Origin of Both Great Vessels from the Right Ventricle Associated with the Trisomy-18 Syndrome

By Terry R. Rogers, Jack W. C. Hagstrom, M.D., and Mary Allen Engle, M.D.

The first descriptions of the trisomy-18 syndrome were in 1960 by Edwards, Patau, and Smith and their associates. Although there was disagreement concerning which of the three pairs of chromosomes had an extra number, it now appears to be pair 18. The major malformations involve the skin, face, heart, and the central nervous, musculoskeletal, gastrointestinal, and urogenital systems. Overlapping digits (clinodactyly) and “rocker-bottom” feet are especially noteworthy.

Heretofore the major congenital cardiac anomaly reported in this syndrome was a defect in the interventricular septum. Patent ductus arteriosus, patent foramen ovale and, more rarely, atrial septal defect, atresia of the mitral valve, and bicuspid aortic or pulmonic valves, or both, have been noted. Gottlieb and associates reported two patients in whom the aorta was dextroposed and overrode the ventricular septal defect. Crawfurd further documented this association in a patient who had dextrocardia and in whom both great vessels originated from the right ventricle. It is the purpose of this paper to describe the cardiac findings in seven infants who had the trisomy-18 syndrome with a ventricular septal defect and origin of both great vessels from the right ventricle.

Material

The trisomy-18 syndrome has been diagnosed in nine patients examined at this medical center from 1954 to 1963. In six patients the clinical diagnosis was confirmed by chromosomal analyses; in the three remaining patients the diagnosis was made from the clinical and pathologic findings. All nine patients died and were autopsied. Of this group, seven patients had origin of both great vessels from the right ventricle associated with a ventricular septal defect. The physical findings are presented in table 1. These seven patients comprise the basis of this report.

Results

In four patients in this group the diagnosis of trisomy-18 was established by chromosomal analyses of leukocytes or skin cells. The other three patients died before such analyses were available; however, they had the clearly defined clinical and pathologic features of the trisomy-18 syndrome (table 1). A careful review of the patients' histories failed to disclose consanguinity or any other discernible etiologic factors before or during pregnancy. Five of the seven infants were born between July and September; three were born in August. The birth weight was low and out of proportion to the gestational age. Even those born postmaturely had birth weights in the premature range (table 2). The mother of patient 4 had a history of 6 years of infertility prior to this pregnancy. Five infants were products of first pregnancies. The age range of the mothers was 18 to 40 years; four were 30 years of age or older. The babies died from cardiac failure and respiratory distress. Five deaths were in the first 3 months of life.

At postmortem examination all patients had large ventricular septal defects posterior to the crista supraventricularis. In addition, both the pulmonary artery and the aorta arose from the right ventricle; the pulmonary valve

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### Table 1

#### Summary of Physical Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Low-set ears</th>
<th>Micrognathia</th>
<th>High arched palate</th>
<th>Webbed neck</th>
<th>Shield chest</th>
<th>Hip contractures</th>
<th>Clinodactyly</th>
<th>Rocker-bottom feet</th>
<th>Genitourinary abnormalities</th>
<th>Gastro-intestinal abnormalities</th>
<th>Additional findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (G.G.)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Meckle's diverticulum</td>
<td>Hypoplastic falc cerebri and thymus</td>
</tr>
<tr>
<td>2 (J.D.)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Horseshoe kidney</td>
<td>Meckle's diverticulum</td>
<td>Bilateral inguinal hernias</td>
</tr>
<tr>
<td>3 (C.R.)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bifid left kidney</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 (G.R.)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Spina bifida</td>
</tr>
<tr>
<td>5 (B.W.)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Undescended testes</td>
<td>Diverticulum of colon</td>
<td>-</td>
</tr>
<tr>
<td>6 (A.Q.)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Undescended right testis</td>
<td>Meckle's diverticulum</td>
<td>-</td>
</tr>
<tr>
<td>7 (G.J.)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Diverticulum of jejunum; ectopic pancreas</td>
<td>Hypoplastic thymus</td>
</tr>
</tbody>
</table>
was in the normal position, and the aortic valve was entirely to the right of the ventricular septum (fig. 1). In addition, an atrial septal defect of the secundum type was present in three infants (fig. 2). Three others had atresia of the mitral valve (fig. 3) associated with hypoplasia of the left atrium and left ventricle (fig. 4). Bicuspid pulmonic valves were found in three patients (fig. 5). None were obstructive, nor was there infundibular pulmonic stenosis. A bicuspid aortic valve was noted in one patient (case 5) in which both the aortic and pulmonic valves contained multiple fibrotic nodules. The interrelationships of these lesions are de-

Table 2

Gestational History

<table>
<thead>
<tr>
<th>No.</th>
<th>Age of mother</th>
<th>Age of father</th>
<th>Sex</th>
<th>Gestation period</th>
<th>Birth weight</th>
<th>Number of pregnancy</th>
<th>Living children</th>
<th>Chromosome analysis</th>
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<tr>
<td>1</td>
<td>28</td>
<td>39</td>
<td>F</td>
<td>1 month premature</td>
<td>1425</td>
<td>1</td>
<td>0</td>
<td>Trisomy 18</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>35</td>
<td>M</td>
<td>Full term</td>
<td>1990</td>
<td>4</td>
<td>2</td>
<td>Trisomy 18</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>29</td>
<td>F</td>
<td>1 month past term</td>
<td>2260</td>
<td>1</td>
<td>0</td>
<td>Not done</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>19</td>
<td>F</td>
<td>? Full term*</td>
<td>2380</td>
<td>1</td>
<td>0</td>
<td>Not done</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>33</td>
<td>M</td>
<td>2 months premature</td>
<td>960</td>
<td>1</td>
<td>0</td>
<td>Trisomy 18</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>36</td>
<td>M</td>
<td>1 month past term</td>
<td>2410</td>
<td>3</td>
<td>2</td>
<td>Not done</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>27</td>
<td>F</td>
<td>Full term</td>
<td>1460</td>
<td>1</td>
<td>0</td>
<td>Trisomy 18</td>
</tr>
</tbody>
</table>

*Gestational information not certain.

was in the normal position, and the aortic valve was entirely to the right of the ventricular septum (fig. 1). In addition, an atrial septal defect of the secundum type was present in three infants (fig. 2). Three others had atresia of the mitral valve (fig. 3) associated with hypoplasia of the left atrium and left ventricle (fig. 4). Bicuspid pulmonic

Figure 1

Anterior view of heart of case 7 shows the normal origin of the pulmonary artery (PA). Although the position of the aorta (A) appears normal externally, the accessory incision in the right ventricle (arrow) showed that the aortic valve was located in proximity to the ventricular septal defect and entirely to the right of the interventricular septum.

Figure 2

View of left atrium of case 4 shows extensive, fenestrated defect of atrial septum. The left ventricle is smaller than the right ventricle.
TRISOMY-18 SYNDROME

Figure 3
Lateral view of left atrium of case 7. Arrow indicates dimple of atretic mitral valve.

Figure 4
Lateral view of left atrium (LA) and left ventricle (LV) in case 7; the lateral wall is lifted to show the ventricular septal defect, which is the only outlet for the thick-walled left ventricle. The left ventricular chamber is hypoplastic.

Figure 5
Photograph showing bicuspid pulmonic valve in case 2.

scribed in table 3. As the chart is read from above down, the spectrum of lesions becomes increasingly complex. Cases 1 and 2 have uncomplicated origin of both great vessels from the right ventricle, whereas subsequent cases have additional defects, notably atrial septal defect and atresia of the mitral valve. Except in case 6, the prognosis of patients with the more complex anomalies is reflected in an earlier age at death.

Discussion
Ventricular septal defect has been reported in 20 of 21 autopsy specimens from patients with the trisomy-18 syndrome. In our experience with nine specimens, the defect was high and posterior to the crista supraventricularis; in seven of these both great vessels originated from the right ventricle. In the eighth specimen the aorta arose mainly, but not entirely, from the right ventricle and, in the last, there was normal position of the aortic valve. Therefore, origin of both great vessels from the right ventricle is more commonly associated with a ventricular septal defect in the trisomy-18 syndrome than has heretofore been appreciated.

The abnormal position of the aortic valve may easily be overlooked, especially if there is atresia of the mitral valve or hypoplasia of the left ventricle or both. To recognize the abnormal position of the aortic valve, it is essential to identify the outflow tract of the left ventricle. If the left ventricular outflow tract cannot be easily demonstrated by making the classical incision in the wall of the left ventricle next to the interventricular septum in the direction of the aorta, it is helpful to make an additional incision along the anterolateral border of the right ventricle into the right wall of the aorta (fig. 1).
Pathologic Findings

<table>
<thead>
<tr>
<th>No.</th>
<th>Ventricular septal defect</th>
<th>Origin of aorta</th>
<th>Atrial septal defect</th>
<th>Atresia of the mitral valve</th>
<th>Hypoplastic LV &amp; LA</th>
<th>Aortic valve</th>
<th>Pulmonic valve</th>
<th>Age at death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>RV</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Normal</td>
<td>Bicuspid</td>
<td>6 wk.</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>RV</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Normal</td>
<td>Bicuspid</td>
<td>7 mo.</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>RV</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
<td>7 mo.</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>RV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bicuspid</td>
<td>Nodular</td>
<td>8 da.</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>RV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Bicuspid</td>
<td>1 da.</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>RV</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Normal</td>
<td>Nodular</td>
<td>2 mo.</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>RV</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
<td>1 wk.</td>
</tr>
</tbody>
</table>

Key: RV, right ventricle; LV, left ventricle; LA, left atrium; +, present; −, absent.

With such an exposure, it is possible to trace the anomalous left ventricular outflow tract through the right ventricle to the dextroposed aortic valve and into the aorta. The ventricular septal defect posterior to the crista supraventricularis is then clearly visible. It can be seen that the ventricular septal defect is the terminus of the outflow tract of the left ventricle and that the entire aortic valve is to the right of the interventricular septum. Atria of the mitral valve with hypoplasia of the left ventricle is part of the spectrum of abnormalities associated with this form of double-outlet right ventricle in which there is dextroposition of the aortic valve.20 In these infants we have noted the presence of patent ductus arteriosus and patent foramen ovale. In this young infant age group, however, these should not be considered malformations, but instead the normal persistence of fetal structures.

Summary

Origin of both great vessels from the right ventricle in association with a ventricular septal defect was found in seven of nine autopsied patients with the clinical features of the trisomy-18 syndrome. In four of these patients trisomy-18 was confirmed by chromosomal analyses. This experience indicates that origin of both great vessels from the right ventricle may in fact be an additional component of the trisomy-18 syndrome.

Acknowledgment

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References


Circulation, Volume XXXII, November 1963

Blood as a Physico-Chemical System.
Lawrence J. Henderson—1878-1942

The synthesis, the integration of "blood as a physico-chemical system" had still to be done. This was the achievement of Lawrence J. Henderson (1878-1942) of Harvard. After taking his undergraduate and medical degrees there, he visited the chemist Hofmeister in Germany for a brief period; then he returned to Harvard, and began, more or less on his own, an inquiry into the equilibrium between carbon dioxide, carbonic acid, and bicarbonate in water solutions. Great things came from Henderson's contemplation of this apparently simple system. The concept of the acid-base balance in biological systems, hitherto no more than hinted at, took form. It was further developed by many others. Henderson advanced his fundamental idea also into a broader philosophical expression with his essay, The Fitness of the Environment. In a second, The Order of Nature, he pursued the concept of fitness to its logical conclusion and argued for teleology as a positive and necessary tenet in the philosophy of organic mechanism.—André Cournand, M.D. Circulation of the Blood. Edited by Alfred P. Fishman, M.D., and Dickinson W. Richards, M.D. New York, Oxford University Press, 1964, p. 60.
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