Cardiovascular Clinics

VOLUME TWO | NUMBER ONE

Congenital Heart Disease

Daniel F. Downing, M.D. | Guest Editor

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F. A. DAVIS COMPANY, PHILADELPHIA

 Library of Congress Catalog Card Number 77-123778
International Standard Book Number ISBN 0-8036-2780-7

Editor's Commentary

The 1960's witnessed remarkable advances in the diagnosis, therapy, and understanding of the natural history of many important cardiac anomalies. Many of these advances, and other important considerations relating to congenital heart disease, are detailed in the present volume. As an adult cardiologist, I can only express unabashed admiration for the extraordinary contributions made by my colleagues in pediatrics. A very special "thanks" to the Guest Editor of this volume, Dr. Dan Downing.

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Etiology of Congenital Heart Disease

Eugenie F. Doyle, M.D., and
Monika Rutkowski, M.D.

Malformations of the cardiovascular system are among the most frequently occurring of all congenital defects.[1] Their etiology in most cases remains unknown. Recent advances in the fields of genetics, embryology, and infectious and metabolic diseases, however, have provided explanations for at least some of the many defects encountered. Most of the studies performed during recent years suggest a multifactorial relationship between environmental and genetic factors in the pathogenesis of congenital heart disease.[2–5] The factors that at present appear important in impairing cardiac development will be considered.

ENVIRONMENTAL FACTORS

Intra-uterine Infections

Intra-uterine infections may have teratogenic effects and cause cardiac malformations. This effect has not been shown for bacterial infections, but has been clearly demonstrated for viral diseases. Probably less than 10 per cent of all congenital cardiac malformations are caused by intra-uterine viral infections, including the 2 to 4 per cent caused by rubella virus.[6] The types of cardiovascular defects seen in infants whose mothers had clinical rubella in the first trimester of pregnancy have been extensively studied.[6–13] These studies showed a high incidence of patent ductus arteriosus (PDA) and some form of pulmonary artery obstruction.

Among 376 infants and children with virologically proved intra-uterine rubella who have been followed by the Rubella Project at our institution,[14] 182 (48 per cent) had congenital cardiovascular anomalies. Eighty-seven of these patients had cardiac diagnostic studies, which demonstrated patent ductus arteriosus in 78 per cent, right pulmonary artery stenosis in 70 per cent, left pulmonary artery stenosis in 56 per cent, brachiocephalic artery anomalies in 33 per cent, and coarctation of the aorta in 1 per cent. Except for valvular pulmonic stenosis, which occurred in 40 per cent, intracardiac anomalies were less common.[15]

Coxsackie B virus infections have been incriminated in the etiology of endocardial fibroelastosis.[16] Serologic evidence of an intra-uterine Coxsackie infection has been correlated with an increased incidence of congenital heart disease without a type-specific lesion.[17]

No evidence of increased congenital cardiac malformations has yet been seen with intra-uterine infections with cytomegalic inclusion disease, toxoplasmosis, chickenpox, or influenza.[6, 18] Whether the mumps virus has any pathogenetic relationship to endocardial fibroelastosis is still a matter of discussion.[19–21] Measles has been considered of possible teratogenic effect, but the data are inconclusive.[22] The correlation between Down's syndrome and viral hepatitis [23] has been seriously disputed.[24] Though vaccinia during the first trimester of pregnancy may increase fetal mortality significantly, no specific correlation with congenital heart disease has been seen.[25]

Radiation

The teratogenic effect of radiation depends largely on dosage and gestational age of the fetus, the most radiosensitive period being the first 16 weeks of gestation.[26] Radiation during that time may result in fetal or neonatal death, as well as in genital, skeletal, neurological, and ocular malformations.[26, 27] Specific effect on cardiovascular development is not available, however. It is generally agreed that radiation for therapeutic or diagnostic purposes should not be applied later than 10 days after the last menstrual period.[27, 28] This view is supported by the series in which a relationship between maternal X-ray exposure and increased incidence of Down's syndrome was found.[29, 30] Clinical experience suggests that in the total picture of congenital heart disease, the percentage of cases in which there is a history of maternal exposure to radiation during the first trimester is indeed low.

Metabolic Disorders

These disorders have been clearly proved to play a role in the etiology of congenital heart disease.

Diabetes mellitus

The exact mechanism of the teratogenic effect of diabetes is unknown; however, its existence is clearly demonstrated by the significantly increased incidence of lethal congenital malformations (2.9 per cent) in infants of diabetic mothers.[31] An increase in incidence of congenital cardiac malformations is reported by Driscoll and coworkers[32] who described, in their series of 95 postmortem examinations, six infants with a ventricular septal defect (VSD) and a number of more complicated anomalies. They also emphasized the tendency to cardiomegaly. A case with tetralogy of Fallot and another with cor triloculare biventriculare in a series of 140 diabetic offspring has been described.[33] The incidence of diabetes in families of infants with transposition of the great vessels appears to be higher than in families with other cardiac malformations.[34]

Phenylketonuria

Phenylketonuria may be associated with cardiovascular malformations. A family study of two female phenylketonuric patients with a total of ten offspring showed that seven of these had cardiovascular defects, usually coarctation of the aorta or patent ductus arteriosus. However, other reports on offspring of 16 phenylketonuric parents have not mentioned any cardiac malformations.[35]

Hypercalcemia

In this syndrome, supravalvular aortic stenosis, peripheral pulmonic stenosis, aortic hypoplasia, abnormal facies, faulty dentition, and varying

degrees of mental retardation may be associated. In spite of many reports [36–41] and animal experimental studies,[42] there is as yet no agreement as to whether this syndrome results from an increased calcium sensitivity in the mother or fetus, an overdosage of vitamin D, or a genetic defect. This syndrome may well demonstrate a multifactorial basis for cardiovascular anomalies, there being present a genetic defect that becomes potentiated by abnormal calcium metabolism. Figure 1 demonstrates a severe degree of supravalvular aortic stenosis of the diffuse type in a 4-year-old boy who also had severe stenoses in his pulmonary arterial tree. His brother had milder pulmonic stenoses.

Drugs

Many drugs cross the placenta readily and may exert a teratogenic effect on the fetus. The magnitude of the adverse effect depends on the type of drug, the dosage, and the time given. A definite relationship to congenital malformations, including cardiac anomalies, has been established for only a small number of drugs. Many more have been incriminated, but inconclusively.[43] The time of highest incidence of cardiac malformations appears to be between the 40th and 45th days after the last menstrual period.[34] Definite cardiac teratogenicity has been shown for thalidomide [44] without predilection for a specific lesion. One single case of transposition of the great vessels has been described with the use of dextroamphetamine.[43] Aminopterin and Amethopterin, both anticarcinogenic drugs, are documented to cause multiple congenital anomalies, including cardiac malformations.[45]

Drugs such as digitalis and thyroid stimulants, as well as antithyroid

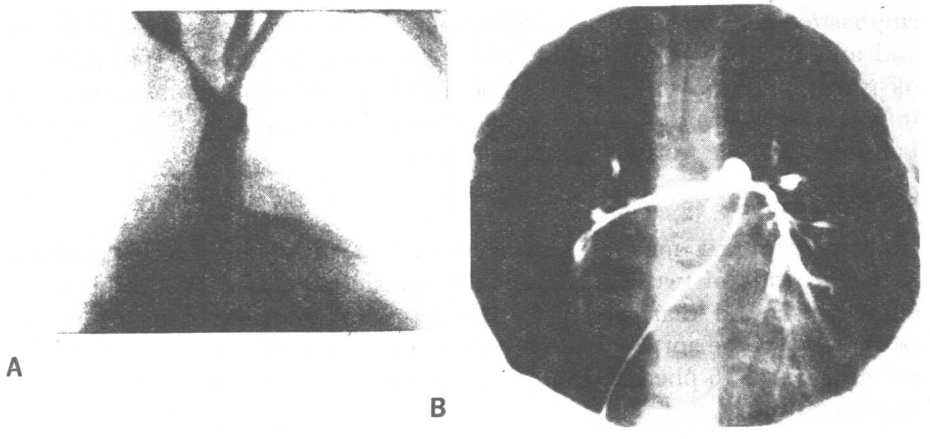

Figure 1. Supravalvular aortic stenosis syndrome. A, note the extreme degree of diffuse supravalvular aortic obstruction in this 4-year-old boy. Constriction of the right innominate artery is striking. B, severe stenosis of right and left pulmonary arteries and peripheral branches.

agents, do not exert a cardioteratogenic effect when used in therapeutic doses.[34]

Obstetric Considerations

Parental age

The association between increasing maternal age and congenital heart disease is not clearcut. Some investigators found that increased maternal age had no definite influence on congenital cardiac malformations,[3, 5] whereas others found a statistically significant correlation between maternal age and the occurrence of VSD and tetralogy of Fallot.[4] This controversy is in contrast to the clearcut relation between maternal age and occurrence of Down's syndrome.[46] Advanced paternal age appears at present of significant influence only in the group of 21/22 translocation.[47]

Prenatal factors

The history of antepartum bleeding during the first 11 weeks of gestation has been found to be associated not only with a high fetal loss rate, but also with a significantly increased risk of congenital anomalies, low birth weight, and neonatal mortality in the liveborn.[48] The exact relation between cardiac anomalies and obstetric complications is not known, though in clinical experience one frequently obtains a history of threatened spontaneous abortion in the pregnancy that resulted in an infant with congenital heart disease.

Prematurity

Prematurity apparently has some influence, whether direct or indirect, on congenital heart disease, since the incidence of PDA and VSD is increased.[31]

Geographic conditions

An increased incidence of PDA and atrial septal defect has been found in children born at high altitudes.[49]

GENETIC FACTORS

Recognized chromosomal aberrations and mutations of single genes account for approximately 6 per cent of all congenital heart disease.[2] The exact pathogenetic mechanism whereby genetic abnormalities cause congenital defects still is unknown; nevertheless, an increasing number of studies are yielding data on relationships between recognizable genetic disorders and congenital heart defects.

Chromosomal Aberrations

Chromosomal aberrations contribute probably less than 5 per cent of all cardiac malformations. The following syndromes associated with known chromosomal aberrations are presented in detail to illustrate current thoughts on possible relations between genetic and environmental factors.

Down's Syndrome

The features of this syndrome were first described by Down in 1860. The major manifestations are listed here.

Hypotonia
Severe mental retardation
Characteristic eye signs:
  Inner epicanthus folds
  Upward lateral slant
  Speckling of iris
Low nasal bridge
Protrusion of tongue
Short broad neck
Stubby hands and fingers
Simian crease pattern
Gap and/or frontal furrow, 1st and 2nd toes
Decrease in acetabular, iliac angle
Cardiac defects

According to most series, the incidence of congenital heart disease in mongolism can be estimated as between 12 and 44 per cent.[51] Most reports agree on the high frequency of endocardial cushion defects.[52–55] (See Fig. 2.) Next in frequency are VSD, PDA, atrial septal defect, and isolated aberrant subclavian artery. Less often encountered are transposition of the great arteries, tetralogy of Fallot, truncus arteriosus, left superior vena cava, coarctation of the aorta, anomalies of the aortic and pulmonic valves, and endocardial fibroelastosis.[51, 52] Thus, a wide spectrum of cardiovascular defects has been encountered with this syndrome.

Most patients with Down's syndrome have a karyotype of 47 chromosomes with a trisomy of the G-group (21–22) chromosomes that presumably results from a nondisjunction during the meiotic process in a parental gamete, usually maternal.[56] The etiology of the nondisjunction still is uncertain. Statistics suggest some relation with maternal age (Table 1).

A relation to increased paternal age had been suspected but could not be demonstrated except for the group of 21/22 translocation.[47] An association between maternal radiation exposure and mongolism has been reported.[29, 30] An increased incidence of thyroid antibodies has been found in the mothers of the age group 17 to 34 years who had children with Down's syndrome.[58]

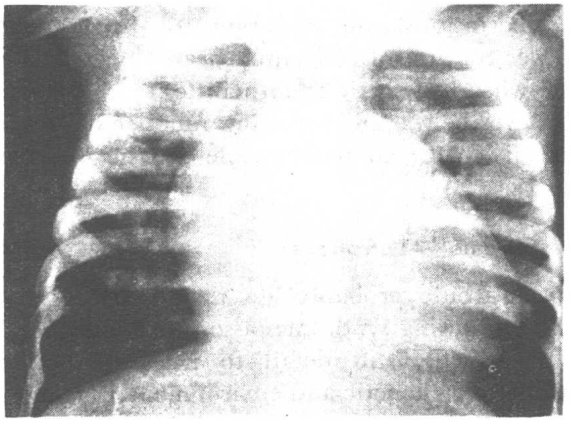

Figure 2. Down's syndrome. X ray of 9-month-old mongoloid infant in severe congestive heart failure with complete form of endocardial cushion defect.

Table 1. Risk for Down's syndrome related to maternal age

Maternal Age	Risk/live birth
15–19	1/1850
20–24	1/1600
25–29	1/1350
30–34	1/800
35–39	1/260
40–44	1/100
45–49	1/50

Trisomy 13–15

This syndrome with trisomy of the group D (13–15) was first described in 1960.[59] Its incidence is 1 per 5000 live births.[50] Forty per cent of mothers of reported affected infants were older than 35 years at the time of delivery. Most affected infants (65 per cent) were female. The most distinctive features of the syndrome are summarized in Table 2. The incidence of

Table 2. Frequency of clinical features and necropsy findings in reported cases of trisomy 13–15[50,56]

Area	Common (50% or more)	Less common occurrence
General	Apneic spells	Hypertonia, hypotonia
CNS system	Mental deficiency; deafness; minor motor seizures; agenesis of external olfactory lobes	Fusion of frontal lobes; agenesis of corpus callosum; cerebellar hypoplasia
Cranium	Sloping forehead	Microcephaly, wide sagittal sutures
Eyes	Microphthalmos, colobomata	Shallow supraorbital ridges; slanting palpebral fissures; absent eyebrows; hypertelorism
Auricles	Abnormal helices; low-set ears	
Mouth, mandible	Cleft lip, palate	Micrognathia, narrow palate
Skin	Capillary hemangioma	Localized scalp defects; loose skin at neck
Hands	Horizontal palmar crease; hyperconvex, narrow fingernails; flexion and overlapping of fingers	Retroflexed thumb; ulnar deviation of hand and fingers
Feet	Polydactyly of hands and feet; posterior prominence of heel	Dermal hallucal arch fibular pattern; syndactyly; hypoplastic toenails
Abdomen	Accessory spleen; large gallbladder; incomplete rotation of colon	Umbilical inguinal hernia; omphalocele; heterotopic pancreas tissue
Renal		Hydronephrosis; double pelvis and ureter.
Genitalia	Cryptorchidism; abnormal scrotum; partial bicornuate uterus	
Cardiac	Malformation	Rotational anomaly; VSD; ASD; PDA; anomalous venous return; bicuspid aortic valve; overriding aorta

associated heart disease is approximately 80 per cent. The most frequent anomaly is VSD; dextrorotation also has been reported.[50]

The outlook for these children is very poor, cardiac failure and bronchopneumonia being the most frequent causes of death.[50] Over 80 per cent died before the age of 6 months.[56] However, one of our patients with this syndrome, whose karyotype is seen in Figure 3, survived to age 4 despite a large VSD with pulmonary hypertension and ultimately succumbed to renal failure.

Trisomy 18

The incidence of the syndrome Trisomy 18,[60] first described in 1960,[61] is 1 per 3500 live births.[62] Seventy-eight per cent of all reported cases were females. The syndrome has been reported chiefly in Caucasians, but has been seen in Puerto Ricans, Negroes and Chinese. The mean maternal age is 34.3 years.[63] The percentage frequencies of clinical features and necropsy findings are presented in Table 3.

A high incidence of associated heart disease has been reported. In 90 per cent, a VSD was found.[64–66] The VSD was described by Townes [67] as being triangular and in the posterior membranous septum. Other associated cardiovascular lesions include PDA, patent foramen ovale, thickened valvular leaflets, bicuspid aortic and pulmonic valves,[64] double outlet right ventricle,[68] infantile arteriosclerosis,[69] and dextrocardia.[70]

The prognosis for these babies is extremely poor. Over 80 per cent have died before the age of 6 months from congestive cardiac failure, bronchopneumonia, or infections of the genitourinary tract.[66]

Cri du Chat Syndrome

This syndrome belongs to the group of chromosomal deletions, of which an increasing number have been recognized in recent years. Lejeune,[71] in 1963, reported three patients who had a peculiar cry, physical and mental retardation, microcephaly, small body size, low-set ears, antimongolian slant

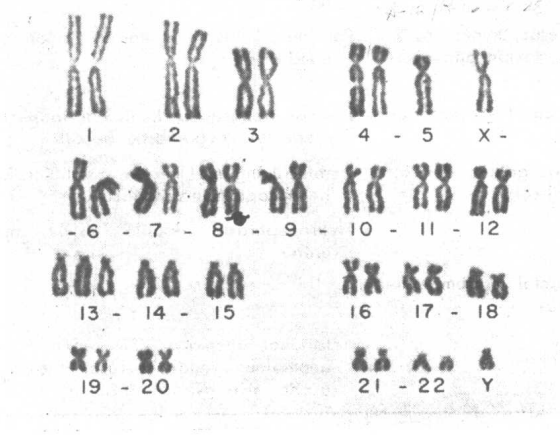

Figure 3. Karyotype of patient with trisomy 13–15. Note the extra chromosome in the D group. Patient had ventricular septal defect with severe pulmonary hypertension, extreme mental and motor retardation, low set ears, bifid 5th digits. Death at age 4 resulted from renal failure complicating extreme hydronephrosis.

Table 3. Frequency of clinical features and necropsy findings in reported cases of Trisomy 18[50,57,64,65]

Area	High frequency (80–100%)	Common (50–80%)	Less common occurrence (10–50%)
Growth	Birth weight < 6 lb.; failure to thrive		
CNS	Mental deficiency; muscular hypertonicity		
Cranium		Prominent occiput	Metopic sutures
Ears	Low-set, malformed		
Eyes			Ptosis; inner epicanthic fold; corneal opacities; small palpebral fissures
Mouth and mandible	Micrognathia; narrow palatal arch		Cleft lip and palate; small mouth
Hands	Fingers flexed; index finger overlaps 4th		Simian crease; single crease 5th finger; hypoplasia of fingernails; ulnar or radial deviation of hand
Feet	Hallux short or dorsiflexed		Rocker-bottom feet
Thorax		Short sternum	Wide chest or widespread nipples
Pelvis and hips		Small pelvis; limited hip abduction	
Genitalia		Cryptorchidism	
Renal			Horseshoe kidney; double kidney; double ureter
Cardiac	VSD	PDA; PFO	ASD; bicuspid aortic valve; nodular or fibrotic thickening of valve leaflets

of the eyes, hypertelorism, and divergent strabismus. The karyotype revealed a deletion of the short arm of chromosome 5. Seven additional cases have been reported thus far. The distinctive weak, mewing cry results from weakness and underdevelopment of the larynx, with a small, soft, very mobile epiglottis; it may disappear as the child grows older.[72] The exact incidence of the syndrome is unknown. A correlation with increasing maternal age does not exist.

Heart disease occurred in two of the ten reported cases. One had a PDA; [72] the other patient,[71] an atrioventricular canal with pulmonic stenosis, transposition of the great arteries, and partial anomalous systemic venous return to the left atrium. The mortality rate in this syndrome is low compared to that of the trisomies.

Turner Syndrome

Turner [73] originally described seven female patients with short stature, webbed neck, cubitus valgus, and infantilism (Fig. 4). Subsequently,