, Inf. V.C. puring into the l. atra</td>
</tr>
<tr>
<td>WMC-1880</td>
<td>11 mo</td>
<td>f</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** A-V region = atrio-ventricular region, C = common atrioventricular canal, C-T region = cono-truncus region, T = transposition of the great vessels, S = stenosis, A = atresia, T (anomalous pulmonary venous return) = total, P = partial, Sup. V.C. = superior vena cava, Inf. V.C. = inferior vena cava, Portal V. = portal vein, O = obstruction. Abdominal heterotaxy includes partial or complete heterotaxy.
Table 3. Summary of cardiovascular anomalies

<table>
<thead>
<tr>
<th></th>
<th>Child group (9 cases)</th>
<th>Infant group (21 cases)</th>
<th>Total (30 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent common atroventricular canal</td>
<td>7</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Transposition of the great vessels</td>
<td>8</td>
<td>14 (unknown 6)</td>
<td>22</td>
</tr>
<tr>
<td>Stenosis or atresia of the pulmonary trunk</td>
<td>9</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Total or partial anomalous pulmonary venous return</td>
<td>2</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>3</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Shunt preservation between aortic system and pulmonary artery due to patent ductus arteriosus or surgery</td>
<td>6</td>
<td>18</td>
<td>24</td>
</tr>
</tbody>
</table>

Number in each column expresses the total number of positive cases.

RESULTS

The detail of 30 autopsy cases, collected as splenic agenesis syndrome with more or less other anomalies, are shown in Table 1 and 2. The child group (one year or more of age) consisted of nine cases (three males and six females), and the infant group (less than one year of age) of 21 cases (15 males and six females).

Table 3 shows the types and distributions of cardiovascular anomalies seen in these cases. In almost all cases, common atroventricular canal in the atrio-ventricular region, transposition of the great vessels of the cono-truncus region, and atresia or stenosis of the pulmonary trunk were found in the cardiovascular system (Figs. 1, 2, 3, and 4). These did not show any relation to the age of patients. Tricuspid atresia, mitral atresia, persistent truncus arteriosus, and absence of transposition of the great vessels were also observed occasionally. In consequence, the heart did show the figure to be called cor bilocular or cor triloculare with hypoplastic tendency of the right ventricle, since the atrial septum was only rudimentary and ventricular one was also largely defected.

There were often total or partial anomalous pulmonary venous return, which was more predominant in the infant group. The shunt was found actually set almost between the aortic and pulmonary arterial systems compensating stenosis or atresia of the pulmonary trunk in way of patent ductus arteriosus or shunt operation (Blalock’s or Waterston’s operations), in both of the child and infant groups.

Abnormal symmetry with right-sidedness and location abnormality of blood vessels and visceral organs, seen in our cases, are shown in Table 4. Bilateral superior venae cavae were persistent in most of the cases. Bilateral
Table 4. Abnormal symmetry and heterotaxy of vascular system and visceral organs

<table>
<thead>
<tr>
<th></th>
<th>Child group (9 cases)</th>
<th>Infant group (21 cases)</th>
<th>Total (30 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent bilateral superior vena cavae</td>
<td>6</td>
<td>13 (unknown 2)</td>
<td>19</td>
</tr>
<tr>
<td>Three-lobation of bilateral lungs</td>
<td>8 (unknown 1)</td>
<td>15 (unknown 2)</td>
<td>23</td>
</tr>
<tr>
<td>Complete or partial abdominal heterotaxy</td>
<td>7</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Abnormality of efferent hepatic veins</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Number in each column expresses the total number of positive cases.

three-lobation of the lung was also almost unexceptionally present. Abnormality of the efferent hepatic veins (persistent bilateral efferent hepatic veins) was seen less frequently in the child group, being associated with abnormal distribution of the inferior vena cava. Abnormalities of the location of visceral organs, including symmetric or left-sided liver, complete or partial situs inversus of the gastrointestinal tract, that of the pancreas, etc., were present in most of the cases, although their degree varied greatly from case to case. Figs. 4 and 5 show samples of abnormality of the vascular system and abnormal distribution of the intraabdominal arteries. As shown in Fig. 5, the splenic artery was found drawing a loop and ending at the pancreas-tail in one particular case.

As the secondary changes caused by the above described cardiovascular anomalies, medial hypoplasia, fibrous, intimal thickening, and organized or fresh thrombus formation, which was predominant at the branching portion, were seen in the small pulmonary artery (Figs. 6 and 7). These changes were more frequently seen in the child group (Table 5), except for the fresh thrombus formation which was occasionally found also in the infant group. Since abundant capillary formation was not present and cellular element was scanty, the organized thrombi, which were also seen in the present cases occasionally, could easily be differentiated from the so-called glomoid lesion\(^{8,10}\) which was reported to be seen occasionally in congenital heart disease, or from the “Sperrarterien”\(^{11}\) which is said to be rarely found in immature infants. The status to be called morbus caeruleus\(^{12-15}\) which is thought to appear in cases of cyanotic congenital heart anomalies, was frequently seen in the liver, kidney, and mucosal or submucosal layer of the gastro-intestinal tract, particularly in the child group. Namely, slight fibrosis around the portal triad and centrilobular or diffuse fatty change, of a mild degree, in the liver (Fig. 8), swelling and sclerosis of the glomeruli in the kidney (Fig. 9), and slight fibrosis of mucosal or submucosal layer of the gastro-intestinal tract were the findings considered as morbus caeruleus.
Table 5. Frequency of fresh or old thrombus formation in the small pulmonary arteries

<table>
<thead>
<tr>
<th></th>
<th>Child group (9 cases)</th>
<th>Infant group (21 cases)</th>
<th>Total (30 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent thrombus formation</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Old thrombus or organized thrombus formation</td>
<td>8</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Number in each column expresses the total number of positive cases.

Table 6. Frequency of formation of lymph follicles or aggregates of lymphocytes in the bone marrow and lung

<table>
<thead>
<tr>
<th></th>
<th>Child group (9 cases)</th>
<th>Infant group (21 cases)</th>
<th>Total (30 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>7 (unknown 2)</td>
<td>0 (unknown 6)</td>
<td>7</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
<td>6 (unknown 1)</td>
<td>15</td>
</tr>
</tbody>
</table>

Number in each column expresses the total number of positive cases.

These showed a tendency that the longer the survival period of patients, the severer the degree of histological changes.

Some findings related to congenital agenesis of the spleen are shown in Table 6. Multiple lymph follicles were discovered in the bone marrow of all cases of the child group, while they were not found in the infant group at all. They consisted of various types of follicles, including primary follicle, secondary follicle, and a simple cluster of aggregated lymphocytes (Figs. 10, 11, and 12). Active phagocytosis by “starry sky” histiocytes was observed in the germinal centers of secondary follicles (Fig. 13), as well as in the surrounding areas of primary follicles or lymphocyte aggregation. Silver impregnation for reticulin fibers showed the structure of these follicles, and small arteries were also recognized clearly in them (Fig. 14). Cellularity in the bone marrow was rich in degree, in most of the cases. Lymph follicles of various kinds were seen appearing in the peribronchial region of the lung (Fig. 15), particularly in the child group. The thymus was relatively well preserved, showing enough formation of Hassal bodies, but its weight was a little lighter than that of the controls (Fig. 16). Other lymph apparatus, including the palatine tonsil, mucosal lymph apparatus of the gastro-intestinal tract, the appendix vermiformis, and lymph nodes in general, showed more or less hyperplasia, especially in the child group.

As for the direct cause of death, infectious of various kinds were seen in five cases, including hemorrhagic pneumonia in WMC-1780, septicemia in WMC-2928, aspiration pneumonia in SN-3277, postoperative infection in SN-2989, and purulent meningitis in WMC-5847, all of which belonged to
the infant group. In other cases, decompensation of the cardio-pulmonary system was thought to be responsible as the direct cause of death.

**Discussion**

Cardiovascular anomalies, which occur quite often in cases of congenital agenesis of the spleen, are very characteristic in nature\(^2\)\(^4\)\(^5\)\(^6\). In the present study, it was ascertained that common atrio-ventricular canal formation resulting in cor triloculare or cor biloculare, transposition of the great vessels in the cono-truncus region, and atresia or stenosis of the pulmonary trunk were the most common ones (Table 9). Localization abnormality of vessels and visceral organs with unusual symmetry or right-sidedness was also present being associated with the above-mentioned cardiovascular anomalies, such as persistent bilateral superior venae cavae, three-lobation of the bilateral lungs, symmetric or left-sided liver, partial or complete situs inversus of the gastro-intestinal tract, right-sided aortic arch, etc. These localization abnormalities of visceral organs, e.g. median position of the liver and three-lobation of the bilateral lungs, may be the sign of the right-sidedness, as Moller\(^16\) suggested. On the other hand, symmetry\(^17\)\(^18\) of the venous system including persistence of bilateral superior venae cavae and bilateral efferent hepatic veins, perhaps imply the remaining of fetal vascular system. Persistent left superior vena cava corresponds to the left duct of Cuvier\(^19\), and bilateral efferent hepatic veins directly pouring into the cardiac atrias correspond to the bilateral venae revehentes\(^19\) in embryo.

Splenric primordia appears in the dorsal mesogastrium\(^20\)\(^21\) at the same time (in embryo of about 10 mm C.R. length, 5 weeks of gestation) as the critical point of septation of the cardiac tube, embryologically\(^6\). Moreover, the gut begins to rotate at the same time. Thus, development of the spleen naturally is closely related to the positions of blood vessels and visceral organs\(^22\)\(^23\). Any attack on the embryo, which influences the development at this fetal stage, may cause abnormality of the spleen, cardiovascular system, and the whole visceral position. It is acceptable to take these anomaly complexes as one syndrome (splenic agenesis syndrome or Ivemark's syndrome) when the pathogenesis of the above described way is considered\(^2\)\(^7\). There seems to be three major elements in this syndrome, as stated above, and this syndrome can be classified according to the grade of combination of these, as follows:

1) Complete type: Congenital agenesis of the spleen with characteristic cardiovascular anomalies (e.g., common atrioventricular canal, transposition of the great vessels, stenosis or stasis of the pulmonary trunk) and visceral location anomalies with right-sidedness (abdominal heterotaxy).
2) Incomplete type: Congenital agenesis of the spleen with either one of characteristic anomalies of the cardiovascular system or visceral location anomalies with right-sidedness.

3) Simple type: Congenital agenesis of the spleen without other anomalies mentioned above.

Among the cases collected for this study, 23 cases belonged to the complete type, and seven cases to the incomplete, and the remaining two considered to be the simple type, in which any other anomalies were not found. In literature, this third type of asplenia has already been mentioned. Furthermore, we experienced one case (WMC-5719) in which cardiovascular anomalies with situs inversus were quite similar to those of this syndrome but the spleen was present in normal form. These facts suggest that there may be many grades in the factors producing this kind of anomaly complexes, and that they act on the fetus in almost same period, but the results are quite variable in degree or in character.

In patients with cardiovascular anomalies, absence of anomalous pulmonary venous return and abnormal efferent hepatic veins as well as preservation of the shunt between aortic and pulmonary arterial systems may give a good influence for survival because both of these anomalies were found less frequently in the child group than in infant group.

As for the histological changes secondary to the cardiovascular anomalies, hypoplastic tendency of the media of small pulmonary arterial walls was seen, which should have resulted from stenosis or atresia of the pulmonary trunk. Besides, fresh or organized thrombi were frequently seen in the small pulmonary arteries particularly in the child group (Table 5). It seems to be rational to presume this phenomenon as a result from longstanding pulmonary low flow due to stenosis or atresia of the pulmonary trunk, on the one hand, and from hypercoagulability due to secondary polycythemia caused by the characteristic severe cardiovascular anomalies. This supposition seems to be supported by the fact that thrombus formation tends to occur in the pulmonary arteries also in cases of tetralogy of Fallot. However, its frequency is much higher in cases of this syndrome than in those of tetralogy of Fallot and, therefore, it is possible that the tendency for thrombus formation in this syndrome may also be influenced by some other factors due to absence of the spleen.

Findings of the so-called morbus caeruleus, including slight fibrosis around portal triads of the liver, swelling and sclerosis of the renal glomeruli, and mucosal or submucosal fibrosis of the gastro-intestinal tract, were also seen in the present cases of asplenia as well as in control cases of congenital cyanotic cardiac malformations of other types. Slight fatty change of the liver, which was encountered quite often, may also be a result from
chronic anoxia due to long-existing circulatory failure\textsuperscript{20}.

It is usually said that Howell-Jolly body, Heinz body, normoblast, and target cell appear in the peripheral blood after splenectomy\textsuperscript{27,28}, while anemia occurs in the condition of hypersplenism which is clinically termed\textsuperscript{29}. These facts suggest the presence of some mysterious functional relationship between the spleen and bone marrow. It is interesting that multiple lymph follicles were found histologically in cases belonging to the child group of this syndrome, although it is very rare to see lymph follicles formed in the bone marrow of children\textsuperscript{20}. Actually, the total of these follicles must have been a considerable amount, and furthermore, it seems likely that these follicles were relatively active in function, because phagocytosis was often found in them. Appearance of these lymph follicles or lymphocyte aggregation in the bone marrow (Table 6) in this syndrome may signify a compensatory action, \textit{i.e.}, a reaction possibly to the congenital absence of the spleen. This supposition seems to be supported by the fact that the lymph follicle is also apt to appear in the bone marrow in other splenic or hepatic diseases\textsuperscript{50}. This compensatory action in the bone marrow perhaps begins to appear about one year after birth, because the lymph follicle is not found in the infant group. Thus, the functional relationship between the spleen and bone marrow seems to be really existing, as it has long been assumed clinically, but without any definite evidence.

The peripheral lymph apparatus, including the lymph nodes, periportal lymphatic tissue, palatine tonsils, and mucosal lymph apparatus of the gastro-intestinal tract, were examined to see whether they showed any compensatory reaction to absence of the spleen, as was seen in the bone marrow. Although they showed a tendency of hyperplasia throughout the whole body in each case, it could not be determined to be the compensatory action, since hyperplastic tendency of a similar nature was also seen in control cases of other congenital cardiac malformations of the matched age\textsuperscript{31}. Compensatory hypertrophy of the lymph node was previously suspected to be one of the major signs in splenic agenesis syndrome, without definite evidences\textsuperscript{30}, but the data in our hand do not support this hypothesis.

In cases of congenital cyanotic cardiac malformations of other types (with patients of three to five years in age), the value, g liver weight/kg body weight, is usually 30-85\textsuperscript{12,32}. However, the value was found larger in this syndrome, particularly in cases of relatively older age (for example; WMC-8077 (5-year-old female) 40 g/kg, WMC-763 (6-year-old female) 40 g/kg, WMC-1216 (9-year-old female) 50 g/kg). This fact also suggests that the liver may show some compensatory reaction to absence of the spleen, as a member of the reticuloendothelial system\textsuperscript{39}. However, no remarkable histological change showing hyperactivity of the reticuloendothelial system was found in
the liver, so that this overweight of the liver may be the result of abnormal distribution of intra- and extra-hepatic vascular systems. It is difficult to determine which of the two is actually working as the real cause for this kind of liver enlargement.

It is said that splenectomized infants and children are easily susceptible to infectious diseases, particularly menigitis, from both statistical data\(^{34-36}\) and immunological aspects\(^{37}\). Only five cases from the present collection of congenital agenesis of the spleen showed some inflammatory changes at autopsy. This presumably low frequency of infection may be due to the recent improvement of therapeutic methods against infection, on the one hand. However, it is interesting that all five cases, in which infectious changes were seen, belonged to the infant group, and no sign of infection was found in the child group. This phenomenon is quite parallel to the appearance of the lymph follicle in the bone marrow, and suggests that some compensatory reaction of the lymphatic tissue may prevent the patients from infection, on the other hand.

**CONCLUSION**

Thirty-two autopsy cases of the so-called splenic agenesis syndrome (or Ivenmark's syndrome) were studied, and the following points have been clarified.

1. Cases of congenital splenic agenesis are frequently associated with cardiovascular anomalies, such as common atrioventricular canal in the atrioventricular region, transposition of the great vessels in the cono-truncus region, stenosis or acresia of the pulmonary trunk, persistent bilateral superior vena cavae, and persistent bilateral efferent hepatic veins.

2. Visceral heterotaxy with right-sidedness (e.g., three-lobation of bilateral lungs, symmetric or left-sided liver, and partial or total situs inversus) is also found quite often combined with these cases.

3. Thus, this syndrome mainly consists of three elements, namely congenital agenesis of the spleen, characteristic cardiovascular anomalies, and abdominal heterotaxy. The syndrome is classified into three types, (1) complete type (asplenia with cardiovascular anomalies and abdominal heterotaxy), (2) incomplete type (asplenia with either cardiovascular anomalies or abdominal heterotaxy), and (3) simple type (only agenesis of the spleen).

4. Survival of the patients with this syndrome is largely influenced by the absence of anomalous pulmonary venous return and abnormal efferent hepatic veins with abnormality of the inferior vena cava, and preservation of shunt between the aortic and pulmonary arterial systems.

5. As for the secondary changes resulting from severe characteristic cardio-
vascular malformations, various following changes are found which are severe in older children:
In the lung; hypoplasia of the small pulmonary arterial wall and fibrous intimal thickening, and formation of various kinds of fresh or old thrombi in the small arteries.
In the liver; slight fibrosis and fatty change.
In the kidney; swelling and sclerosis of the renal glomeruli. The changes in the liver and kidney correspond to that of morbus caeruleus.
6. As for the compensatory reaction probably due to congenital absence of the spleen, multiple lymph follicles, which are considerably active in histology, appear in the bone marrow about one year after birth. A slight, hyperplastic tendency is also seen in other peripheral lymph apparatus.
7. Some infectious changes are suspected as the direct cause of death in five cases, all of which are under one year of age. On the other hand, decompensation of cardio-pulmonary system is considered as the major, direct cause of death in all other cases.

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References

Plate 1

Fig. 1. Macroscopic view of cardiovascular system and visceral organs (WMC-5947). Note the left-sided heart, three-lobeation of the bilateral lungs, symmetric liver, and absence of the spleen.

Fig. 2. Typical cardiac anomalies (WMC-4918). Note the rudimentary atrial septum (arrow) with large defect and absence of the ventricular septum. A sample of persistent common atrioventricular canal in the atrio-ventricular region.

Fig. 3. Cono-truncus region of the same heart as in Fig. 2. The cardiac ventricle is single or common, and the dilated aorta deviates to the anterior portion. Pulmonary trunk with atresia is located in the posterior part and aortic arch is right-sided. A sample of transposition of the great vessels in the cono-truncus region.

Fig. 4. Scheme of the cardiovascular anomalies and abdominal heterotaxy (WMC-5739). Note the persistent bilateral superior vein cavae (R. or L. Sup. V.C.), transposition of the great vessels, stenosis of the pulmonary trunk, right-sided aortic arch, total anomalous pulmonary venous return (pouring into the right atria), persistent bilateral efferent hepatic veins with abnormality of the inferior vena cava (Inf. V.C.), three-lobeation of the bilateral lungs, left-sided liver, and right-sided stomach. PV indicates pulmonary vein. PA, pulmonary artery.

Plate 2

Fig. 5. Scheme of the intra-abdominal arteries (WMC-5739). Note the splenic artery drawing a loop at the pancreas-tail.

Fig. 6. Hypoplastic tendency of the media and fibrous thickening of the intima, which may be organized thrombus, in the small pulmonary artery (WMC-
5449). Note severe, fibrous thickening of the intima with stenosis of its lumen ($\times 40$, Masson’s trichrome staining).

Fig. 7. Bizarre fibrous thickening of the intima and fresh thrombus formation in the small pulmonary artery (WMC-5449, $\times 100$, Masson’s trichrome staining).

Fig. 8. Slight fibrosis and fatty change of the liver (WMC-4913). Note fibrosis around the portal triads and fatty change ($\times 100$, Masson’s trichrome staining).

Plate 3

Fig. 9. Swelling and sclerosis of the renal glomeruli (WMC-4913). Note swelling with congestion, sclerosis, and destruction of the glomeruli ($\times 100$, Masson’s trichrome staining).

Fig. 10. Lymph follicles in the bone marrow (WMC-5378). Note two secondary lymph follicles with clear borders ($\times 25$, Masson’s trichrome staining).

Fig. 11. Lymph follicle in the bone marrow (WMC-3077). Note formation of the primary lymph follicle with blood vessels in it ($\times 100$, Masson’s trichrome staining).

Fig. 12. Aggregate of lymphocytes in the bone marrow (WMC-4913). Note aggregation of lymphocytes without blood vessels in it, and slight relative increase of megakaryocytes ($\times 100$, Masson’s trichrome staining).

Plate 4

Fig. 13. Higher magnification of the secondary lymph follicle in the bone marrow (WMC-5378). Note active phagocytosis by histiocytes (arrow) ($\times 400$, periodic acid Schiff staining).

Fig. 14. Blood vessels of the secondary lymph follicle in the bone marrow (WMC-5378). The upper half of this photograph is occupied by the lymph follicle. Note the germinal center rich in blood vessels ($\times 100$, silver impregnation for reticulin staining).

Fig. 15. Peribronchial lymph follicle in the lung (WMC-5449). No remarkable inflammatory changes in the surrounding pulmonary tissue ($\times 100$, Masson’s trichrome staining).

Fig. 16. Hassal bodies in the thymus (WMC-5449). Note formation of Hassal bodies in the medulla and preservation of cortical lymphocytes ($\times 100$, Masson’s trichrome staining).
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Plate 3