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Cor Biloculare and Associated Malformations

William W. Temple and Colin M. Bloor
Department of Pathology, University of California,
San Diego, School of Medicine, La Jolla, California, USA

Summary. We report the clinical and autopsy findings of four unusual cases of the rare entity, cor biloculare, collected within a 4-year period. The cases are interesting for (1) the striking similarity of the associated anomalies, in contrast with the diversity of associated anomalies reported before; (2) the greater incidence of anomalous pulmonary and systemic venous return, pulmonic valve malformations and visceral heterotaxia than reported before; and (3) the normal, full-term, uncomplicated pregnancies. Family and gestational histories were unrevealing. All four cases had severe pulmonic valve malformations, pulmonary artery atresia, and visceral heterotaxia. Three of the four had anomalous pulmonary venous drainage and the fourth had anomalous systemic venous drainage. All four cases had polysplenia or asplenia. Correlating these associated anomalies with stages of embryonic development and with various studies of altered embryonic blood flow, suggests an etiologic role for altered blood flow in the development of this complex malformation.

Key words: Cor Biloculare – Congenital heart disease – Embryology – Anomaly

Introduction

Cor biloculare is a rare congenital anomaly of the heart comprising 0.5 to 1.5% of all cardiac anomalies (Goerttler 1963; Nizankowski, Rajchel and Zialkovski 1976). It is characterized by a single or common atrium communicating with a single or common ventricle by a single atrioventricular valve. The designation "single" atrium excludes fairly large atrial septal defects, allowing only a very small rudimentary septum to be present (Moller et al. 1967). A similar definition should be applied to "single" ventricle. This cardiac anomaly is

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Offprint requests to: Colin M. Bloor, M.D., Department of Pathology, M-012, UCSD School of Medicine, La Jolla, CA 92093, USA

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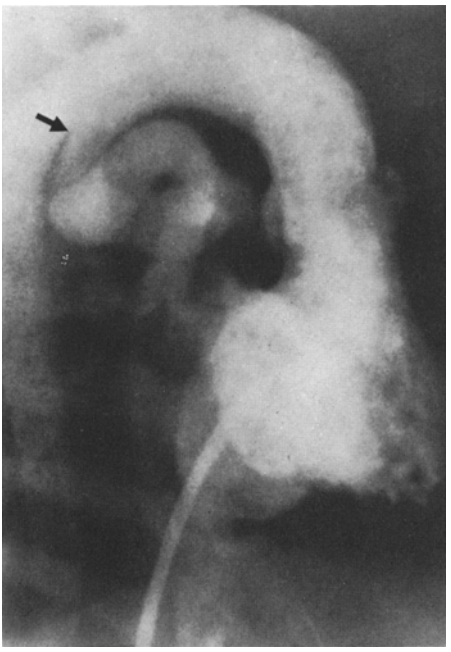


Fig. 1. Case 2. Aortic angiogram shows filling of a right side aortic arch from which a large accessory pulmonary artery (*arrow*) arises

most frequently seen as part of the asplenia or polysplenia syndrome. In fact most case reports of cor biloculare are presented as part of an asplenia or polysplenia syndrome. Ivemark (1955) described 32 cases of cor biloculare as part of the asplenia syndrome. But, these cases are associated with a variety of other anomalies, including valvular malformations, anomalous pulmonary venous drainage, various degrees of situs inversus, and pulmonary isomerism. We report the clinical and autopsy findings of four unusual cases of cor biloculare collected over a 4-year period. The cases are interesting for (a) the striking similarity of the associated anomalies, in contrast with the diversity of anomalies reported before; (b) the greater incidence of anomalous pulmonary and systemic venous return, pulmonic valve malformations and visceral heterotaxia than reported before; and (c) the normal, full-term uncomplicated pregnancies. We discuss these features as they differ from previous reports of cor biloculare, and as they suggest a role for altered embryonic blood flow in the development of this complex malformation.

Case Reports

Case 1

Clinical History. This 2-month-old boy was born after an uneventful, uncomplicated, 9-month gestation. The 19-year-old, gravid II mother denied exposure to any harmful substances or infectious diseases. The family history was unremarkable. At birth, the infant was cyanotic but resuscitation was unnecessary. He was transferred to University Hospital where he was cyanotic on crying. After discharge, the infant tolerated feedings moderately well, yet gradually became cyanotic during feedings and severely so while crying. Becoming increasingly dyspneic, the infant was readmitted to University Hospital. Cardiac catherization showed a single atrium, a single ventricle, and a

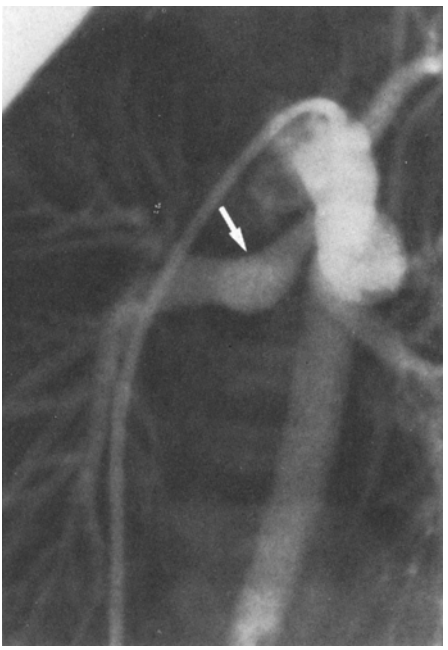


Fig. 2. Case 2. In a later filling phase of the aortic angiogram, the pulmonary arteries (*arrow*) can be visualized after dye passed through the accessory pulmonary artery into the proximal branches of the right and left pulmonary arteries

right-side aortic arch. It was also thought that the main pulmonary artery was atretic and a large patent ductus arteriosus supplied the right and left pulmonary arteries. The infant was taken to surgery for creation of an aortopulmonary window. Post-operatively, he did reasonably well until the fifteenth day, when he became increasingly hypoxic and acidotic, and subsequently died.

Autopsy Findings. The inferior and superior vena cavae entered the right posterior wall of a common atrium. The atrial chamber was partially divided by a very rudimentary, crescent-shaped septum arising from the superior wall. The left portion of the atrial chamber had the anatomic features of a right atrium. A single atrioventricular valve consisting of three leaflets was present between the single atrium and the single ventricle. The coronary sinus was absent. The chordae tendinae of the valve leaflets were attached to papillary muscles extending from the apex. The only outlet tract from the ventricular chamber was located anteriorly and to the right. There was transposition of the great vessels. A normal aortic valve was present leading to a right-side aorta. The pulmonic valve was absent and the first 2 mm of the pulmonary artery were atretic. Distally a pulmonary artery arose to the left and somewhat posterior to the aorta. A large patent ductus arteriosus was present, being the only source of blood supply to the lungs. The coronary arteries arose from the aorta and followed a normal course. The pulmonary venous drainage was totally anomalous, comprising a large vessel entering the right side of the single atrium. This large vessel received normal venous branches from the right lung; but from the left lung, it received drainage via a network of several veins that communicate between both lungs. Several of the communicating veins were stenotic and could not be probed. Externally the right and left lungs each had three distinct lobes. Right pulmonary isomerism was confirmed by the presence of an eparterial upper lobe bronchus in the left lung. No other pulmonary abnormalities were noted.

Examination of the abdominal viscera showed a transverse liver, a right-side pancreas, and right-side stomach. The spleen was absent. The aorta was located to the left of the inferior vena cava. The remaining autopsy findings were normal.

Case 2

Clinical Features. This 7-day-old boy was born after an uneventful, uncomplicated 9 month gestation. The 20-year-old mother (gravid I, Para 0, abortus 1) denied exposure to any harmful substance

Fig. 3. Case 2. Right pulmonary isomerism. A lateral view of the left lung shows it to have 3 lobes. Confirmation of right pulmonary isomerism includes eparterial bronchi to the upper lobes in both lungs

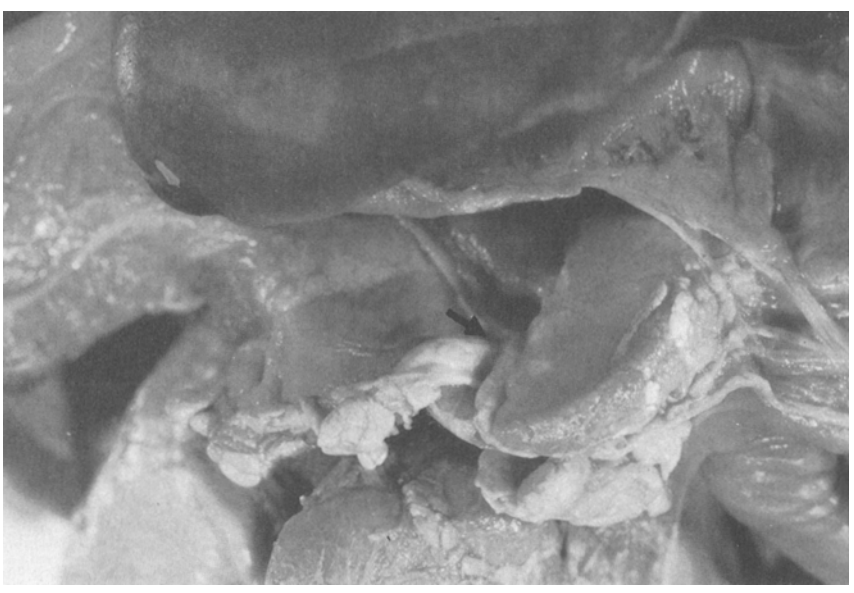


Fig. 4. Case 2. Partial visceral heterotaxia. Anterior view of abdominal viscera shows stomach and pancreas (*arrow*) located on the right side while the remaining viscera were in normal position. No spleen was present

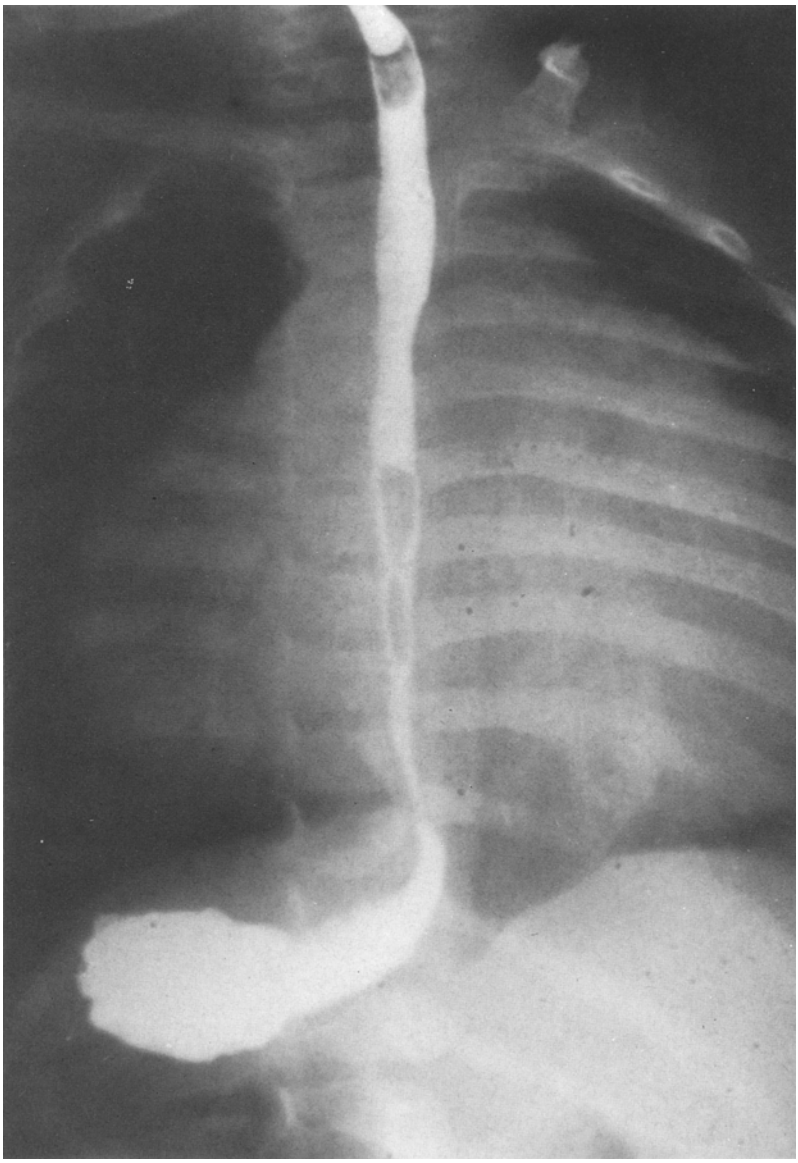


Fig. 5. Case 3. Barium swallow X-ray examination shows the right-side stomach

or infectious disease during pregnancy. The family history was unavailable. At birth, the infant was cyanotic and was transferred to an intensive care nursery. Cardiac catheterization showed L-transposition of the great vessels, pulmonary atresia and infra-diaphragmatic totally anomalous pulmonary venous drainage. The infant was taken to surgery where he died during the procedure.

Autopsy Findings. A single superior vena cava entered the right portion of a common atrium as did a hepatic vein which entered its right inferior wall. The inferior vena cava entered the lateral wall of the left portion of the common atrium. Both right and left portions of the common atrium had anatomic features of a right atrium. The coronary sinus was absent. A single atrio-

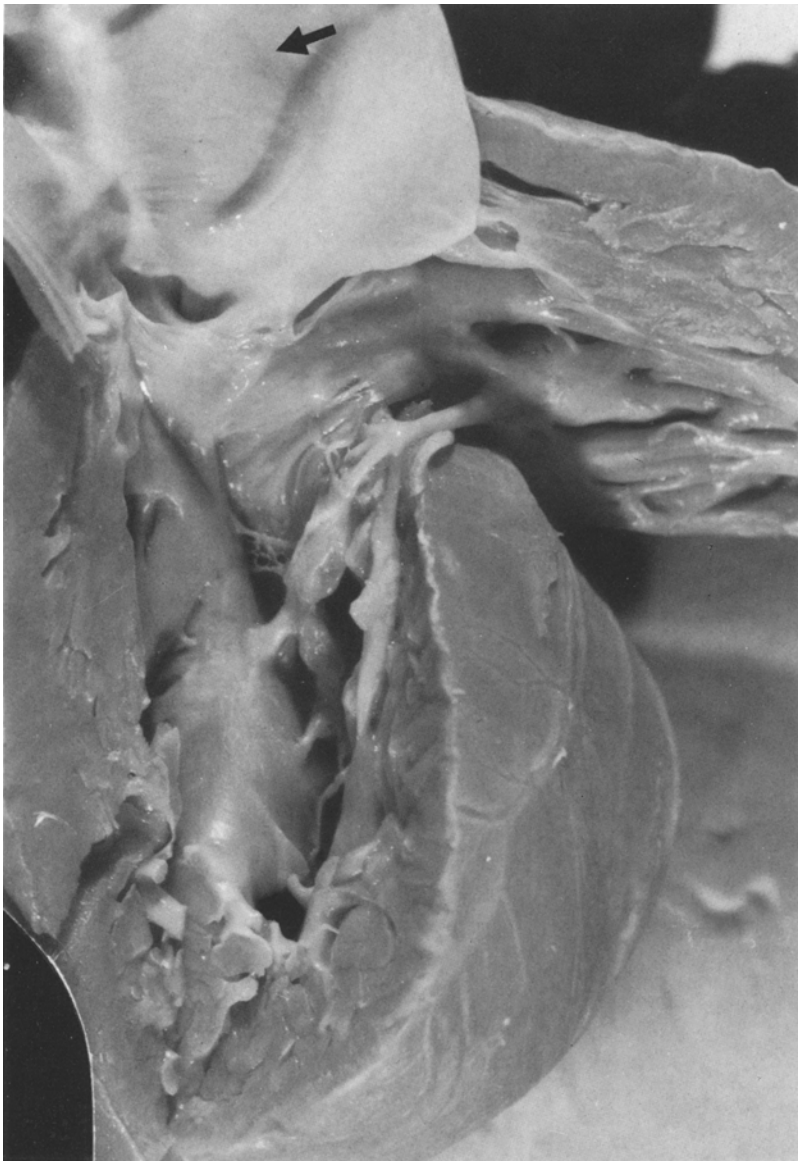
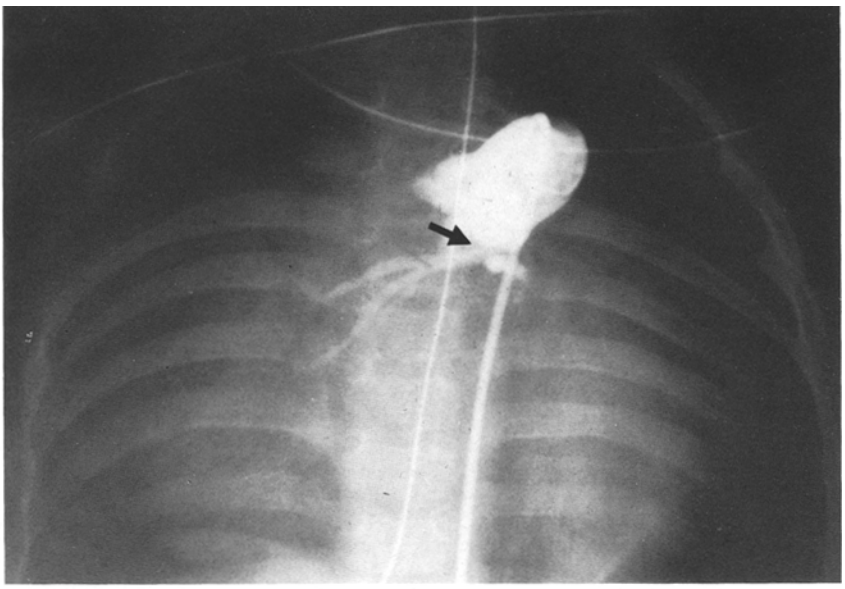


Fig. 6. Case 3. The common ventricular chamber has been opened along the line of the outflow tract into the aorta. The aortic valve is normal. Above it the aortic arch (*arrow*) is on the right side. Beneath it and to the right is the common atrioventricular valve (mitral type) which has thick leaflets and thickened chordae tendinae

ventricular valve with three cusps connected the common atrium to a common ventricle. There was L-transposition of the great vessels. A normal aortic valve was located anteriorly on the left side and had three normal cusps. The aorta arose from this valve and proceeded into a right-side aortic arch (Fig. 1). The coronary ostia were normally located. The pulmonic valve was absent. The main pulmonary artery was atretic. The right and left pulmonary arteries were supplied by an accessory pulmonary artery which coursed to the hilum of the left lung where



A

B

Fig. 7. Case 3. Single coronary artery. **A** Aortic angiogram shows only one coronary artery (*arrow*) arising from the aortic bulb and filling with opaque dye. **B** Autopsy specimen. The aorta is opened at the level of the aortic valve and only one coronary artery (*arrow*) arises from the sinus of Valsalva

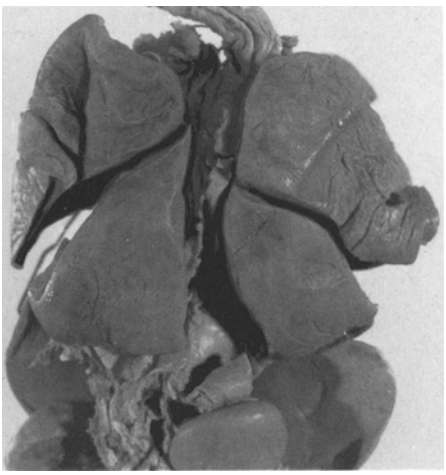


Fig. 8. Case 3. Left pulmonary isomerism. A posterior view show both lungs to be bilobed. Additional confirmation of left pulmonary isomerism was the presence of bilateral lingular segments and a hyparterial bronchus to the upper lobe in each lung

Fig. 9. Case 3. Polysplenia. A small accessory spleen (*arrow*) was located at one margin of the normal size spleen

it joined the pulmonary arterial tree (Figs. 1 and 2). A large pulmonary vein drained both lungs and passed through the diaphragm where it joined the inferior vena cava 3 cm below the diaphragm.

Externally both lungs had three lobes (Fig. 3). Both lungs had eparterial bronchi to their upper lobes, confirming right pulmonary isomerism. Inspection of the abdominal viscera showed a transverse liver with the gallbladder located in the midline. The stomach and pancreas were located on the right side, but the remaining viscera were in normal position (Fig. 4). The spleen was absent. The aorta was to the left of the inferior vena cava. Remaining autopsy findings were normal.

Case 3

Clinical Features. This 18-month-old Mexican girl was born after an uneventful, uncomplicated 9 month gestation. The mother denied exposure to any harmful substances or any infectious diseases during pregnancy. The family history was unremarkable. At birth the infant was cyanotic, congested, and sommulent. After admission to the hospital, X-ray showed a right-side stomach (Fig. 5) and a liver-spleen scan showed a transverse liver and a nonvisualizing spleen. Cardiac catheterization studies showed a single ventricle and a single atrium with transposition of the great vessels, interruption of the inferior vena cava with flow into the azygous system, bilateral superior vena cava,

and diminished pulmonic blood flow. The patient was taken to surgery for a Blalock-Taussig operation. Post-operatively the child developed complications and died.

Autopsy Findings. Bilateral superior vena cavae were present. The inferior vena cava was absent. Venous drainage from the abdomen and lower extremities was via an enlarged azyos vein. The hepatic veins drained directly into the right portion of the common atrial chamber. The right and left portions of the common atrial chamber had the anatomic features of a left atrium. This common atrium connected with a common ventricle by a single atrio-ventricular valve with two thickened leaflets (Fig. 6). Chordae tendinae from the leaflets were attached to two papillary muscles however, one of the "papillary muscles" was a septum-like structure. A normal aortic valve in the usual position leads to a normal aorta. The aorta arch was on the left side. A single coronary artery (Fig. 7) arose from the aorta and immediately divided into two major branches. The pulmonic valve was in the normal position but had thickened cusps and was stenotic. The main pulmonary artery was small, about half the size of the adjacent aorta. The pulmonary veins drained into the common atrium through the left lateral wall. A normal coronary sinus was present. Externally, the lungs were bilobed, showing bilateral lingular segments (Fig. 8). Each lung had a hyparterial bronchus to the upper lobe, confirming left pulmonary isomerism. Abdominal viscera showed a broad transverse liver with a right-side stomach and descending colon. The gallbladder was on the left side. There were two large spleens in apposition but separated by the dorsal mesogastrium. A small accessory spleen was present (Fig. 9).

Case 4

Clinical Features. This one-day-old boy was born after an uncomplicated, uneventful term pregnancy. The 19-year-old gravid I mother denied exposure to harmful substances or to infectious diseases during the pregnancy. The family history was unremarkable. At birth, the infant was cyanotic and was immediately transferred to the intensive care nursery. Cardiac catheterization showed a single atrium, a single ventricle, probably anomalous pulmonary venous drainage, and a large patent ductus arteriosus supplying small pulmonary arteries. Shortly after cardiac catheterization the infant died.

Autopsy Findings. Bilateral superior vena cavae were present. The inferior vena cava coursed along the left side of the abdominal aorta and entered the left portion of the common atrial chamber. The common atrium leads to a common ventricle through a tricuspid valve. The pulmonic valve and main pulmonary artery were absent. A normally located aortic valve was the sole outlet from the ventricle into a right-side aortic arch. A patent ductus arteriosus arising directly from the right-side aortic arch supplied the right pulmonary artery. The left brachiocephalic artery connected with the left pulmonary artery. Large right and left pulmonary veins were present but no outlet was evident. Instead, pulmonary venous drainage was by multiple small veins from both right and left lungs which formed a small conduit that emptied into the left superior vena cava. Both anatomic right and left lungs were identified.

Partial situs inversus of the abdominal viscera was identified. The major portion of liver and the gallbladder were on the left side. The spleen and two small accessory spleens were located on the right. The pancreas was on the right as was the descending colon. Other abnormalities included a Meckel's diverticulum and a double ureteral collecting system for the right kidney.

Discussion

Although cor biloculare is a rare congenital anomaly of the heart, it has frequently been classified under the asplenia or polysplenia syndromes. These syndromes have been extensively reviewed (Aguilar et al. 1956; Goerttler 1963; Ruttenberg et al. 1964; Moller et al. 1967; Van Mierop et al. 1972). Van Mierop et al. (1972) reported 145 cases of asplenia in the literature and 35 cases of polysplenia. Two of our cases can be classified as examples of the asplenia syndrome. Certain features of the asplenia syndrome and pertinent to our cases have been cited (Van Mierop et al. 1972). There is a striking male predominance, ranging from

62–82%. Right pulmonary isomerism occurs in 96–100%. A right-side stomach and pancreas are found in 50% of the cases. Anomalous pulmonary venous drainage occurs in 88%. Transposition of the great vessels is seen in 56–70%, pulmonary stenosis or atresia in 68–76%, a right-side aortic arch in 30%, and a single ventricle in 50–60%. Van Mierop et al. (1972) state that in asplenia syndrome large defects of the atrial septum are almost invariably present. Our other two cases can be classified as examples of the polysplenia syndrome. Certain features relevant to these are cited (Van Mierop et al. 1972). Bilateral superior vena cavae were found in 43% of the cases of polysplenia with absence of the inferior vena cava in 70%. In cases with absence of the inferior vena cava, drainage by the azygous system is the rule. The stomach and pancreas are located on the right in 66% of cases and left pulmonary isomerism is present in 65%. Pulmonary stenosis or atresia is present in 12% of cases. Although our cases had single ventricles, more than 90% of the hearts in the polysplenia syndrome have two ventricles.

Our four cases have certain features that differ from previous reports. Unlike other reports of cor biloculare, these four cases appeared at the end of normal, full-term, uncomplicated pregnancies. Family histories revealed nothing contributory. Our series presented a striking similarity between associated anomalies in all four cases (Table 1). Previous reports have shown considerable diversity in the associated anomalies. All of our series had severe pulmonic valve malformations and pulmonary artery atresia. Three of the four had anomalous pulmonary venous drainage, and the fourth patient had anomalous drainage of the systemic venous return. All of our patients showed visceral heterotaxia, and had polysplenia or asplenia. This incidence of anomalous pulmonary venous drainage, pulmonic valve malformations, and visceral heterotaxia in our series is significantly greater than that previously reported.

The specific etiologic factors that produce this array of anomalies remains unknown. However, a clue to when the factors may be operating during gestation may be obtained by correlating these anomalies we observed with certain stages of embryologic development. Early work (Bacon 1945) with removal of a square area from the dorsum of an embryo, halfway down its back, with 180° rotations resulted in situs inversus of the heart and other viscera. Embryologic review shows that situs of the viscera is determined before signs of heart asymmetry at 25–26 days while splenic development, and formation of the inferior vena cavae are seen between 33–36 days (Campbell and Deuchar 1967). This implies a much earlier point of vulnerability. In our cases, the exposure histories for both chemical and infectious agents were negative, as were the family histories in three cases. Despite this an early genetic defect seems the most likely cause.

The association of cardiac, splenic and inferior vena caval anomalies has a common point in their dependent embryonic blood flow for normal development. The blood supply at day 25–26 changes from symmetrical to asymmetrical with the developing asymmetry of the primitive heart. These cardiac changes are perhaps the most pivotal. Campbell and Deuchar (1967) speculate that blood flow determines the lobe predominance in the liver and whether splenic primordia will meet with extending vessels. Thus Willis (1962) considers the spleen to be essentially part of the cardiovascular system. Even later developing

Table 1. Associated anomalies in cor biloculare

Case	1	2	3	4
Sex	Male	Female	Male	Male
Age	2 months	18 months	1 day	7 days
Atria	Single common	Single common	Single common	Single common
Ventricles	Single common	Single common	Single common	Single common
A–V Valve	Single 3 leaflets	Single 2 leaflets	Single 3 leaflets	Single 3 leaflets
Pulmonary valve	Absent	Stenotic	Absent	Absent
Pulmonary isomerism	Right	Left	None	Right
Anomalous venous return	Total anomalous pulmonary return to common atrium	Anomalous systemic return	Total anomalous pulmonary return to superior vena cava	Total anomalous pulmonary return to inferior vena cava
Heterotaxia	Partial visceral	Partial visceral	Partial visceral	Partial visceral
Spleen	Asplenia	Polysplenia	Polysplenia	Asplenia
Other	Rt. side aortic arch	Dextrocardia without transposition	Accessory pulmonary artery	Accessory pulmonary artery
	Patent ductus		Meckel's diverticulum	
		Single coronary artery	Double ureteral collecting system for right kidney	

cardiac anomalies may be due to alterations of embryonic blood flow. Hypoplastic left heart malformations, e.g. mitral atresia, aortic atresia, and hypoplastic aortic arch, were produced by Harh and co-workers (1973) by altering embryonic blood flow. Rychter (1962) produced ventricular septal defects with aortic arch malformations by applying silver clips to the third, fourth, and sixth aortic arches in developing chick embryos. Gessner (1966) and Gessner and Van Mierop (1970) placed a fine wire beneath the embryonic cono-truncal region in developing chick embryos and produced ventricular septal defects in the mature embryos. While these interventions were artificial, they did alter embryonic blood flow. These investigators concluded that abnormal blood streaming in the embryo during particular stages of gestation can cause cardiac malformations.

This embryologic experimentation reinforces the idea that altered embryonic blood flow, which is secondarily determined by cardiac symmetry and ultimately by early genetic influences on situs results in these malformations and not

whether the spleen is present, absent, or multiple. Ivemark (1955) describes cases that closely resemble the "asplenia syndrome" but which had single or multiple spleens. Van Mierop et al. (1972) state the asplenia syndrome may occur in patients who have splenic tissue. Consequently, we think the terms asplenia and polysplenia, when applied to these syndromes, are misleading. Conversely the terminology, mentioned by Van Mierop et al. (1972) of the syndrome of bilateral right-sideness or bilateral left-sideness with a subnotation of the particular cardiac defect would be more appropriate and reflect the embryology of the complex malformation.

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