REVIEW OF LITERATURE
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INCIDENCE AND PREVALENCE:

An acceptable estimate of incidence of congenital heart disease in general population is not yet available. McKeown and Record (1960) & Carter (1961) considered that total incidence of all major malformations is 2.4% and those of heart form one quarter of these i.e. 0.6%. Malpas (1937) found only 10 patients with heart defects among 13,964 (0.7 per thousand) and Deporte and Parkhurst (1945) noted 142 in 300,795 births (0.5 per thousand). Sampson et al (1938); Rauh (1939) and Weiss (1941) gave estimates between 0.14 and 0.16 per thousand by examination of school children.

McMohan et al (1953) obtained the information about all cases of congenital heart disease born to Birmingham mothers in the years 1940-49. Diagnosis was confirmed at necropsy or by operation or by a consultant physician or by certification of cause of death. Incidence during whole period was 3.17 per thousand total births and 3.23 per thousand live births, with 1 per thousand still births.

Maier performed a necropsy study at Singapore in decades of 1948-57, found that congenital heart disease accounted for 2.2 percent of all necropsies, and for 8.4% of the necropsies done on children under the age of 10 years. The minimum mean incidence was shown to be atleast
1 per 1000 birth and for all still births, 1.7 per 1000. In America, the incidence was found to be 6.8 (Harris & Steinberg, 1954) and 6.5 (McSantosh et al, 1954) per thousand.

NERICP (New England Infant Cardiac Programme) figures shown incidence of congenital heart diseases to range between 1.5 per 1000 to 2.48 per 1000, average being 2.08/1000 live birth during 1969-1974 & 2.43/1000 live birth during 1975-1977.

Carlsson et al (1981) found it to be 9 per 1000 new born after studying all infants born in 1981 in Sweden by using different registries: Swedish Registry of Congenital Malformation, Medical birth Registry, Registry of Death Certificates and Child Cardiology registry.

In the India, Hadley et al (1956) in a series of 2000 autopsies at Vallore, South India found the incidence to be 1.3%.

Padmavati & Datey (1968), on studying prevalence of types of heart diseases in India found the distribution of congenital heart disease in Indian city hospitals to be 4.8% in Delhi (1951-55), 3.6% in Amritsar (1953), 6.3% in Bombay (1952-56), 2.3% in Madras (1946) and 1.6% in Lucknow (1953). This dealt with a very selected population group and was mostly from large hospitals attached to medical schools. They are however, more reliable because of more accurate diagnosis.
The incidence of different types of congenital heart disease, seems much the same as in other parts of world, found on various necropsy studies.

Dry et al (1948) found the incidence of various lesion as :-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>12%</td>
</tr>
<tr>
<td>ASD</td>
<td>20%</td>
</tr>
<tr>
<td>PDA</td>
<td>15%</td>
</tr>
<tr>
<td>Coarctation aorta</td>
<td>12%</td>
</tr>
<tr>
<td>Fallot's tetralogy</td>
<td>9%</td>
</tr>
<tr>
<td>TGA</td>
<td>7%</td>
</tr>
<tr>
<td>Others</td>
<td>30% including truncus arteriosus great vessels anomaly, common AV canal etc.</td>
</tr>
</tbody>
</table>

McMohan et al (1953) found the following incidence in Birmingham (U.K.) :-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>15.3%</td>
</tr>
<tr>
<td>ASD</td>
<td>8.6%</td>
</tr>
<tr>
<td>PDA</td>
<td>17.6%</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>10.6%</td>
</tr>
<tr>
<td>Fallot's tetralogy</td>
<td>4.0%</td>
</tr>
<tr>
<td>TGA</td>
<td>14.9%</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>6.5%</td>
</tr>
<tr>
<td>Others</td>
<td>22.5%</td>
</tr>
</tbody>
</table>
Gibson (1956) described distribution of different lesions as follows in London:

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>8.5%</td>
</tr>
<tr>
<td>ASD</td>
<td>10.0%</td>
</tr>
<tr>
<td>PDA</td>
<td>4.5%</td>
</tr>
<tr>
<td>Fallot's tetralogy</td>
<td>20.5%</td>
</tr>
<tr>
<td>TGA</td>
<td>15.3%</td>
</tr>
<tr>
<td>Coarctation</td>
<td>4.0%</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>2.0%</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>2.5%</td>
</tr>
<tr>
<td>Fibroelastosis</td>
<td>7.5%</td>
</tr>
<tr>
<td>Others</td>
<td>25.5%</td>
</tr>
</tbody>
</table>

Muir (1959) gave the distribution pattern from a necropsy study of Singapore to be:

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>23.1%</td>
</tr>
<tr>
<td>ASD</td>
<td>11.9%</td>
</tr>
<tr>
<td>PDA</td>
<td>11.4%</td>
</tr>
<tr>
<td>Coarctation</td>
<td>4.6%</td>
</tr>
<tr>
<td>Fallot's tetralogy</td>
<td>10.4%</td>
</tr>
<tr>
<td>TGA</td>
<td>5.1%</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>2.6%</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>8.0%</td>
</tr>
<tr>
<td>Others</td>
<td>23.8%</td>
</tr>
</tbody>
</table>
Keith et al (1978) reported the incidence of specific (major congenital defect in different age groups as following:

<table>
<thead>
<tr>
<th>Defect</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>29.0%</td>
</tr>
<tr>
<td>ASD</td>
<td>10.3%</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>9.9%</td>
</tr>
<tr>
<td>PDA</td>
<td>9.8%</td>
</tr>
<tr>
<td>Fallot's tetralogy</td>
<td>9.7%</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>5.1%</td>
</tr>
<tr>
<td>TGA</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

These comprises of 85% of congenital heart disease. Others are hypoplastic congenital heart syndrome, Total anomalous pulmonary venous drainage, Tricuspid atresia, Truncus arteriosus and other rare defects.

In India Vijay Priya et al (1979) conducted a clinical, hemodynamic and angiocardiographic study in 18 cases of cyanotic congenital heart disease. Fallot's tetralogy was found to be most common.

Kinare et al (1981) described the pattern of anomalies in 270 autopsied cases of congenital heart disease during first year of life in the department of Cardio-pathology, KEM hospital, Parel, Bombay during the year 1969 to 1979. Commonest during neonatal period was fetal coarctation (16%), followed by transposition complexes.
(12.1%) and mitral and/or aortic atresia complexes (10.2%). Tetralogy of Fallot's (11.8%) was commonest during first year of life followed by transposition complexes (11.8%) and coarctation (7.7%). Associated non-cardiac anomalies were present in 9.2% cases with a higher frequency of gastrointestinal anomalies.

In an other autopsy study done at PGI, Chandigarh from January, 1971 to December, 1974 by Banerjee et al in 250 infants of less than one month of age, 19 showed major cardiac anomalies. Clinical & necropsy records of them were reviewed and information regarding period of gestation at birth, age at death, sex, cause of death and associated pathology and extracardiac malformation were recorded. Hypoplastic left heart syndrome was the commonest and was seen in 6 (31.5%), Right sided obstruction in other 6 (31.5%), TGA in 2 and acyanotic heart disease in 5. Extracardiac malformation were present in 6 (31.5%) of which 4 were associated with hypoplastic left heart syndrome.

Campbell (1965) also found VSD to form 20% of total, then PDA, ASD, Coarctation of aorta, Pulmonary stenosis, Fallot's tetralogy & TGA are each responsible for about 10% and aortic stenosis for about 5%, this makes 85% of total, leaving 15% for other less common malformations.
Their distribution among older children shows some striking differences because of heavy early mortality especially in 1st year of life. VSD, ASD, PDA and PVS, each form about 15% of total, Fallot's tetralogy 12% and coarctation and aortic stenosis each 6% leaving 16% for other less common malformation. The incidence in general population of older children will be lower, about 3.6 per 1000. For ASD this is more than twice as high as the 0.2 per 1000 found by Seldon et al (1962) among the Australian population aged 15-65 years.

Scott et al (1984) reviewed the diagnosis and age at presentation of 1665 infants with symptomatic heart disease, who were admitted to Brompton hospital, London during the period 1973-82. The frequency of certain conditions had changed during the period of the study. Complete TGA and critical aortic stenosis had become less common whereas frequency of right ventricular outflow tract obstruction, and of critical pulmonary stenosis had increased.

Most of the cyanotic infants presented during the first 14 days of life i.e. at the time of ductal closure. As expected this was also true of other duct dependent circulatory disorders as coarctation and interrupted aortic arch. Aecyanotic infants with potentially large left to right shunts tended to present during the second month of life when the pulmonary vascular resistance fall. The
study also emphasize that most symptomatic infants with heart disease present during the first two months of life.

CLASSIFICATION:

Congenital heart disease are classified in different ways given by various authors. Nadas & Fyler presented the classification based on anatomical lesion or without being hindered by division of cyanotic or noncyanotic disease.

ANATOMICAL CLASSIFICATION:

I. Communication between systemic and pulmonary circuits with dominantly left to right shunts.

A. Interatrial communication -
   1. Patent foramen ovale;
   2. Secundum atrial defect;
   3. Endocardial cushion defect.

B. Interventricular communication -
   1. Simple VSD with or without pulmonary arterial hypertension;
   2. Complicated VSD with -
      - Pulmonic stenosis
      - Aortic regurgitation
      - Artial defect
      - PDA
      - Coarctation of aorta
3. Single ventricle syndrome
   a. Absent or extreme hypoplasia of RV
   b. Absent or extreme hypoplasia of LV
   c. Absent septum

4. Left ventricle - right atrial shunt

C. Communication between great vessels -
   1. PDA Simple
   2. PDA complicated with other defects
   3. Aortopulmonary fenestration
   4. Truncus arteriosus
   5. Ruptured aneurysm of sinus of valsalva
   6. Coronary AV fistula

II. Valvular or vascular lesion with a right to left shunt or no shunt at all.
   A. Coarctation of aorta
   B. Vascular ring
   C. Aortic stenosis
   D. Aortic runoffs
   E. Hypoplastic left heart syndrome
   F. Mitral stenosis
   G. Mitral regurgitation
   H. Cor Triatriatum
   I. Pulmonary vascular obstruction syndrome
      a. Primary
      b. Secondary
J. Pulmonary stenosis
   . with intact septum
   . with VSD

K. Pulmonary atresia

L. Pulmonary regurgitation

M. Underdeveloped right ventricle
   . Tricuspid atresia
   . Pulmonary valve atresia

N. Right ventricular dysplasia syndrome
   . Ebstein's anomaly
   . Uhl's disease

III. The transpositions -

A. Complete transposition of great arteries
   (D transposition)

B. Corrected transposition of great arteries
   (L transposition)

C. Double outlet right ventricle

D. Double outlet left ventricle

E. Other transpositions

IV. Venous anomalies -

A. Anomalous pulmonary venous drainage
   . Complete
   . Partial

B. Systemic venous drainage anomalies
V. Intrinsic dextrocardias -

A. Without heart disease -
   . Situs invertus totalis with L loop
   . Situs solitus with D loop

B. With heart disease -
   . Situs inversus
   . Situs solitus
   . Asplenia with situs symmetricus

VI. With or without axial inversion.

CLINICAL CLASSIFICATION :

(a) Bohan & Hughes classification:

This depends upon presence or absence of cyanosis.

I. Congenital heart disease with cyanosis.
   (Dominant right to left shunt).

1. Tetralogy of Fallot
2. Pulmonary atresia with or without VSD
3. Tricuspid atresia
4. Double outlet right ventricle with PS
5. TGA (L and D)
6. Total anomalous pulmonary venous return
7. Ebstein's disease
8. Truncus arteriosus
9. Single ventricle
10. Eisenmenger syndrome
11. Hypoplastic left heart syndrome
12. Pulmonary AV fistula
II. Congenital heart disease with little or no cyanosis.

1. VSD
2. ASD
3. Partial anomalous pulmonary venous return
4. Endocardial cushion defect
5. PDA
6. Aortico pulmonary septal defect
7. Coronary artery fistula
8. Pulmonary stenosis alone or with left to right shunt
9. Ruptured sinus of valsalva
10. Double outlet right ventricle
11. Coarctation aorta
12. Mitral stenosis or insufficiency, Mitral valve prolapse

(b) **Morgen Classification**:

Morgen (1973) classified them on the basis of presence and absence of cyanosis clinically, estimation of pulmonary blood flow in chest film and electrocardiographic findings. This give a relatively short list of possible diagnosis interferably high degree of accuracy as given in table.
### Classification of Congenital Heart Disease

#### Cyanotic

<table>
<thead>
<tr>
<th>Decreased Pulmonary Blood Flow</th>
<th>Increased Pulmonary Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AVH</strong></td>
<td><strong>RVH</strong></td>
</tr>
<tr>
<td>.PS</td>
<td>.TAPVC</td>
</tr>
<tr>
<td>.PS + VSD (Tetralogy)</td>
<td>.TGA + VSD</td>
</tr>
<tr>
<td>.Pulmonary vascular obstruction (Eisenmenger's)</td>
<td>.TGA + PS</td>
</tr>
<tr>
<td>.Tricuspid Atresia</td>
<td>.Truncus Arteriosus</td>
</tr>
<tr>
<td>.Truncus with hypoplastic pulmonary artery</td>
<td>.Single Ventricle</td>
</tr>
<tr>
<td>.TGA + PS</td>
<td>.Truncus Syndrome</td>
</tr>
</tbody>
</table>

#### Acyanotic

<table>
<thead>
<tr>
<th>Normal Pulmonary Blood Flow</th>
<th>Increased Pulmonary Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AVH</strong></td>
<td><strong>RVH</strong></td>
</tr>
<tr>
<td>.Coarctation</td>
<td>.ASD</td>
</tr>
<tr>
<td>.Mitral stenosis</td>
<td>.All left to right shunt with pulm.</td>
</tr>
<tr>
<td>.Aortic stenosis</td>
<td>.Arteriovenous fistula</td>
</tr>
<tr>
<td>.Mitral regurgitation</td>
<td>.Pulmonary Hypertension (PDA, VSD, ASD)</td>
</tr>
<tr>
<td>.Endomyocardial disease</td>
<td></td>
</tr>
</tbody>
</table>

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**Key:**
- AVH - Right Ventricular Hypertrophy
- LVH - Left Ventricular Hypertrophy
- SVH - Both Ventricular Hypertrophy
- VSD - Ventricular Septal Defect
- ASD - Atrial Septal Defect
- PDA - Patent Ductus Arteriosus
- TAPVC - Total Anomalous Pulmonary Venous Circulation
- TGA - Transposition of Great Vessels
- PS - Pulmonary Stenosis
Etiology:

The etiology of congenital heart disease remains obscure in most cases. A multifactorial inheritance hypothesis is gaining increasing acceptance. Single mutant gene syndromes probably represent less than 1 percent and gross chromosomal abnormalities less than 5 percent of total. In most instances there is combination of genetic and environmental influences.

The various factors based on several studies, which are responsible for causation of the congenital heart disease will be discussed here.

Genetic factors:

Campbell & Polani, 1961 b, mentioned that in few families ASD is inherited through an autosomal dominant gene of low penetrance and there may be few similar families with congenital aortic stenosis. Dominant Mendelian inheritance is also found in familial cardio-myopathy (Bishop et al). Medial necrosis of the aorta is often seen with arachnodactyly (Marfan's syndrome), which is also inherited as mendelian autosomal dominant manner.

Situs inversus is a good example of recessive mendelian inheritance for malformation of the heart as it is more than 10 times the level in first cousins of
propositus than expected in general population of Britain. Fuhrmann (1958) found 40% of monozygotic pairs but only 25% of dizygotic pairs were concordant for some cardiac malformation, most often of the same type. Thus it suggest some genetic predisposition.

The high degree of concordance between malformation in propositus and sib is readily explained by genetic factors.

Miller & Smith (1979) described few families in which inheritance and recurrence risk appeared to be monogenic. This implies that there may be single genes that control specific events in cardiac embryogenesis such as conotruncal septation (CTS). Mutation of such genes could lead to abnormalities in cardiac morphogenesis, resulting in spectrum of cardiac defects grouped in CTS malformation complex. This recognition is important in rendering genetic counselling in cases with strong family history for CTS defects. A higher recurrence risk should be considered rather than the usual polygenic recurrence risk of 3% that is usually found. Evidence for a genetic control of CTS arise from genetic and embryologic studies of similar defects in Keeshond dog model.
Corone et al (1982) done a statistical analysis of pairs of congenital heart lesions observed in families with at least two affected members. The concordant lesions were found in roughly 50% of cases for first degree relatives. The analysis of discordant lesions showed excess in same pairs (Tetralogy, VSD and TGA) highlighting clusters of lesions and suggesting that these lesions, although dissimilar anatomically have some common genetic origin as they all are consequences of construeun septation anomalies. Deficit in some discordant pairs may be a consequence of interaction between effects of genes (epistasis effect). This leads us to think of heart not as a genetic whole but rather is being constituted of different specific genetically determined segments. This concept agrees with the embryologic "segmental approach" suggested by Van Praagh and Van Praagh (1983).

Familial Incidence:

Incidence of congenital malformation of heart is raised in relatives of affected individuals. The evidence is supported by various studies by Abbott, 1927; Dagramaci and Green, 1947; Campbell, 1949 and Lavy et al, 1950.
McKeown et al (1953) found the incidence of congenital heart disease among sibs born after the first propositus to be 18 per 1000 approx six times the incidence in general population of birth (3.2 per 1000). Incidence in first cousins of propositi was also found to be slightly higher (4.3 per 1000).

The incidence also increases with consanguinity of parents in few cases. This support for Cockayne's Suggestion (1938) that this condition may be inherited as a recessive.

Campbell (1965) found a strong tendency for the malformations found in the sibs to be concordant with those in the propositi in 56%, partially concordant in 22% and discordant in only 22%. The number of non-cardiac malformation were about 2.3% which is about the percent of major malformations present in general population.

Incidence of malformation of heart in parents was about 0.3% except A.S.D. malformation in the children of propositi were (4.4%) which is higher than would be expected by chance, especially for cardiac malformations. Consanguinity of parents of propositi was also studied by him & Lamy et al and incidence was found about 1.6%. P.V.S. (2.7%) and A.S.D. (3.1%) have highest index of consanguinity except for situs inversus (5.6%).
Dr. Ray Anderson in 1977 reviewed his experience in 109 sets of twins and triplets with a variety of cardiac defects. He revealed concordance rate for cardiac defects of 8.2% in monozygous twins and 2.2% in dizygous twins. Noonan (1978) also found similar results and on pooling Uchida et al.'s and his twin study concordance rate of 8.8% was found in monozygous and 3.7% in dizygous twins from total of 88 twin pairs. This supports the current concept that most cardiac congenital malformations result from multifactorial inheritance rather than a single genetic trait. In both studies percentage of monozygous twins was disproportionately high. Instead of expected 30%, Anderson reported 58% and Noonan found 44% to be monozygous. In contrast to separate twins, conjoined twins especially thoracopagus twins have a high incidence of cardiac defects that are frequently concordant. Thus he inferred that mechanical factors can be very important in etiology of congenital heart disease as both monozygous and conjoined twins have the same genetic constitution but a very high incidence of congenital heart disease in conjoined twins contrast with the lower incidence in monozygous twins.
**Parental Age and Birth Order:**

Campbell (1965) found no evidence that birth order alone has any general influence on the production of malformation of the heart. Lemy et al. (1957) found that, if maternal age was held constant, birth rank was significantly higher in the congenital heart disease group than in control for the maternal age group 25-29 and 30-34. In their series only significant finding about birth order was linked with maternal age, and more sixth and later children with VSD were born to mothers aged 35 - 39.

Maternal age was rather more important. Only in Tetralogy of Fallot's and VSD did maternal age have a significant influence. After excluding children with mongolism more children with Fallot's tetralogy were born to mothers aged 40 to 45 years. In ABD group more children were of older mothers of 35 and over. MacMahon (1952) also thought septal defects were more common among the children of older mothers.

Fenrose (1955) pointed out that the difference between means of paternal and maternal ages are in some way more useful measurement, since an undue increase of paternal age suggests the possibility of a "failure to copy genes correctly" because of larger number of cell
division in male germ line. The mean paternal age exceeded
the maternal age by more than 2.3 years expected from
the general population (Fowrose, 1957) and ranged from
2.87 in coarctation and 3.03 in ASD to 3.48 in PVS and
3.70 in VSD. Lemly et al. (1957) found the fathers a little
older and mother a little younger in their congenital heart
disease group than in the controls.

Rothman and Fyler (1976) analysed the data of more
than 2000 children born in New England, who were diagnosed
with a congenital heart defect before the first birthday
and enrolled in MARCH. Subjects with diagnosis of Down's
syndrome were excluded. Positive trends in risk with
increasing birth order were present for pulmonic stenosis
and transposition of great vessels and negative trends was
seen for PDA. PDA and TGA displayed a pattern of risk
with increasing maternal age. VSD had an erratic pattern
of high risk for infants born of mother age 20–24 and low
risk for older mothers, with mother less than 20 showing
intermediate risk.

Mitsewell et al reported a 70 percent increase in
risk for all congenital heart disease when comparing subjects
with maternal age 30 or more to subjects with maternal age
37 or less after excluding subjects with Down's syndrome.
With regards to specific defects, Pelani and Campbell (1958);
Kenna et al (1965) and Campbell (1965) all found risk to tetralogy of Fallot to be associated with greater maternal age but only Kenna et al (1965) found birth order also to be associated with tetralogy. They also reported positive associations of birth order with FDI and maternal age with Pulmonic stenosis.

ASSOCIATED MALFORMATIONS:

MacMahon et al (1952) observed other malformation in 101 (21%) of the 488 subjects while doing a study in Birmingham. The commonest association is with mongolism in 6% of cases. The incidence of other defects were much higher in children with congenital heart disease than in general population. In decreasing order of frequency they were alimentary tract anomalies, skeletal, genitourinary and nervous system anomalies, among which maximum are with septal defects.

In the series of MERICF from July, 1966 to June, 1977, 642 infants (28%) had new cardiac anomalies in addition to congenital heart disease among 2,381 infants. The percentage of extracardiac anomalies especially those graded "severe" i.e. having major effect on the life or well being of amenable to therapy, was highest among infants with endocardial cushion defects. This is largely the
result of association of mongolism within the group. After excluding the mongols the percentage falls to 16% with infants with endocardial cushion defects. Truncus arteriosus, Secondum ASD or PDA had a high percentage, while those with pulmonary atresia and intact septum, TGA or aortic stenosis had only a small percentage of associated anomalies.

 Syndromes were not common overall, but were found in 20% of infants listed as having severe extracardiac anomalies, most commonly with PDA. Skeletal anomalies were most common anomalies in almost all types, anomalies of respiratory and central nervous systems were most frequent among infants with PDA. Gastrointestinal anomalies were seen most often among infants with PDA or endocardial cushion defects. Urinary anomalies were most frequent with PDA, Coarctation or truncus arteriosus and those in heterotaxia.

 Campbell (1965) revealed that non-cardiac malformation occurs much more often than would be expected by chance. In his group the proportion varied from 5% in ASD to 13% in coarctation and PVS and averaged 9%. In the series of Levy et al (1957), the figure was about 16% and varied between 7% to 26% in their different groups. Wood (1956) says that other malformation are present in form 10% to 20%, the figure in clinical series higher one in those found at necropsy.
Greenwood et al (1975) seen that extracardiac anomalies occured in 25% of infants during first year of life. Often they are multiple and one third of affected infants have some established syndroms. The presence of extracardiac anomaly significantly increases the mortality in infants with congenital heart diseases.

When a patient has one malformation of heart he is more liable than others to have a second one. The proportion varied from 8% with coarctation to 15% of those with ASD and 21% with PVS. The average figure for all acyanotic groups was 13%, about 20 times the expected figures. This includes some well known associations as aortic stenosis or PDA with coarctation but excludes the two malformation that must be present in more cyanotic malformation as VSD and PVS in Fallot's tetralogy.

Among chromosomal anomalies trisomy - 21 i.e. mongolism is so often accompanied by malformation of heart especially septal defects, that these too might be caused, in part at least, by the trisomy. Recently other syndromes with multiple malformation including most often VSD have been described. These were E1 or chromosome 17 - 18 and D1 chromosome 13 - 14 trisomy where VSD was present in 20 out of 23 cases of former and 9 out
of 15 cases of the latter syndrome (Taylor and Polani, 1964; Campbell and Goldwin, 1965). The association of turner's syndrome with coarctation of the aorta (Campbell and Polani, 1961), suggest that it too may be due to abnormal X0 chromosome complement.

Cullum et al (1965) in California went through the death records between 1957 to 64 and found that 4.8 percent of all deaths due to congenital heart diseases were associated with Down's syndrome. The type of defects were VSD (32%) AV canal defect (24.8%), ASD (20.1%), PDA (11.5%), Tetralogy (10.8%) and others (8.6%).

Laursen (1975) investigated total 1504 children with congenital heart disease under age of 15 years and found 80 patient with Down's syndrome i.e. 5.1%. Among those VSD was most commonly found (49%). He also noted that eisenmenger's syndrome appeared at earlier age in mongoloid children with VSD compared to other ones.

Corne et al (1982) reported the unusual association of stenotic dysplastic pulmonary valve, peripheral pulmonary stenosis, right aortic arch, aberrant left subclavian artery and complex aortic coarctation in a boy with Noonan's syndrome. Congenital heart disease occur in 50% of patients with Noonan's syndrome but most frequent is dysplastic pulmonary valve.
Sex incidence:

The overall sex ratio between male/female is 55/45 - Carlgren (1959), 53/47 McMahon et al, 51/49 Gardiner and Keith (1951) and 51/48 Muir (1959). In NERICP series also male babies predominated at 53.7%, but decreased to 51.8% of the one year survivors. There was female infants (37.8%), which is not surprising since male infants tended to have more lethal cardiac lesions. The relative incidence of the high risk factors were 53.8% in females. In general mortality among male infants was about 5% greater than among female infants. Banerjee et al (1975) found it to be 1.7:1 in study done in PGI, Chandigarh.

The different distribution of the two sexes in so many common malformation of heart has been recognized for a long time. FDA is the only condition more common in the female sex at birth and through life. Pulmonary stenosis shows an equal incidence in both sexes and transposition (70%) and Fallot's tetralogy (60%) show excess of male cases (Campbell, 1965).

Bretschcher & Campbell, (1958) concluded that boys reversed the left to right shunt at an earlier age than girls and became cyanotic and died earlier; and suggested that this might be because boys are less willing to limit
their exertion to an appropriate standard. Campbell & Polani (1961 b) found that the sex distribution was about equal in first decade, but in the third decade and after the male/female ratio became 1 : 2 and remained at that level for ASD.

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<th>Sex incidence at birth &amp; later</th>
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<tr>
<td>Condition</td>
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<td>Fallot's tetralogy</td>
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<td>Transposition</td>
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Environmental factors:

Environmental influences during pregnancy may be implicated as the cause of congenital heart disease. Various infections, diseases, medication or over exposure of radiation in mother of propositi may be found. Rubella affecting the mother during the first trimester of pregnancy is most clearly proved environmental cause.
Julia Bell (1959) studied 421 cases of maternal rubella in early pregnancy. Various malformations as deafness, cataract, congenital heart disease, mental retardation, microcephaly and others can occur, either alone or in combination. Among the heart malformation, PDA was commonest (56%) than VSD (18%), PDA & VSD both in (6%), ASD, Tetralogy of Fallot's and pulmonary valve stenosis each occur alone in 6% of cases.

Campbell (1961) found rubella in first trimester of pregnancy to be best established of all causes, but it does not explain a large proportion of cases. The risk of abortion or of malformation is high, between 40% and 60% during the first four weeks, between 30% and 50% during the second four weeks, between 20% and 40% during third four weeks, still perhaps a little during fourth four weeks, but not increased late, than this. Maternal rubella may be responsible for between 1% and 2% of all malformation of the heart.

Other viral infections responsible for malformation following maternal infection during pregnancy are measles, chickenpox, whooping cough, herpes zoster and infectious hepatitis—only one or two instances of each was reported. Mumps, poliomyelitis, influenza and toxoplasmosis (Frasen, 1959) has been incriminated in isolated cases.
At the congress of congenital heart disease in London in July, 1960, population of all those cases caused by maternal rubella and other viral infections was thought to be less than 10%.

Michalis and Mellin, 1960, have also proved rubella virus to be teratogenous for heart. Teratogenicity of Coxsackie B virus causing in later months of pregnancy was also proved by Kibrick et al, 1956, 1958. It can also give rise to congenital cardiopathies when infection occur during first month of gestation (Brown, 1966, 1969).

Alzamora et al, 1953; Chavez et al, 1953; and Epsimo-Vela, 1967 proved that there is a higher incidence of congenital heart disease with Arteriovenous shunt in children born in regions at an altitude of above 3000 meters and over above sea-level, as compared with populations at sea level comparing the cities of Junin and Lima in Peru and at altitude of Mexican Plateau. These suggest that hypoxia is a possible causal factor and this in turn is supported by experimental work of Ingalls et al (1952), who proved its teratogenic effect in mice by producing VSD. The frequent occurrence of congenital heart disease has been seen in children born of mothers with congenital heart disease. This could be due to an intrinsic factor related to sex or to an extrinsic factor represented by hypoxia of maternal tissues.
Several malformations of heart occurred after pregnancies in which there had been severe bleeding or threatened abortion or in which injection of Corpus luteum or other preparations had been given to avoid miscarriage. Lamy et al (1957) also found a history of such episodes twice as often as in their control series.

Harlap et al (1975) interviewed pregnant women and mothers in West Jerusalem in 1966-68 and found 3.8% babies to be born after definite or probable administration of estrogen or progesterones. 47 out of these 432 babies had one or more major or minor malformation - a rate of 108.8 per 1000, compared with 77.6 per 1000 babies with no history of exposure to hormones. There was excess of heart defects and other defects of blood vessel development in babies born to mother who probably took hormones in early pregnancy.

An excess of malformation would be expected among babies born to mothers with threatened or previous miscarriage, whether or not they were also given hormones. ASD was found usually after administration of stilbestrol specifically. The defects reported approx. twice the expected among infants with prenatal exposure to hormones.
Rothman et al, 1979 took the history of oral contraceptive use, hormonal pregnancy tests, prescribed hormones and other drugs before or during pregnancy in Massachusetts, Boston and positive history was obtained from 390 mothers of infants with congenital heart disease and 1254 mothers of normal infants. A small positive association between hormonal exposure and cardiac malformation was found. The prevalence ratio of exposed to non-exposed being 1.5. No association was evident between hormones and trunco-conal or any other class of defect among the cases.

Nora et al, 1976 also reported association between maternal exposure to progesterone/oestrogen at the vulnerable period of embryogenesis and congenital malformation involving several systems including cardiovascular, skeletal, gastrointestinal and genitourinary. CVS anomalies were VSD in 5 (in 4 cases) with early spontaneous closure) PDA in 2 and TAPV in 1 case among 100 live born infant. The overall risk after hormone exposure seems to be 2–4 times that of general population.

Heinonen et al, 1977 showed positive association between cardiovascular defects and phenobarbitone, phenothiazines and hormones as well.
Aminopterine (aboricient), busulphan and thalidomide all have produced malformations in man as well as in animals; but no drug has so far been incriminated as a cause of many malformation of the heart (Campbell, 1965).

Nora & Nora in 1977 reported that maternal rubella, ingestion of Thalidomide, folic acid antagonist during early gestation and chronic alcohol abuse are various environmental factors known to interfere with normal cardiogenesis. Maternal therapy with anti-convulsant agents especially Diphenylhydantoin and Trimethadione, Dextroamphetamine, Lithium chloride, Progesterone/Oestrogen, Warfarin and overexposure to radiation are associated with high incidence of congenital heart disease. Maternal lupus erythematosus during pregnancy has been linked to congenital complete heart block.

Cox (1964) found that malformation in general were twice as common in children of mothers who had been exposed to frequent X-ray examinations for congenital dislocation of hip.

Deprivation of vitamins and other abnormality in diets, can produce malformations of many types. Wilson et al (1953) found the malformation of aortic arches and bulbus and defects of ventricular septum
occurred if mother rats were kept on diets deficient in vitamin A. The poor diet and malnutrition of many mothers have led to such malformations. Experimental study of extrinsic factors has proved the following other agents to cause congenital cardiopathies - hypervitaminic 'A' diet (Kalter and Warkany, 1961), deficiency of pyridoxal glutamine acid (Nelson, 1960; Baird et al, 1954), deficiency of riboflavine (Kalter and Warkany, 1957; Nelson et al, 1956), Tryptan blue (Fox and Goss, 1958; Wilson, 1955).

**Seasonal influences:**

The season of conception provides some environmental factors that may have an influence on causation of malformations but it is easier to talk about the season of birth. Record and McKeown (1933) in Birmingham, found a seasonal increase of PDA for girls, but not for boys from May to December, with a peak in July and August with coarctation of aorta, more boys were born in March and April and fewer in September and October. With PVS three times as many boys were born in July - September quarter as in April - June quarter, but girls were evenly distributed. With ASD nearly twice as many boys were born in January - March quarter than other but girls were evenly distributed.
Symptomatology:

Certain congenital anomalies are of no clinical importance since they produce neither subjective symptoms, physical signs nor other objective abnormalities. These include bicuspid aortic valve is often complicated by calcific aortic stenosis and by bacterial endocarditis. In pure dextrocardia with situs inversus there are no symptoms but physical signs and roentgenoscopic and electrocardiographic examinations reveal a characteristic picture. There may be abnormalities in blood pressure as in cases of coarctation of aorta or PDA which may be associated with altered circulatory dynamics as those in cases of free aortic regurgitation.

Dyspnea or exertion is a common symptom and often appears early in course of the disease. A striking form of dyspnea is that which appears in paroxysms and is usually associated with intensification of cyanosis (Anoxic Spell). In many cases exertional dyspnea is secondary to pulmonary congestion associated with left sided heart failure. Often it is due to excessive arterial oxygen unsaturation.
especially following exercise with consequent anoxia of carotid sinus and respiratory centre. In cases of cyanotic congenital heart disease, there is in addition a further intensification of arterial hypoxemia, a rise in arterial $P_{CO_2}$ and a fall in pH.

Squatting especially after exercise is common in certain form of congenital heart disease with cyanosis and characteristically with tetralogy.

Cough complicates dyspnea when later is due to pulmonary congestion but both may be due to tracheal compression by a double aortic arch, anomalous vessel or aberrant vessel or congestion of abdominal viscera from right sided heart failure. Dysphagia and hoarseness may occur due to compression of Cesophageus and recurrent laryngeal nerve respectively.

Poor feeding, subnormal gain in weight, constipation, excessive fatigability and weakness are relatively common.

Cerebral symptoms including faintness, dizziness and headache are observed occasionally and rarely syncope, convulsion, delirium and coma especially in patients with cyanosis. These are due partly to cerebral hypoxia especially during exertion and partly to polycystemia with consequent circulatory stasis or complicating cerebral thrombosis or hemorrhage. These may also be due to
inadequate cerebral blood flow in case of aortic stenosis or to ruptured congenital aneurysm of circle of willis in coarctation of aorta or to cerebral ascess in cases of septal defects and paradoxical embolism. Stokes adams attacks can occur in cases of congenital heart block.

Cardiac pain may be related to inadequate coronary perfusion during exercise in aortic or severe pulmonary stenosis.

Vascular disturbances in extremities including coldness, numbness and tingling or pain may appear in patients with or without cyanosis or polycythemia. These may occur in coarctation of aorta. Malnutrition and under development may result from deficient peripheral blood supply.

Sudden death is most likely to occur in cases of idiopathic myocardiacopathy, subaortic stenosis or abstein's disease. Otherwise death in congenital heart disease is due to congestive heart failure, anoxia, cerebral complications, vascular thrombosis, bacterial endocarditis or some intercurrent illness.

Cyanosis and clubbed finger are also found, but it is erroneous to believe that these are found in majority of cases. Abbott, in series of 1000 cases found cyanosis of varying intensity in 257 and in 124 it appeared terminally. Clubbing was found in only 132.
A secondary polycythemia occurs frequently in cases with cyanosis. This occurs to compensate for oxygen unsaturation of blood. R.B.C. count usually varies between 6 and 7 millions / cm. mm. Haemoglobin is correspondingly elevated to 110 to 130 percent with moderate and may be upto 200% with extreme polycythemia. The hematocrit usually exceeds 53 percent and often exceeds 65 percent.

Physical and mental development:

Linde et al, 1971 studied 319 children with approximately equal sex and compared intellectual development of cyanotic and acyanotic children with congenital heart disease to that of both their normal sibling and randomly selected well babies. Cyanotic patients scored lower at all ages particularly in earlier years with tests involving gross motor abilities in Gesell and Cattell developmental examinations. Correlation of low test scores to physical incapacity tended to disappear at later ages when stanford - Binet test were given. They also noted that delay in use of first words and first phrases was much less marked in children with heart disease. Cyanotic children were significantly more incapacitated than acyanotic ones. Early motor performance deficit in handicapped child may cause underestimation of intellectual potential.
Ruth et al (1982) also assessed the mental and motor development of 173 infants with congenital heart disease by assessment of Bayley Scale of infants development and clinical neurological examination. Developmental delay i.e. Developmental Index Score of below 80 was manifested by 25% of all infants. About half of them had delay on mental scale alone and half on both mental as well as motor scales. The presence of congestive heart failure was found to be significantly associated with both mental and motor developmental delay. Hypoxemia and hospitalization were associated with delayed motor development.

Life expectancy of children with congenital heart disease:

Macmahon et al (1952), estimated the life expectation at birth based on all cases of congenital heart disease (633) identified at birth or later in population of 199,418 total births. They suggest that of 10 affected children born alive, 2 die by the end of first week, 3–4 by the end of first month and 6 by the end of first year. Between 3 – 4 survive up to ten years.

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