CLINICOPATHOLOGIC CORRELATIONS

Cardiac Malformations Associated with Down’s Syndrome

By Rajendra Tandon, M.D., and Jesse E. Edwards, M.D.

SUMMARY

A review of 55 specimens with congenital heart disease from subjects with Down’s syndrome (Mongolism) showed a variety of malformations. For each case a major anomaly was identified and, when present, additional anomalies were recorded.

The three leading types of major anomalies, in order of decreasing frequency, were (1) persistent common atrioventricular canal (60%), isolated ventricular septal defect (25%), and tetralogy of Fallot either alone or in association with persistent common atrioventricular canal (14.5%).

Of the additional anomalies, the most common took the form either of an atrial septal defect at the fossa ovalis (50%) or patent ductus arteriosus (47%).

Additional Indexing Words:
Mongolism Persistent common atrioventricular canal Tetralogy of Fallot Ventricular septal defect

It is recognized that Down’s syndrome (Mongolism) is commonly associated with congenital heart disease. Figures based upon extensive series indicate that in about one half of subjects with Down’s syndrome some form of congenital heart disease is present.1, 2 Credit for first recognizing such an association goes to Garrod (1894)12 while Abbott,4 in 1924, was the first to associate atrioventricular canal malformations with this syndrome. While this association is dominant, it is evident that a variety of cardiac malformations may be represented. With this fact in mind we have reviewed 55 specimens with congenital cardiovascular malformations from patients clinically diagnosed as having Down’s syndrome.

Thirty specimens were from female and 25 from male subjects. The ages ranged from 16 hours to 44 years. Of these, 27 were below 1 year of age, 12 were between 1 and 5 years and 16 were older than 5 years. The terminology used for the various types of persistent common atrioventricular canal malformations was that of Wakai and Edwards.5 The features of the ventricular septal defect of the atrioventricular canal type were those described by Neufeld and associates.6

For each of the 55 cases of this study, a major congenital anomaly was designated resulting in four groups, one of which was a miscellaneous one (table 1). The latter consisted of one example each of atrial septal defect, patent ductus arteriosus, and a spontaneously closed ventricular septal defect. In addition to the designation, for each case, of its major anomaly, other anomalies were recognized in some of the cases. The latter were called “additional anomalies” and fell into the following categories (table 2): (1) communications between the left and right sides of the central circulation; (2) abnormalities of the atrioventricular valves (each of the former two in addition to those malformations which are part of the various major anomalies); (3) abnormalities of the semilunar valves; (4) left-sided outflow obstructive lesions; (5) right-sided outflow obstructive lesions; (6) nonobstructive malformations of the aortic arch system; (7) other abnormalities were grouped together as miscellaneous. Patent ductus arteriosus, when present, was not considered an abnormality in subjects under 1 month of age unless associated with coarctation or tubular hypoplasia of the aortic arch. This resulted in excluding this diagnosis in two neonates with patent
Table 1

Summary of Essential Data and Major Anomalies Observed in 55 Specimens from Patients with Down's Syndrome and CHD

<table>
<thead>
<tr>
<th>Major anomalies</th>
<th>Number of cases</th>
<th>By sex</th>
<th>By age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Persistent common AVC:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>19</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Transitional</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Partial</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tetralogy of Fallot:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With complete AVC</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Without AVC</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular septal defect:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVC type</td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Membranous</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Miscellaneous:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PDA</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Spontaneously closed VSD</td>
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<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: AVC = atrioventricular canal; ASD = atrial septal defect; PDA = patent ductus arteriosus; VSD = ventricular septal defect; CHD = congenital heart disease.

ductus arteriosus and inclusion of two others with tubular hypoplasia of the aortic arch.

It is to be reemphasized that, while describing "additional anomalies," those abnormalities which form part of a major anomaly were not considered as additional anomalies. For example, in the persistent common atrioventricular canal there are clefts in the anterior mitral and septal tricuspid leaflets which are continuous across the deficient ventricular septum. This is part of persistent atrioventricular canal and hence not considered an additional anomaly. If, however, there was in addition parachute deformity of the mitral valve, the latter was considered as an additional anomaly.

In none of the 55 specimens were there abnormalities involving the position of the heart in

Table 2

Additional Anomalies by Type According to the Association with Major Anomalies Observed in 55 Cases of Down's Syndrome

<table>
<thead>
<tr>
<th>Major Anomalies</th>
<th>Types</th>
<th>Total</th>
<th>Communication between left and right sides</th>
<th>Abnormalities of AV valves</th>
<th>Abnormalities of semilunar valves</th>
<th>Left-sided obstructive lesions</th>
<th>Right-sided obstructive lesions</th>
<th>Nonobstructive malformations of aortic arch</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent common AVC:</td>
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<td></td>
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<tr>
<td>Complete</td>
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<td>2</td>
<td>7</td>
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<tr>
<td>Tetralogy of Fallot:</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>With AVC</td>
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<td>4</td>
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<td>0</td>
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</tr>
<tr>
<td>Ventricular septal defect:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AVC type</td>
<td>8</td>
<td></td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>ASD</td>
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<td></td>
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<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>PDA</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous closure of VSD</td>
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<td></td>
<td>0</td>
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<td>0</td>
<td>1</td>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
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<td>54</td>
<td>15</td>
<td>6</td>
<td>10</td>
<td>3</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: Same as Table 1.
the thoracic cavity, the relationship of the great arteries (transposition) or inversion of ventricles, and in none were there splenic anomalies.

**Major Anomalies**

In addition to a miscellaneous group (group D), there were three categories of major anomalies. These consisted of persistent common atrioventricular canal (group A), tetralogy of Fallot (group B), and ventricular septal defect (group C).

**Persistent Common Atrioventricular Canal**

Persistent common atrioventricular canal was classified into three types as follows: the complete, transitional, and partial. In each type, there is a defect in the lowermost part of the atrial septum. The complete type is characterized by cleft anterior mitral and septal tricuspid valve leaflets, forming a large anterior and a smaller posterior leaflet of a valve common to both sides of the heart. The ventricular septum is deficient.

In the transitional type, the anterior mitral and the septal tricuspid leaflets are each cleft but a bridge of tissue extends between the anterior and posterior leaflets dividing the AV canal into two halves. The partial type has a cleft in one of the atrioventricular valves, usually the mitral. An interventricular communication is usually present in the complete type and may be present or absent in the transitional and partial types.

Some form of persistent common atrioventricular canal was present in 33 of the 55 specimens. These were subdivided into two groups as follows: 28 specimens with classical examples of the complete, transitional, or partial types (group A) and five specimens of complete persistent common atrioventricular canal associated with tetralogy of Fallot, the latter five being part of group B. Group B also included three specimens with tetralogy of Fallot but without the malformation of the atrioventricular canal.

Of the 28 specimens in group A, 19 were of the complete type, five of transitional variety, and four of partial type of persistent common atrioventricular canal. Among the four with the partial type, the mitral valve was cleft in three and rudimentary in one. The latter case exhibited a cleft septal leaflet of the tricuspid valve.

An interventricular communication was present in two specimens with transitional type and three of the partial type of persistent common atrioventricular canal. One specimen of the complete type of atrioventricular canal exhibited absence of the ventricular septum. In this case the great vessels were not transposed.

**Tetralogy of Fallot**

The tetralogy of Fallot was present in eight specimens, five of which were associated with classical features of the complete type of persistent common atrioventricular canal (fig. 1). In these, there was major deficiency of the ventricular septum as part of persistent common atrioventricular canal, while the aorta originated from both ventricles. In addition to this characteristic of the tetralogy, the right ventricular infundibulum was stenotic in each and the pulmonary valve stenotic in three.

In three other cases, the tetralogy of Fallot was present without the characteristics of classical persistent common atrioventricular canal. In these, only one showed any features of the atrioventricular canal anomaly. This was represented by a cleft in the septal leaflet of the tricuspid valve.

Two points were of particular interest with regard to the cases having the tetralogy of Fallot. There was inordinate dominance of the female sex in that seven of the eight specimens were from female subjects. The other point relates to age in that those patients with the tetralogy and persistent

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

Tetralogy of Fallot associated with persistent common atrioventricular canal. View of right ventricle (R.V.) showing aorta (Ao.) rising above the ventricular septal defect. The stenotic infundibulum (I.) of the right ventricle is characteristic for the tetralogy. The large anterior (A.) leaflet of the common atrioventricular canal is also seen.
common atrioventricular canal were older at the
time of death than the average for the complete
type of persistent common atrioventricular canal
alone. This may be explained by a natural
"pulmonary arterial banding" phenomenon by the
pulmonary stenosis of the tetralogy.

**Ventricular Septal Defect**

Isolated ventricular septal defect, present in 16
specimens, was of two varieties. Half of these were
of the "atrioventricular canal" type, the other half
being of the membranous type. The chief character-
istics of the ventricular defect of the atrioven-
tricular canal type is its location immediately be-
neath the tricuspid valve ring. The upper edge of
the defect is separated from the aortic cusps by the
membranous portion of the ventricular septum
which may be recognizable. The defect cuts
obliquely across the muscle of the left ventricular
outflow tract (fig. 2a).

The ventricular septal defect of the membranous
type lies immediately below the aortic valve ring
and tends to run horizontally with respect to the
left ventricular outflow tract (fig. 2b). The aorta
overrides the ventricular septum, arising from both
ventricles.

**Miscellaneous Major Anomalies**

There were three specimens with miscellaneous
types of major anomalies. In one of these, there was
a fossa ovalis type of atrial septal defect associated
with a cleft septal tricuspid leaflet. In the second
specimen, the anomaly was a patent ductus
arteriosus. The third specimen showed a sponta-
neously closed ventricular septal defect resulting
from adhesion of the septal leaflet of the tricuspid
valve to the edges of the defect. Localized
infundibular stenosis of the right ventricle was also
present in this case.

**Additional Anomalies**

Additional anomalies were those which are not
part of the various major anomalies. Each of these
could be placed into one of the seven categories
indicated above and summarized in table 2.

**Additional Communications between Left and Right Sides of the Central Circulation**

A valvular competent patent foramen ovale was
present in the majority of cases and not considered

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**Figure 2**

*Ventricular septal defects associated with Down's syndrome. (a.) Defect of the atrioventricular canal type viewed from the left ventricle (L.V.). Characteristically, the long axis of the defect (D.) cuts obliquely across the left ventricular outflow tract. A.V. = aortic valve. (b.) Membranous type of ventricular septal defect. The defect (D.) lies oriented in a horizontal position with respect to the left ventricular outflow tract and the aortic valve (A.V.).*
an anomaly, while a through-and-through defect was considered abnormal and classified as an atrial septal defect.

An atrial septal defect at the fossa ovalis (so-called ostium secundum type) was present in 28 specimens. In 27 of these, it was an anomaly in addition to a major one whereas in one the defect was the designated major anomaly for that case.

Classically, the defect at the fossa ovalis, when present, was separated by septal tissue from the defect of the atrioventricular canal malformation, yielding two atrial septal defects. In one case, the two defects coalesced resulting in the presence of a single atrium. Table 3 shows that there was no strong tendency for the fossa ovalis type of atrial septal defect to be associated with any one of the major anomalies present.

A patent ductus arteriosus, as defined, was present in 26 of the 55 cases. In 25, this represented an additional anomaly and in one a major anomaly. While this condition was present in nine of the 19 cases of the complete type of persistent common atrioventricular canal, it had an even stronger association with those cases in which a ventricular septal defect was the major anomaly, occurring in 13 of the 16 cases.

A left ventricular-right atrial communication occurred in two specimens both having an interventricular communication as well. The communication was through an aneurysm of the membranous septum in one case and in the other it resulted from the attachment of the rim of a double orifice of the septal leaflet of the tricuspid valve to the rim of the ventricular septal defect.

Abnormalities of the Atrioventricular Valves

In considering the additional malformations involving the atrioventricular valves, distinction has been made between the common valve as seen in the complete variety of persistent common atrioventricular canal, on one hand, and, on the other, the mitral and tricuspid valves when these were formed. The common atrioventricular valve was abnormal in five specimens, three with the complete type of persistent common atrioventricular canal alone and two in which the tetralogy of Fallot was associated with this condition.

The various additional anomalies of a common atrioventricular valve, seen once each, were a floating anterior leaflet resulting from absence of chordal attachment on the left side, accessory tissue in the anterior leaflet forming a pouch, double orifice in the right side of the common valve, modified parachute deformity of the mitral aspect, and attachment of the posterior mitral leaflet directly to the wall of the left ventricle.

Abnormalities of the mitral valve occurred in three specimens. The anterior leaflet was rudimentary but without a cleft in one case with the partial type of persistent common atrioventricular canal. In one specimen with the atrioventricular type of

<table>
<thead>
<tr>
<th>Types of Additional Communications between the Left and Right Sides of the Heart According to the Major Types of Anomalies Observed in 55 Cases of Down's Syndrome with CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major anomalies</td>
</tr>
<tr>
<td>Types</td>
</tr>
<tr>
<td>Persistent common AVC:</td>
</tr>
<tr>
<td>Complete</td>
</tr>
<tr>
<td>Transitional</td>
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<tr>
<td>Partial</td>
</tr>
<tr>
<td>Tetralogy of Fallot:</td>
</tr>
<tr>
<td>With AVC</td>
</tr>
<tr>
<td>Without AVC</td>
</tr>
<tr>
<td>Ventricular septal defect:</td>
</tr>
<tr>
<td>AVC type*</td>
</tr>
<tr>
<td>Membranous*</td>
</tr>
<tr>
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</tr>
<tr>
<td>PDA</td>
</tr>
<tr>
<td>Spontaneous closure VSD</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*One example of left ventricular-right atrial communication also present.

Abbreviations: Same as Table 1.
ventricular septal defect, the anterior mitral leaflet was cleft and in a specimen with membranous type of ventricular septal defect a parachute deformity of the mitral valve was present.

Exclusive of cases with persistent common atrioventricular canal, a cleft septal tricuspid leaflet was seen in three cases, once in each specimen with the following types of major anomalies; atrioventricular canal type of ventricular septal defect, tetralogy of Fallot, and isolated fossa ovalis type of atrial septal defect. Accessory tricuspid tissue resulted in tricuspid stenosis in a case in which the major anomaly was an atrioventricular canal type of ventricular septal defect. In three specimens, the septal leaflet was adherent to the ventricular septal defect resulting in partial closure of a membranous ventricular septal defect in two and complete closure in the third with formation of a pouch bulging into the right ventricle. In one of the former two, the edges of a double orifice of the tricuspid valve were adherent to the rim of the ventricular septal defect leading to the left ventricular-right atrial communication described above.

**Abnormalities of the Semilunar Valves**

Abnormalities of “additional” variety involving the aortic valve were seen in three specimens. The aortic valve was bicuspid in two specimens, one with complete type of persistent atrioventricular canal and the other with atrioventricular canal type of ventricular septal defect. In the third, the valve was hypoplastic resulting in obstruction in a case with the complete type of persistent common atrioventricular canal. This case also showed tubular hypoplasia of the aortic arch and subaortic stenosis from asymmetric hypertrophy of the ventricular septum.

Exclusive of cases with the tetralogy of Fallot; the pulmonary valve was abnormal in three specimens. Bicuspid pulmonary valve was observed once in each of the two types of “isolated” ventricular septal defect (group C). In the third case of which the major anomaly was membranous ventricular septal defect, the pulmonary valve was dysplastic but not stenotic.

**Left-Sided Outflow Obstructive Lesions**

Left-sided obstructive lesions were seen in nine specimens and were of two types, intracardiac and extracardiac. Intracardiac obstructive lesions were present in two specimens, both with complete type of persistent common atrioventricular canal. In one, this was caused by hypoplastic aortic valve and subaortic stenosis and in the other by subaortic stenosis, the latter being in the case with absence of the ventricular septum.

Left-sided extracardiac obstructive lesions in the form either of tubular hypoplasia of the aortic arch or coarctation of the aorta occurred in five and three specimens, respectively. The tubular hypoplasia of the aortic arch was present in four cases of complete and one case of partial type of persistent common atrioventricular canal. A patent ductus arteriosus was present in three cases of the former type. Coarctation of the aorta was present in one case each of the complete type, and the partial type of persistent atrioventricular canal, and the membranous type of ventricular septal defect (group C). The ductus arteriosus was patent in both cases of persistent common atrioventricular canal.

**Right-Sided Outflow Obstructive Lesions**

Excluding those lesions which are part of tetralogy of Fallot, obstruction to the right ventricular outflow occurred in only three specimens. In one, this took the form of stenosis of the origins of the right and left pulmonary arteries in a case with the atrioventricular canal-type of ventricular septal defect. In the second, stenosis of the left pulmonary artery was present in a case of which the major anomaly was tetralogy of Fallot and persistent common atrioventricular canal. The third case showed localized infundibular stenosis in the one example of spontaneously closed ventricular septal defect.

**Nonobstructive Malformations of the Aortic Arch System**

A right aortic arch was present in five specimens. In four it was associated with tetralogy of Fallot and, in the fifth, with the complete type of persistent common atrioventricular canal. In the latter an anomalous left subclavian artery arose as the fourth branch and passed retroesophageally to the left arm. A patent ductus arteriosus ran between the anomalous left subclavian and the left pulmonary artery, thus forming a vascular ring.

An anomalous right subclavian artery was present in six specimens. It occurred in two cases each of the complete type and partial type of persistent common atreioventricular canal and in one case each of transitional type of persistent atrioventricular canal and tetralogy of Fallot with the complete type of persistent atrioventricular canal.
Miscellaneous Abnormalities

Persistent left superior vena cava joining the coronary sinus was present in four specimens of which three were from group A and one from group B.

Aneurysm of the membranous ventricular septum occurred in two specimens. One of these was in a case with the transitional type of persistent atroventricular canal and the other in a case of atroventricular canal-type of ventricular septal defect. The aneurysm presented between the edges of a cleft tricuspid leaflet in both.

One specimen with the complete type of common atroventricular canal showed atresia of the right upper and both left pulmonary veins, in each close to their union with the left atrium.

General Comments

It is evident from the foregoing that many of the individual "additional anomalies" were of little functional significance but others, in contrast, were significant. Examples of the latter included pulmonary venous or arterial obstruction and, in particular, additional left-to-right communications.

Among the latter, atrial septal defect was a common additional anomaly, being seen in 27 of the 55 cases (50%). In some cases this was the only basis for a left-to-right shunt. Considering this type of atrial septal defect and the frequent nature in Down's syndrome of persistent common atroventricular canal, of which a characteristic atrial septal defect is part, it is apparent that some form of atrial septal defect was present in 42 (76%) of our cases of congenital heart disease associated with Down's syndrome.

A ventricular septal defect, either isolated or part of another major anomaly, was present in 48 of 55 cases (87%). In subjects dying when over 1 month of age, a patent ductus arteriosus was present in 26 cases (47%). The association with Down's syndrome of persistent common atroventricular canal is generally recognized and was seen in 33 of our 55 cases (60%).

It has, however, been emphasized by Berg and associates\(^1\) and by Rowe and Uchida\(^2\) that other anomalies are not infrequent in Down's syndrome. Our observations conform to these in that we observed isolated ventricular septal defect in 16 of 55 cases (29%). In contrast to the observations of others, we found the tetralogy of Fallot to be fairly common, this condition occurring either alone or in association with persistent common atroventricular canal, in eight cases (14.5%). Similarly, we observed obstructive anomalies of the aortic arch not to be uncommon. Either tubular hypoplasia of the arch or coarctation was found as additional anomalies in eight other cases (14.5%).

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