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Etiology of congenital heart disease

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THE ETIOLOGY OF CONGENITAL HEART DISEASE

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INTRODUCTION

The objective of this paper is to evaluate and discuss the known and postulated etiologies of congenital cardiac lesions, and the possibility of effective prophylactic measures. Source and reference material have been gathered from the medical literature and from an analysis of records of patients at the University of Nebraska Hospital, Omaha, Nebraska.

EMBRYOLOGIC CARDIAC DEVELOPMENT

A clear understanding of intrauterine embryologic cardiac development is essential for an adequate appreciation of the various factors responsible for congenital cardiac defects. Thus, one can more readily understand the interrupted scheme of development, the resulting pathologic anatomy, and the probable time of intrauterine occurrence of these defects.

By the third week of intrauterine development, the primitive heart begins to take recognizable shape. At the end of the eighth week, a functional circulatory system has been developed and the embryologic development as such has been completed. Therefore, it is obvious that the majority of alterations of cardiac architecture have occurred during the initial eight weeks of intrauterine existence. (31) (9)

The primitive cardiac structure is evolved from the fusion of paired cardiac primordia. During the time of fusion, they bear alternate dilatations and constrictions indicative of the future atria, ventricles and bulbus.

Such a heart shows three divisions; paired atria (fusion not completed), single ventricle and bulbus. Within the next two days of development the fourth division, the sinus venosus, becomes recognizable. The fifth division, the truncus arteriosus, has now developed at the cephalic pole of the rudimentary heart. This structure serves as a conduction vessel to the aortic sac. (3)

During the early stages of development, the rate of growth of the cardiac tube exceeds that of the pericardial chamber. As a result, the heart is compelled to assume at first a simple bend and later a spiralled "S". These changes result in a reversal of the cephalo-caudal relationships of the primitive heart. The developing atrium is located between the sinus venosus dorsally and the bulbus-truncus ventrally. Lateral expansion, forming sacculations on each side of the bulbus is the only route of growth available.

Another major change resulting from the torsion and folding of the heart has been to place the cardiac inflow and outflow tracts in close apposition at the cephalic pole of the developing cardiac structure. (3) (16)

From the fourth to the fifth week the common atrial canal is divided into the left and right atria by a thin sickle-shaped membrane progressing downward from the mid-dorsal wall of the common atrial cavity. This is the septum primum whose free edge fuses with the paired endocardial cushions located at the junction of atrial and ventricular chambers. By the time the septum primum has arrived, these cushions, dorsal and ventral, have fused in a figure of eight fashion and divide the atrio-ventricular canal into paired right and left canals.

Prior to its fusion with the endocardial cushions, the semicircular defect at the free margin of the septum primum was known as the foramen primum. Simultaneously with this fusion, the septum

thins and becomes perforate in a previously intact area, forming the foramen secundum (interatrial foramen).

During the seventh week the septum secundum appears at the right of the septum primum. It is an incomplete membrane. Its prominent aperture is known as the foramen ovale. The growth of these septa proceeds in such a manner that each persists as a separate perforate membrane, each covering the defect of the other. (31) (3)

The primitive atria are further modified by the incorporation into their walls of much of the sinus venosus and stem portions of the pulmonary veins. The residual of the sinus venosus becomes the oblique vein of the left atrium and the coronary sinus. This results in two entries into the right atrium, superior and inferior vena cava. The single pulmonary vein is absorbed into the wall of the left atrium past the original bifurcation into right and left pulmonary veins and through their respective divisions resulting in four pulmonary venous apertures. (3)

Simultaneously with the atrial septation, a ventricular median partition begins to project from the base of the common ventricle. This septum is increased in prominence by the enlargement and deepening of the paired ventricular chambers. This septum develops as a crescentic plate whose two horns meet and fuse with the endocardial cushions. The remaining defect, the interventricular foramen, will be closed by the membranous

portion of the ventricular septum. This foramen is closing by the end of the seventh week. (3) Tissue to effect this closure is derived from the ventricular septum, proximal bulbar septum, and especially from the fused endocardial cushions. The resulting thin membrane is the septum membranaceum. The original ventricular septum, becomes the septum musculare of the adult heart. (3) (26)

The proximal portion of the bulbus becomes incorporated into the wall of the right ventricle due to slow growth and possible atrophy of the bulboventricular fold, developed during the flexion and rotation of the cardiac tube.

Two prominent longitudinal thickenings develop in the truncus and distal bulbus. These ridges pursue a spiral course, meet and fuse, forming two independent lumens, the ascending aorta and pulmonary artery in their final spiralled courses. In addition to the two longitudinal ridges, two narrow thickenings appear in the region of the aortic and pulmonary valve roots. With the division into aorta and pulmonary arteries, three thickened masses remain in each lumen. These disappear distally, then hollow out on their distal surfaces and form the semilunar valves. (3) (16)

An important valve develops in each of the newly formed atrio-ventricular canals. Elevated folds appear at the margins of these canals. Three form about the right canal and two about the left. These flaps are developed by an undermining

process in which the attached muscular cords decrease in number. Degeneration of muscle tissue transforms the valve cusps to fibrous flaps and the muscle cords into the chordae tendineae. Their terminal portions persist as the papillary muscles. (3)

As would be expected from the duplicate cardiac primordia, the outflow tract is also a paired structure. In the fourth week of development the paired dorsal aortae have fused distally and are connected to the heart by paired aortic arches. Six pairs of aortic arches develop, but all are not present at any one time. (3) The period of development of these arches extends through the fourth week and their transformation occupies the fifth, sixth, and seventh week. (3)

Early involution between the third and fourth week characterizes the first and second pairs of arches with little contribution to the final vascular architecture. The third arches persist, retaining their connections with the paired dorsal aortae and forming the common carotid arteries.

The fourth arches persist but their fates differ. The left persists as the arch of the aorta. The right side merges with a portion of the aortic sac to become the right innominate artery. The distal union with the aorta is completely lost.

The fifth arches, inconstant, incomplete and transitory disappear without contribution to the final vascular network.

The sixth arches from the paired aortae merge with the primitive pulmonary arteries arising from the aortic sac. On

the right, the pulmonary artery loses its connections with the right dorsal aorta but retains it on the left as the ductus arteriosus. (3)

The previously described division of truncus and bulbus occurs in such a manner that the right ventricle communicates with the composite sixth arch, pulmonary artery, while the left ventricle is in communication with the fourth left arch, aortic arch and dorsal aorta. (16) (3)

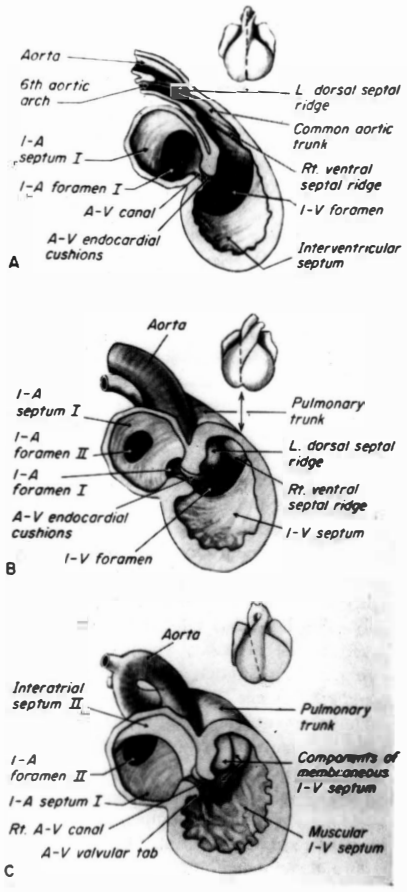

Fig. 1-8. A. The heart at 38 days, when the septal structures are developing rapidly but still permit free communication between the chambers, seen in para-sagittal section. B. The heart at 42 days, showing the septal structures nearing completion, in para-sagittal section. Potentiality for maldevelopment will persist, however, until final closure of all presently existing communications between the right and left sides of the heart. C. The heart at 48 days, seen in parasagittal section, after partitioning of the chambers is complete except for the interatrial communica- tion, which is not closed until after birth. The inter-atrial septum secundum will continue to grow across the right face of the septum primum until the fora- men secundum is obscured from view.

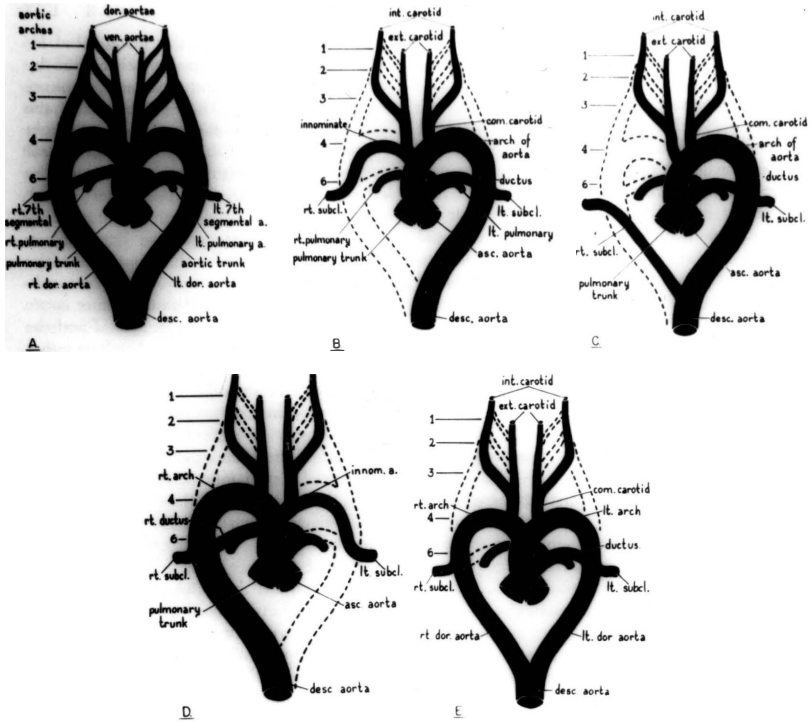

Fig. 1-6. Diagrammatic representation of differentiation in the aortic arch system. A. Composite view of the arches as they would appear if all were present at one time. B. Definitive pattern of arteries resulting from persistence of some parts (black) and regression of other parts (broken lines) of the embryonic pattern. C. Abnormal right subclavian artery resulting from absence of the right fourth arch and persistence of the right dorsal aorta between the seventh segmental artery (to upper extremity) and the descending aorta. D. Right-sided arch of aorta resulting from persistence of right instead of left dorsal aorta between the fourth arches and the descending aorta. E. Double arch of aorta (vascular ring) resulting from persistence of both dorsal aortas between the fourth aortic arches and the descending aorta.

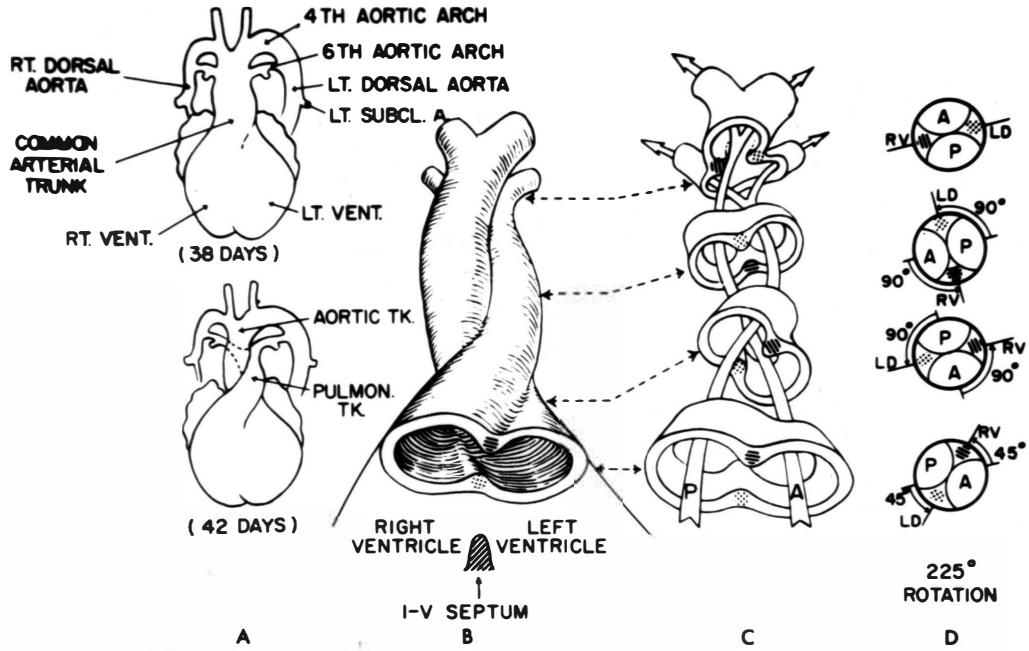

Fig. 1-9. Formation of the aortopulmonary septal ridges. A. The heart and caudal part of the aortic arch system at 38 and 42 days to show the development of the externally visible septal grooves. B. Detail of truncoconal region. C. Sections of the truncoconal region to show the changing position of the aortopulmonary septal ridges as they spiral in clockwise direction in proceeding from the sixth aortic arches toward the ventricular region of the heart. D. Schematic representation of the ridges to show the degree of spiral at different levels. *LD*, Left-dorsal septal ridge; *RV*, right-ventral ridge; *A*, aorta; *P*, pulmonary artery.

INCIDENCE AND EFFECT OF DEFECTS

An accurate evaluation of the frequency of occurrence of congenital cardiac defects in a population is exceedingly difficult because of the varied methods of reporting, and whether still births are included or not. Erroneous diagnoses, failure to perform necropsy examinations and a host of other factors are responsible for the varied incidences reported in the literature. An asymptomatic lesion, incomplete anatomical closure of the foramen ovale, is thought to occur in nearly one out of four individuals, but physiologically the aperture is non-functional. (3)

British authors report an overall incidence of 3/1000 births and 1/1000 at ten years of age. (31) Richards and her associates reported an overall incidence of 0.83% in a series of 60,000 babies in New York. (41)

Autopsy statistics, including still births, reveal an incidence of congenital heart disease of about 8/1000. (18) Congenital heart disease accounts for approximately ten to fifteen percent of all cardiac lesions. (26) (18)

Further discrepancies are noted in the reports of incidence of specific types of defects. This is readily understandable if the source of the material is considered.

Incidence of Major Congenital Cardiac Lesions in Maude Abbott's 1,000 Autopsied Cases of Congenital Heart Disease. (1)

Pulmonary stenosis with open ventricular septum	115
Patent ductus	105
Coarctation	85
Ventricular septal defect	62
Complete transposition of great vessels	49
Pulmonary stenosis with closed ventricular septum	35
Atrial septal defect	33
Dextrocardia	29
Cor biloculare or triloculare	27
Aortic stenosis	23
True truncus arteriosus	21
Tricuspid atresia	16
Aortic atresia	12
Aortopulmonary fenestration	10
Anomalous pulmonary venous drainage	4
Miscellaneous	374

Incidence of Major Congenital Cardiac Lesions in 200 Clinically Studied Cases. (53)

Pulmonary stenosis with ventricular septal defect	40
Atrial septal defects	35
Patent ductus arteriosus	29
Pulmonary stenosis without ventricular septal defect	24
Ventricular septal defect	24
Coarctation	16
Tricuspid atresia	6
Aortic stenosis	6
Eisenmenger complex	2
Complete transposition of great vessels	2
Miscellaneous	16

Incidence of Major Cardiac Lesions in 100 Infants Dying In First Month of Life. (33)

Transposition of great vessels	27
Ventricular septal defect	18
Cor triloculare, cor biloculare	12
Coarctation of aorta	11
Tetralogy of Fallot	4
Miscellaneous	28

Incidence of the More Common Congenital Lesions in 577 Proved Cases at the Children's Hospital of Boston. (24)

Patent ductus arteriosus	101
Atrial septal defect	97
Pulmonic stenosis	83
Ventricular septal defect	68
Tetralogy of Fallot	54
Coarctation of aorta	63
Transposition of great vessels	36
Eisenminger Syndrome	27
Tricuspid atresia	17
Total anomalous pulmonary venous drainage	13
Truncus arteriosus	11
Single ventricle	4
Ebstein's disease	2
Primary pulmonary vascular obstruction	2
Miscellaneous	4

Incidence of Major Congenital Cardiac Lesions in 196 Cases Subjected to Cardiac Catheterization at University of Nebraska Hospital.

Ventricular septal defect	60
With other anomalies	11
Atrial septal defect	33
With other anomalies	5
Pulmonary stenosis	18
Patent ductus arteriosus	11
With other anomalies	4
Tetralogy of Fallot	16
With other anomalies	2
Ventricular septal defect plus atrial septal defect	7
Eisenmingers Complex	6
Aortic stenosis	3
Miscellaneous	20

An autopsy series such as Maude Abbott's will probably not reflect an accurate accounting of the defects responsible for minor physiologic or hemodynamic changes. A series arising from a group of surgical cases will not include the minor defects nor those incompatible with life or those responsible for death in the first one to two years. An autopsy series of cardiac lesions

responsible for death in the first month post partum will report those incompatible with life or responsible for major hemodynamic disturbances. A series of proved diagnoses such as those from Children's Hospital of Boston will not include the very severe lesions responsible for death, nor will it contain those of a minor nature. The series from Nebraska is not an accurate representation of cardiac lesions found at large. As in other series it contains neither the very minor nor the markedly severe lesions. The catheterization series are those patients considered for cardiac surgery as well as diagnostic problems. Further variance is noted when age is considered. Series of patients ten years of age or older will show a significant variation from those of one-two years, due to the markedly higher mortality in the first few years secondary to defects causing severe hemodynamic alterations.

The congenital cardiac lesions are conveniently classified according to their alteration of normal hemodynamic and physiologic function. (9)

I. Malformations not associated with a shunt (acyanotic)
   A. Malformations of the left side of the heart
   B. Malformations of the right side of the heart

II. Malformations with a circulatory shunt
   A. Malformations with left to right shunt (acyanotic)
   B. Malformations with right to left shunt (cyanotic if shunt is of large volume)

III. Malformations with combined shunts, predominantly left to right (cyanotic in specific instances)

ETIOLOGY

Historical Introduction

The appreciation of cardiac anatomic defects, and the resulting hemodynamic and physiologic disturbances, has evolved comparatively recently. Accumulation of knowledge of the varied and multiple etiologies and the appreciation that these are not merely developmental accidents are phenomena largely of the last twenty years.

Hippocrates is said to have written that the heart was not subject to disease. Galen disagreed with this opinion and classified cardiac lesions as wounds and inflammations, pericarditis and pericardial effusions, and palpitations. (25) Botalli, improving upon Galen's theory that blood passed from right to left heart through spaces between the trabeculae of the ventricular septum cited instances of patent foramen ovale as the probable route of flow (36)

William Harvey's monumental work provided the basis for a clear understanding of anomalous cardiac anatomy and function. Senac provided one of the first descriptive series of cardiac anomalies (19) while Morgagni is credited with having established the anatomic concept of cardiac disease. (25) Meckel explained various cardiac defects as embryologic developmental failures and Farre classified the known defects on a functional basis, as those that caused mingling of the blood and those that resulted

in impediment of the circulation. (19)

Great contributions to present day knowledge have been made by Lannec, Rokitansky, Born, Heberden, Aschoff, His, Adams, Stokes, Abbott, Patten, Taussig and a host of others.

ENVIRONMENTAL EFFECTS

Intrauterine hypoxia has been suspected of having a causal relationship to human congenital defects although the pathogenic role of fetal hypoxia is difficult to establish. There is a growing body of epidemiological and clinical evidence that indicates a definite relationship. Experimental evidence of the deleterious effects of fetal hypoxia is abundantly available. Experimental procedures designed to subject the embryo to hypoxia has induced developmental defects in fish, birds and mammals. (22)

In a survey of 176 cases gathered from the mountainous areas of Peru, Alzamora has reported an apparent relationship between altitude and its associated lowered oxygen tension, and certain congenital cardiac defects. Patent ductus arteriosus was observed to occur at a statistically significantly higher rate than its expected frequency in babies born above 3,000 meters elevation. Intra atrial communications occurred at a significantly higher rate than expected in babies born above

3,500 meters altitude and an incidence of pulmonic stenosis is suggestive but not conclusive in these altitude ranges. (2)

In the area from which these cases originated, communicable diseases except for typhus are not common. Rheumatic fever is uncommon, sub-acute bacterial endocarditis is very rare and rubella is practically non-existent. This would tend to rule out the possibility of maternal infection playing a role in these defects. (10)

Additional support for the role of hypoxia in teratogenesis is provided by seven family studies, where each of the mothers had cardiac defects, as did the majority of their progeny and also one third generation member. The possibility of intrauterine hypoxia is strongly suggested as a causal factor in the repetition of these defects in the second and third generation (22) Other factors such as severe maternal anemia, poor placental function, carbon monoxide poisoning, placental infarct and numerous other factors that could lead to intrauterine hypoxia have been implicated, but the relatively small numbers of these cases coupled with incomplete case histories make it impossible to state a definite relationship. (22)

The factors leading to closure and obliteration of the ductus arteriosus and closure of the foramen ovale are not entirely clear but it appears that oxygen tension as well as mechanical factors may be involved. As this closure occurs in early post-natal life, birth or neonatal hypoxia would be implicated rather than

intrauterine conditions. (2) (22)

A remarkable correlation is noted between altitude and pulmonary hypertension in the presence of patent ductus arteriosus defects. Severe pulmonary hypertension was found with small shunts, early in childhood which was comparable in severity to that found at sea level in an older age group with markedly larger defects. Low oxygen tension of altitude and the resulting increased pulmonary blood flow, when added to the shunting from a patent ductus appears to produce an intolerable burden upon the pulmonary vasculature and results in hypertension that would not be expected until a later age. (10) It has been further postulated that low oxygen tension and the resulting increased cardiac output necessary to maintain life is responsible for the marked absence of cyanotic cardiac defects in this population. Persons with these severe defects are thought to die at birth or in the neonatal period. (10) (22)

In a survey of 434 cases of congenital cardiac anomalies it has been reported 9.5% of the fathers were chronically exposed to lead as painters or workers in lead smelters or battery plants. This is a significantly higher exposure than is found in the population at large and points to the possibility of damaged germ plasm or chromosomal variants secondary to paternal exposure to noxious agents. (11)

Various cardiovascular anomalies are reported among the numerous defects produced in the rat and mouse by experimental

vitamin A, riboflavin, pteroylglutamic acid and folic acid deficiencies and irradiation. (51) (20) Also administration of excess vitamin A has been shown to produce litters with fifty percent anencephalic embryos. (15) No data are available on this last series concerning effects on cardiogenesis.

Of the teratogenic vitamin deficiencies studied to date, that of pteroylglutamic acid, (P.G.A.), is noted for the wide range and high incidence of congenital defects produced in the rat. It appears that the biochemical reactions requiring this vitamin are key reactions in the embryo during differentiation and organogenesis. The embryonic requirements are so high that development is inhibited long before maternal signs of deficiency appear. The types and incidence of congenital anomalies produced by experimentally induced deficiencies varied, as would be expected with the stage of fetal development, duration and severity of the deficiency. Central nervous system, cardiovascular, optic, kidney, palate and skeletal deformities were noted. Alterations of the placenta were not evident and it appeared that the primary effects of the deficiency were directly on embryonic tissue. (32)

There are many reports of the teratogenic effects of various tumor inhibiting chemicals. Perhaps the most widely recognized effect is associated with the antimetabalite aminopterin, a folic acid antagonist. As would be expected, its effects are similar to those following severly acute P.G.A. deficiencies.

In animal experimentation resorption of fetus or normal survival are reported with little evidence of malformations. (30) Aminopterin has been used as a powerful human abortifacient although its use is believed related to numerous severe congenital anomalies in instances where it failed to induce abortion. (30) (29) (48) (52) Other tumor inhibiting chemicals are reported to induce stunting, edema, gross malformations and skeletal malformations. Unfortunately, there is no specific record of cardiac anomalies if present. (30) Limited experience indicates that the greatest danger to the human fetus from cytotoxic or tumor inhibiting agents is during the first trimester. However, the danger never disappears completely. (43)

Actinomycin D has not only antimicrobial but also a marked cytotoxic action. Its teratogenic effect becomes apparent with exceedingly small doses, several times less than those recommended for the clinical use of this drug. In experimental work with the rat the frequency and gravity of the malformations vary with the date of administration and doses employed. Resorbtion, malformation or both are reported. The malformations are very pleomorphic, involving eyes, nervous system, cardiovascular system, viscera and skeleton. (49)

It has been postulated that diabetes mellitus, "prediabetes of pregnancy" and hypothyroidism exert their well known deleterious effect on the fetus by metabolic disturbances

in the transformation of pro-vitamins to vitamin A. A selected series of cases with a known history of malformations, abortion and stillbirths responded very favorably when treated with insulin, thyroid extract or both. Whether this beneficial effect was due to vitamin A production or correction of the previously existing "hormonal imbalance" is not clearly understood. (20)

MALFORMATIONS SECONDARY TO SPECIFIC MATERNAL INFECTIONS

During the past twenty years the causal relationship between maternal rubella infections and abortion, stillbirth and congenital defects of the fetus has become widely accepted and well substantiated. It is also quite clear that the infections occurring early in pregnancy have the gravest prognosis and the most serious effects. (46) (34)

Infections occurring during the first trimester of pregnancy and the phase of embryological development are responsible for the majority of the pathology. The specific stage of embryological development at the time of infection is reflected in the type of defect produced. (46) (34)

It has been well established that the genesis of congenital cataract takes place about the fifth week of embryological development, almost a month before the genesis of post rubella deafness. It is likely that certain types of cardiac defects, tetralogy of Fallot, transposition of the great vessels and coarctation of the aorta are results of interrupted development earlier in the scheme of cardiogenesis than atrial and ventricular septal defects which occur in the late phase of cardiac development. (22)

Many authors feel that risk encountered after the fourth month of pregnancy is negligible. A summation of several series (13) (17) (23) reported reveals that first trimester maternal rubella is associated with ten percent stillbirths and seven

percent defective infants, second trimester with seven percent stillbirths, six percent defective infants, while no deaths or defects were noted in third trimester rubella. Many authors reporting series do not agree that second trimester infections produce as much as six to seven percent deaths or deformities. The incidence of fetal death or defect in cases of first trimester maternal rubella is reported as 17% in a series of 1,067 cases in Sweden (24) and 28% in an Australian series. (35)

Questions concerning the virulence of the rubella epidemic in Australia have arisen and it is thought that this was either an extremely virulent strain or very low host resistance in an area where rubella was not thought to be endemic.

An American series restricted to cases occurring during first trimester only reported 22.7% death or defect. (34) In view of these and other studies, it would appear that if maternal rubella is contracted during the first three months of pregnancy, the probability of death or defect in the infant is in the range of ten to twenty percent.

Cardiac defects most frequently noted following maternal rubella infection in order of their occurrence are: patent ductus, atrial septal defect, tetralogy of Fallot, and pulmonary stenosis. (31) Maternal rubella is thought to be responsible for the following congenital defects singly or in combination: congenital cataract, deaf mutism, cardiac disease, microcephaly, and mental retardation. (46)

Gregg (17) noted the following defects in his series of cases following the Australian epidemic: deaf mutism, ophthalmic and cardiac disease singly or in combination and possibly mental retardation. Large numbers of these children are below average birth weight. Most of them are below average weight for age, have poor physique and show variable degrees of microcephaly. Many are late in sitting and walking, and feeding problems are common. Signs of central nervous system instability are common during early life. There appears to be no relationship between the severity of maternal infection and the presence, nature or extent of defects in the child.

In every sizeable series of congenital cardiac anomalies, one will find instances of maternal infections of various etiologies. These do not appear to have occurred at an appreciably higher rate than found in the population at large.

Maternal Asian influenza infections, especially first trimester have been subject to considerable attention, with suggestive but inconclusive evidence to date. Ingalls (22) cites statistics from Coffey and Jessop's review of 220 cases of first trimester maternal Asian influenza infections showing the incidence of congenital deformities was about two and one half times that in the progeny of 220 controls who were not ill during pregnancy. The defects were anencephaly, spina bifida, meningocele and mongolism. However, the vital statistics of the Department of Maternal and Child Health at Harrisburg, Pennsylvania, following

the heavy outbreak of Asian influenza in October and November, 1957, reveal no statistically significant increase from previous years although rates for hemangiomata, club foot, cleft lip and palate, mongolism and anencephalus show their highest incidence for the year in March through June of 1958. No specific rates for cardiac disease are reported in this series. (22) An Australian series reports three cases of maternal influenza with two of the three resulting progeny with "heart disease", two with cataracts, and all three microcephalic. (47) Mumps infection has been implicated as predisposing to congenital defects. Swan (46) reports one case of congenital corneal opacities secondary to maternal mumps infection while in a series of 434 congenital cardiac disease cases, polio, rubella, "grippe", rheumatic fever, chorea, syphilis, bacterial infections, allergic manifestations, ptomaine poisoning, thyroid disturbances, trauma and exposure to lead are all listed as having occurred during the early portion of the pregnancy. (11)

The theory has been advanced that maternal toxoplasmosis infection during the first eight weeks of pregnancy could lead to congenital cardiac defects. In a series of 6 cases where the mother exhibited positive eye ground changes and positive Sabin-Feldman tests four of the infants died within five months of birth and exhibited autopsy findings of cardiac defects while the other two had clinical evidence of ventricular septal defect. Toxoplasmosis infection in the newborn is in all probability of

transplacental origin. (44) Maternal infection during early pregnancy by Japanese "B" encephalitis is thought responsible for mental retardation and occasional congenital anatomic defects. There are no large series published at the present time and accurate evaluation is therefore impossible. (12)

CHROMOSOMAL ABNORMALITIES

The etiology of congenital heart disease is unknown in the vast majority of instances. It is thought that hereditary factors may play a role since the incidence in siblings is significantly higher than that found in the general populations. (31)

Chromosomal abnormalities may be divided into three groups. First, errors in the numbers of sex chromosomes, secondly, errors in the numbers of autosomes, and thirdly, structural abnormalities. Mechanisms of origin are commonly thought to be (a) nondysjunction, implying the failure of the two members of a bivalent pair to separate at the first of the two meiotic divisions of gametogenesis. By extension it is applied to the second meiotic division and also to somatic mitosis; (b) structural change; these involve the breakage of the chromosomal threads in two or more places followed by rejoining the broken ends to produce changed sequences of chromosomal segments. Chromosomal structural changes are known to be brought about by ionizing radiation, certain chemical agents and also to arise spontaneously. These changes can be whole chromosome changes while the chromosomes are single strands in early interphase or chromatid changes secondary to breakage and reunion after the chromosomes have duplicated. There is an important distinction between the two, chromosome changes result in simple rearrangement of segments without changes of proportion or genetic balance, reciprocal translocations, in-

versions and rarely the insertion of a segment of one chromosome into another. Chromatid changes can produce the previously mentioned rearrangements as well as duplications and deficiencies. (14)

There is a clinical impression, partially corroborated by statistical and genetic investigations that heredity plays a role in each of the four major varieties of cardiovascular disease; hypertension; rheumatic fever and rheumatic heart disease; and congenital malformations of the cardiovascular system.

In pointing out a genetic factor in congenital malformations, one must not underrate the importance in the same or other cases of nongenetic factors operating in the intrauterine environment. (27)

Recent evidence of genetic factors has been of the following types; A. familial aggregation in sizeable controlled series B. consanguinity studies C. twin studies and D. animal analogue studies. Several reports indicate an increase in congenital cardiac malformations in the brothers and sisters of affected propositi as compared with controls. Also there is probably an increased incidence in the first cousins of these patients. One series of 1,188 cases showed the percent of siblings with congenital cardiac disease total 1.46% compared to a control of 1,483 children with no defects (0%) Percentages varied from a high of 3.74% with pulmonary stenosis to a low of 0.42% with

miscellaneous uncommon defects. (27)

A series of 151 patients with coarctation of the aorta was reported as having eight percent siblings with other congenital malformations of the heart, eight percent siblings with noncardiac congenital malformations and three percent of their siblings with major malformations. (6)

A series of 261 cases of patent ductus arteriosus revealed that six percent of these patients had other malformations while two percent of their siblings had congenital heart defects. The majority of these defects were patent ductus arteriosus. 1.6% of the first cousins were found to have congenital heart lesions also. (40)

There are large numbers of family groups with similar cardiac defects in two and sometimes three successive generations. From a genetic point of view these fraternities may be categorized as Mendelian recessive traits. Abbott (1927) reported eleven instances of brothers and/or sisters with similar heart defects. Brown (1939) reported six similar instances. Taussig (1947) has seen four families where more than one member exhibited congenital heart disease. In two of these families the lesions occurred in two successive generations. In a third family a grandfather, two of his three children, and one of two grandchildren had patent ductus arterioses. Walker and Ellis (1940) report a father and four of his eight children with patent ductus arteriosus. Barber (1945) reported a mother with coarctation of the

aorta, her two children both with patent ductus arteriosus. (5) One family study of mother, daughter and granddaughter all with atrial septal defect was attributed to a Mendelian dominant trait. (21) A series of case reports of four families and a summary of 141 families with multiple congenital heart disease was reported in 1958 and described as conforming best with a single recessive autosomal mode of genetic transmissions.(8)

The increased likelihood of consanguinous marriages giving rise to offspring with congenital cardiac defects, on a genetic basis is in part borne out by literature reports. Recessive Mendelian characteristics are often very difficult to detect, but the frequency with which some lesions appear following consanguinous marriages, especially between first cousins, offers one clue to their presence. Roesler (1928) observed consanguinity associated with ten percent of his cases of cardiac defects. Dextrocardia with transposition of viscera occurs at the rate of 1/20,000 patients. Marriage in first cousins should increase the rate to 0.6-0.9% if this is a recessive Mendelian trait, and 5-9% of the total numbers of a series should be associated with first cousin marriages. A series of fifty-three of these cases was reported with six associated consanguinous marriages. Fifteen of the above cases also exhibited tetralogy of Fallot, giving rise to the interesting possibility that other defects may be carried by the same or a closely related gene. (5) A reported series of 170 patients with atrial septal defects

reveals 1.9% consanguinous marriages, a considerably higher incidence than that found in the population at large, and strongly suggestive of a recessive Mendelian characteristic. (7) A family report of five children of a first cousin marriage shows: first child deceased, bronchopneumonia; second child died, age five days, unknown etiology; third child died, age one year, eight months with congenital cardiac disease; fourth child, underdeveloped but doing well; fifth child, died age two years, four months with cardiac type of glycogen storage disease. (54)

Studies of congenital heart disease in twins suggest a relatively weak genetic factor with low order of magnitude. Numerous pairs of monozygotic twins with only one affected by congenital heart disease have been reported with rather few instances where both twins were affected. It is thought that in many twin cases, the congenital defect resulted from in utero competition for blood supply. (27) A survey of 377 families of children with congenital heart disease showed no association with twinning. (39) While environmental gestational factors in many specific instances are causative of congenital defects, the material presented here appears to conform best with a single recessive autosomal mode of transmission. (8)

PROPHYLAXIS

The prophylactic approach to congenital cardiac diseases is severly hampered by the general lack of knowledge of their etiologies.

The known and accepted relationship of maternal rubella infections lends itself well to both a preventative and therapeutic approach. Deliberate exposure of pre-pubertal or non-pregnant females of an older age group to rubella has been long recommended and accepted as a desirable procedure. (35) (24) The production of lasting immunity to the disease is widely accepted. (42) (50)

One obvious drawback to the above procedure is that it will tend to spread the disease in a community and the possibility of exposure of susceptible pregnant women is markedly increased.

All pregnant females should be appraised of the dangers involved if exposure occurs. An increased awareness by the general public of the potential dangers could help markedly in preventing maternal infection. (35)

There is some evidence that gamma globulin will prevent rubella when given not later than the eighth day of the 2-3 week incubation period. (4) Large doses of gamma globulin (20 cc.) given as early as possible after exposure may prevent the disease in a pregnant woman exposed to rubella and without a history of the disease. This measure is recommended even though results are not assured. Damage to the fetus may result even though the infection in the mother has been inapparent. (42)

Results of three groups of persons exposed to rubella, treated with 0.1 cc./lb. gamma globulin, and subsequently contracting the disease, reported by Krugman and Ward are as follows:

	Incidence of Rubella	
A.	6%	Treated with 0.1 cc./lb. g.g.
	18%	Control
B.	13%	Treated with 0.1 cc./lb. g.g.
	13%	Control
C.	20%	Treated with 0.1 cc./lb. g.g.
	58%	Control

(Note: On the basis of these and other results the authors felt that the gamma globulin used in group B was defective.) (24)

Some persons feel that hyperimmune gamma globulin must be utilized to achieve worthwhile results. (50)

Therapeutic abortion, a certain method of preventing congenital defects, is frequently discussed, with widely divergent opinions expressed.

Eastman states, "....it is my own feeling that if the attack of rubella has been observed by a dependable physician and if the validity of the diagnosis is beyond question, and provided that the disease occurred in the first three months of pregnancy, therapeutic abortion is justifiable if the mother and her husband do not want to assume the obvious risks involved. After the end of the third month the incidence of congenital malformations as the result of maternal rubella is decidedly less; from the fourth month the chances of the infant's being affected are almost nil." (13)

While therapeutic abortion may be justifiable with young healthy parents, it would not be indicated with the patient who for reasons of age, health or fertility problem is much less likely to become pregnant again. (24)

As a result of a rubella epidemic in Sweden in 1951, the employment of therapeutic abortion was practiced on a wider scale than had been heretofore recorded in the literature. In support of this procedure Lundstrom cites a seventeen percent incidence of stillborn and/or defective infants from 1,067 mothers that contracted rubella as opposed to 3.2% instance in a control group of 2,226 that did not contract the disease. (24)

The question of therapeutic abortion cannot be answered easily nor can a set pattern be established. The physician confronted with this problem must reach his decision after consideration of age and health of the patient, possibility of further pregnancies, parental desires and religious factors. (50)

Further study of the rubella virus and an effective program of childhood immunization would probably be of considerable value.

Hyperimmune mumps gamma globulin, although quite expensive, is recommended by some practitioners in cases with known exposure during first trimester. Influenza immunization is in itself a rather controversial subject among many practitioners. Decisions regarding its use during first trimester pregnancy, in view of the questionable relationship between influenza and congenital defects should be reached on an individual basis between patient and prac-

titioner. Theruse of these immunizations can in themselves cause mild to marked reactions in some persons.

While accurate statistics concerning the relationship between maternal infection and fetal mortality or morbidity are not available, it appears to be exercizing good judgement to avoid risk both to the mother and the fetus whenever possible by avoiding exposure to toxic agents and communicable and infectious diseases.

The prevention of fetal and neonatal hypoxia become primarily obstetric but in part pediatric problems. Fetal hypoxia may result from maternal anemia, diminished cardiac output, secondary to maternal cardiac defects, etc. The alert obstetrician will make every attempt to prevent these occurrences. Also careful management during labor and at the time of delivery may do much to prevent neonatal hypoxia. Establishing airway, providing increased oxygen concentration, humidity, etc., will also improve fetal salvage rates. Advice concerning adequate dietary intake, the dangers of exposure to toxic agents, e.g., lead poisoning, as well as prompt treatment if exposure occurs is also a part of adequate prenatal care. Prompt and effective therapy of diabetes mellitus and hypothyroidism are also necessary to good management.

The use of various cytotoxic or tumor-inhibiting agents to induce therapeutic abortions is probably contraindicated at this time due to the possibility of producing congenital anomalies in cases where abortion is not induced. Use of these agents or irradiation in the treatment of malignancies, leukemias, etc.,

during pregnancy, especially first trimester, is attended by very grave risks, either of inducing abortion or congenital anomalies. Their use must be accompanied by full realization of these dangers, both by the physician and the patient. Exposure to these agents is considered by some to be indication for therapeutic abortion in the event that abortion does not spontaneously occur. (48)

Reasons for the importance of analysis of genetic factors are: recognition of genetically susceptible individuals for more efficient application of preventative measures; accumulated knowledge of the mechanisms by which genes determine increased vulnerability will lead to methods for breaking the chain leading to disease. (27)

SUMMARY

Congenital defects account for ten to fifteen percent of all cardiac lesions. Their incidence is approximately 3/1000 births, although probe patent foramen ovale may be demonstrated in approximately twenty-five percent of autopsy cases. These lesions vary in severity, from asymptomatic to those incompatible with life. Among the most frequently encountered are atrial septal defect, pulmonic stenosis, and patent ductus arteriosus.

The study of congenital malformations is still in its early stages but one fundamental fact is now well established; the ova of mammals can, during development, be subjected to the influence of environmental factors. An ovum that was originally normal may produce an abnormal embryo when the mother is submitted to harmful influences during the gestation period. The number of agents and conditions recognized as being capable of inducing malformations is being expanded as interest in this field increases.

While various maternal factors such as first trimester rubella, diabetes mellitus, anemia and hypothyroidism are generally accepted as having teratogenic effects, numerous other conditions such as maternal mumps, Asiatic influenza, Japanese B encephalitis, vitamin deficiencies, exposure to various cytotoxic and tumor inhibiting agents, ionizing radiation, to list but a few, are strongly implicated. The small number of reported cases and the hazards of extrapolating animal experimental evidence make proof in the

individual case impossible at this time.

To distinguish clearly between environmental and genetic causes in the light of new knowledge is becoming increasingly difficult. Until recently in the study of human malformations the genetic aspect has been neglected and its importance little appreciated. In the future it must of necessity become an integral and basic feature in these studies. It is now known that certain chemicals, ionizing radiation and spontaneous mutations are responsible for chromosomal aberrations. These manifestations are more readily appreciated in the light of family studies and consanguinity series which demonstrate a pattern of occurrence similar to a Mendelian recessive trait in many cases.

The time of occurrence of the insult, in relation to stage of embryonic development is of major importance. The derangement of normal cardiovascular development leading to congenital heart defects occurs during the first eight weeks of intrauterine existence.

Anomalies of the aortic arches with the exception of patent ductus arteriosus, take place during the third and fourth week of development. Patent ductus arteriosus may owe its presence to predisposing factors early in development as well as at the time of birth. Septation defects occur in the fourth and fifth weeks in the atria and seventh and eighth in the ventricle.

Prophylaxis can best be effected by prompt and vigorous treatment of maternal infections and diseases, good obstetric practice

at the time of delivery and during the neonatal period. In the unusual situations where cytotoxic agents or irradiation must be employed during pregnancy, these agents must be used with knowledge and a full awareness of their possible teratogenic effects.

CONCLUSIONS

It may be safely stated that the etiology of the majority of congenital cardiac defects cannot be diagnosed with certainty. The physician must be alert to the various possible etiologies and utilize all possible practical preventative and therapeutic measures to prevent the occurrence of these defects. In specific instances such as maternal rubella infection, therapy of neoplasms during pregnancy, he should discuss the potential teratogenic effects with the prospective parents, and assure himself that they are aware of the possibilities, although he must not over-emphasize the likelihood of their occurrence.

A careful study should be made of the course of the pregnancy and the genetic background of the family producing a congenitally defective child. This will enable the physician to discuss the possible etiology as well as the likelihood of recurrence during subsequent pregnancies; prognosis, suggested care and treatment both prophylactic antibiotic and chemotherapeutic and/or definitive surgical procedures with the parents.

In view of present knowledge there is little probability of a marked reduction occurring in the incidence of congenital cardiac disease as has been demonstrated in various other disease states in the past fifty years.

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