# 7

# Epidemiology of congenital heart disease: etiology, pathogenesis and incidence

**Julien IE Hoffman**

## Introduction

Congenital heart disease (CHD) is, by definition, cardiovascular disease present at birth. Most CHD is due to gross structural developmental cardiovascular anomalies such as septal defects, stenosis or atresia of valves, hypoplasia or absence of a ventricle, or abnormal connections between great vessels and the heart. A few children are born with arrhythmias (mainly conduction defects) and hypertrophic or dilated cardiomyopathy, although these usually present later in childhood or adulthood. Although asphyxial heart disease is present at birth, it is not included as a form of CHD. As defined, CHD is one of the most common serious congenital anomalies, occurring in up to 5% of liveborn children, and in an even higher percentage of fetuses.

Cardiovascular development involves a series of complex processes, each component of which has to occur at the right time under the orchestration of a cascade of genes and gene products.[1–4] Many of these have been found in studies of chick and mouse heart development, some have been identified in humans, but vast numbers are yet to be discovered. In general, the further upstream (closer to initiation of development) a gene is, the more its malfunction will affect major cardiac architecture. This can be seen by briefly examining the early stages of cardiovascular development. The formation of the heart begins with a straight tube that contains in sequence from the caudal end segments that will develop into the atria, the left ventricle, the right ventricle and the truncus arteriosus. This tube elongates and twists into a d-loop, so that the right ventricle moves to the right side of the left ventricle and the normal asymmetry of the heart is initiated. These changes are brought about by some genes that are expressed early (for example, *lefty*, *nodal*, *fibroblastic growth factor 8*, *zic3*); faulty expression of these genes will produce dextrocardias, l-loops, situs abnormalities (heterotaxies) and complex heart disease.[5,6]

After normal d-looping has occurred, the future atria are still connected to the left ventricle, and this is connected to the right ventricle, which leads to the truncus arteriosus, the precursor of the future aorta and main pulmonary artery. The next major developmental changes are the formation of the primary atrial and ventricular septa, and the movement of the atrioventricular and semilunar valve rings. These changes allow the right and left atria to connect to the right and left ventricles, respectively, and the ventricles to communicate with their respective great arteries. Coordinating these changes are genes involved in cell migration and the formation of the extracellular matrix, so that their malfunction produces gross structural anomalies indicating developmental arrest at a primitive stage. These include double inlet left ventricle (single ventricle), double outlet right ventricle and truncus arteriosus.[7,8] These abnormalities are in part related to abnormal function of the endocardial cushions, and other abnormalities of these cushions lead to the relatively gross distortions of architecture found in atrioventricular septal (endocardial cushion) defects.

Given the importance of precisely orchestrated spatial and temporal gene expression in cardiovascular development, it is not surprising that specific genetic abnormalities are being found in increasing numbers in CHD. These abnormalities may take the form of gross chromosomal rearrangements, microdeletions (both of which affect many genes), or isolated point mutations. In addition, there are well known environmental causes of CHD, and some of these may act by interfering with the action of specific genes. Finally, with the complexity of cardiovascular development, it would not be surprising to find that nonspecific factors and random errors in cell migration produce various defects or influence the severity of others.

## Chromosomal defects

Chromosomal defects vary from gross abnormalities such as trisomies or monosomies to deletion syndromes and microdeletions that involve contiguous genes. About 0.30 to 2.27% (median 0.67%) of all live births are associated with chromosomal defects; these are usually the aneuploidies: trisomies 21, 18 and 13 and the sex polysomies (e.g. XXX and XYY) which increase with maternal age, and monosomy X which is inversely related to maternal age.[9] These and other less common abnormalities are listed in Table 7.1. These infants are survivors of a much larger cohort of fetuses with chromosomal defects; in first-trimester fetuses aborted for nonmedical reasons, 2.6–6.4% (median 4.5%) have chromosomal defects. Therefore, only about 15% of fetuses with chromosomal defects survive to birth. Among spontaneous abortions, the incidence of chromosomal abnormalities is much

**Table 7.1. Chromosomal defects and congenital heart disease (CHD). Based on reference 12**

| *Chromosomal defect* | *Incidence/1000 live births* | *Percentage with CHD* | *Predominant types of CHD* |
|---|---|---|---|
| Trisomies | | | |
| 21 (Down syndrome) | 1–1.5 | 50–60 | AVSD, VSD |
| 18 (Edward syndrome) | 0.2–0.3 | 95 | VSD, PDA |
| 13 (Patau syndrome) | 0.1–0.2 | 90 | VSD, ASD |
| Duplications | | | |
| 3q26-27 (Cornelia de Lange) | | | VSD |
| 4p | | 10–15 | |
| 5p (Opitz) | | 10 | |
| 8 | | 20 | |
| 9p | | Low | |
| 10q | | 50 | |
| 11p | | Low | VSD |
| 12p (Pallister–Killian; Fryn) | | 25 | VSD+, coarctation, PDA, ASC AS, absent pericardium |
| 22p (cat eye) | | | TAPVC, ToF |
| Monosomy | | | |
| X (Turner) | 0.1–0.2 | 50 | Coarctation of the aorta; aortic stenosis or bicuspid aortic valve |
| Deletion syndromes | | | |
| 4p– (Wolf–Hirshhorn) | | 50 | ASD |
| 4q– | | 60 | VSD, PDA, PPS, AS, tricuspid atresia, ASD, coarctation, ToF |
| 5p– (cri-du-chat) | | 30 | Variable |
| 9p– (CHARGE) | | 30–50 | VSD, PDA, PS |
| 11q– (Jacobsen) | | 60 | |
| 13q– | | 50 | |
| 18p– | | 10 | |
| 18q– | | Low | |
| 20p11– (Alagille) | | High | PPS |
| Microdeletion syndromes | | | |
| 22q11 (DiGeorge: CATCH-22); Shprintzen (velo-cardiofacial) | | | Aortic arch anomalies, interrupted aortic arch, truncus arteriosus, ToF |
| 7q11.23 (Williams) | | High | Supravalvar AS, PPS |
| 16p13.3 (Rubinstein–Taybi) | | 25 | PDA, VSD, ASD |

AS, aortic stenosis; ASD, atrial septal defect (secundum); AVSD, atrioventricular septal defect (endocardial cushion or atrioventricular canal defect); PDA, patent ductus arteriosus; PS, pulmonary stenosis (valvular); PPS, peripheral pulmonary stenosis; TAPVC, total anomalous pulmonary venous connection; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

**Table 7.2. Survival of fetuses with chromosomal defects. Reproduced with permission from reference 9**

| | *Aneuploidy* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Sex chromosomes* | | *Autosomes* | | | | | |
| | *Monosomy* | *Polysomy* | *Trisomy* | *Polyploidy* | *Euploidy* | *Miscellaneous* | *% total aberrations* | *Total pregnancies* |
| Liveborn | 17 | 127 | 107 | 1 | 205 | 38 | 0.71 | 70 000 |
| Spontaneous abortion | 4434 | 31 | 7601 | 2848 | 489 | 330 | 52.4 | 30 000 |
| Total | 4451 | 158 | 7708 | 2849 | 694 | 368 | | 100 000 |
| % survival | 0.38 | 80.4 | 1.4 | 0.0 | 29.5 | 10.3 | 3.1 | |

higher, ranging from 15.7 to 69.8% (median 46.6%). The chances of survival to birth depend on the defect. It is about 1% for trisomies 21, 18 and 13, and for monosomy X, but as high as 80% for the sex polysomies (Table 7.2); fortunately, sex polysomies do not have an increased incidence of CHD. One other aspect of chromosomal anomalies is important for the echocardiographer. The percentage of aborted fetuses with chromosomal anomalies is greatest in the youngest fetuses, and decreases to 6–15.9% (median 11.7%) beyond 20 weeks' gestational age. Therefore, the earlier the echocardiographic study, the greater the chance of finding a chromosomal abnormality in a fetus with CHD. These considerations indicate the desirability of karyotyping all early fetuses found to have CHD.

Because all these chromosomal defects except for sex polysomies have a very high association with CHD (Table 7.1), the incidence of CHD in general depends on how many of these fetuses are conceived by older mothers and how many of the affected fetuses reach term alive. As a group, chromosomal defects account for about 6% of all CHD in liveborn infants,[10] but this figure could change dramatically depending on increased survival of the affected fetuses on the one hand or the frequency of therapeutic abortion on the other.

## Genetic abnormalities

Chromosomal abnormalities involve excesses or deficiencies of multiple genes. However, single gene defects are also common, and currently account for at least 3% of all CHD.[11] This figure is likely to grow rapidly. Some gene mutations characteristically cause defects in more than one organ system and produce recognizable syndromes. For example, the Holt–Oram syndrome has septal defects and abnormalities of the radius or thumb, and the Noonan syndrome shows characteristic body habitus and facies as well as dysplastic pulmonary valves and hypertrophic cardiomyopathy. It is likely that the genes responsible for these syndromes are general or "upstream," and function later in development to affect several systems. This is known to occur in the Holt–Oram syndrome which is due to haploid mutations in the TBX5 gene, a transcription factor. Some of the better known genetic syndromes with CHD are listed in Table 7.3; a more detailed list is published by Burn and Goodship.[12] Other genes, however, are specific or "downstream," and function later in development to affect only one organ or part of one organ. Many gene mutations have been found in CHD, usually not as part of a general syndrome.[3] None of these genetic defects to date are very frequent, nor should we expect them to be. In the development of any part of the cardiovascular system there is usually a cascade of genes and gene products involved. Mutation in any one of the members of the cascade would cause a specific cardiac defect, and there is no reason why one particular gene should always be involved. Almost certainly, some genes will be more susceptible to mutations than will other genes in the cascade, so that some mutations might be expected to be more common than others. Nevertheless, it is likely that any given defect can arise from mutations in one of many genes; multiple genotypic abnormalities may converge on a similar phenotype. In addition, there are gene mutations with major effects that are modified by other genes with subtle differences in timing or level of expression that will influence the phenotype.[13] This makes screening for genetic causes of CHD complicated and expensive.

In general, patients who have one congenital abnormality often have abnormalities of other systems. For example, abnormalities of the genitourinary tract occur in about 30% of patients with CHD, and patients with tetralogy of Fallot often have omphaloceles.[10] These are not usually regarded as syndromes, and it is not clear whether these associations stem from a common genetic origin or from some other disturbance during fetal development.

**Table 7.3. Congenital heart disease (CHD) caused by gene mutations (syndromic and nonsyndromic). Based on data from references 12, 27, 47–49. In many of these disorders the specific gene mutations have been identified**

| *Syndrome* | *Chromosome* | *CHD* |
|---|---|---|
| Noonan | 12q24 | Pulmonary stenosis; hypertrophic cardiomyopathy |
| Apert | 10q26 | VSD, coarctation of aorta, PS |
| Holt–Oram | 12q24.1 | ASD+, VSD, AVSD, truncus arteriosus |
| Ellis–van Creveld | 4p16 | Single atrium, AVSD |
| Marfan | 15q21 | Dilatation and rupture of aorta; aortic or mitral regurgitation |
| Ehlers–Danlos type IV | 2q31–32.3 | Arterial rupture |
| Osteogenesis imperfecta | 17, 7 | Aortic root dilatation, aortic or mitral incompetence |
| Pseudoxanthoma elasticum | 16p3.1 | MVP, coronary arterial disease, restrictive cardiomyopathy |
| Mucopolysaccharidoses | 4p16.3; 5q1–13; Xq27.3 | Aortic or mitral incompetence; coronary artery narrowing |
| Hypertrophic cardiomyopathy | 1q32; 2q24; 3p; 1p11.2; 12q23–24; 14q1; 15q4; 15q22; 19q13 | Asymmetric ventricular hypertrophy due to a large variety of mutations in sarcomeric proteins: myosin heavy and light chains, actin, tropomyosin, titin and myosin binding protein |
| Dilated cardiomyopathy | 1p11; 1q32, 2q11–q22; 2q31; 2q35; 3p; 6q; 9q13–q22, 10q21–q23, 15q14 | Dilated (congestive) cardiomyopathy |
| Osler–Rendu–Weber | 9q33–34 | Pulmonary arteriovenous fistulae |
| Long QT | 3, 7, 11, ? | Long QT interval, arrhythmias, death |
| Supravalvar AS | 7q11.23 | Supravalvar AS, PPS |

AS, aortic stenosis; ASD, atrial septal defect (secundum); AVSD, atrioventricular septal defect (endocardial cushion or atrioventricular canal defect); MVP, mitral valve prolapse; PS, pulmonary stenosis (valvular); PPS, peripheral pulmonary stenosis; VSD, ventricular septal defect.

Much has been written about multifactorial inheritance in CHD, especially by Nora.[14] The concept is that certain lesions may be due to the interaction of several genes (polygenic inheritance), the outcome being modulated by environmental factors. This combination of events could explain why CHD could be genetically caused without in general manifesting classical Mendelian genetic frequencies. For example, if one parent (especially the mother) has had CHD, there is an increased risk for CHD in the children, but this risk is usually no more than 5–10%, unlike the 50% risk found for autosomal dominant disease or the 25% risk associated with recessive disease. Carter[15] and Burn[16] have pointed out that, to fit the multifactorial model, six requirements need to be met. These are:

- Recurrence risk to sibs and offspring is approximately the square root of the population incidence.
- The risk to sibs is comparable to the risk to offspring.
- The risk is elevated in sibs and offspring, but much less among more distant relatives.
- The risk is further increased when multiple family members are involved.
- Recurrence risk may increase when the disorder is more severe.
- When there is unequal sex incidence, the risk is greater among relatives of the more rarely affected sex.

Although the relationship of CHD to multifactorial inheritance has not been completely settled,[17] the only form of CHD shown to fit the model well is the patent ductus arteriosus (Zetterqvist, cited by Burn[16]). If this is true, then how do we explain the other forms of CHD? One possible answer lies in the experiments reported by Kurnit and colleagues.[18,19] It is known that, during endocardial cushion development, certain cell adhesion molecules such as platelet endothelial cell adhesion molecules are downregulated when endocardial cells undergo mesenchymal transformation. The quintessential lesion related to endocardial cushion defects, the atrioventricular septal defect, is particularly common in trisomy 21. Studies have shown that, in trisomy 21, fibroblasts cultured from the lung have abnormally increased adhesiveness. Kurnit and colleagues developed a computer model of embryological development in which they programmed differing degrees of adhesiveness, random migration and certain rules for when migration and cell division would cease. With normal cell adhesiveness, the atrioventricular canal region developed normally in their

**Table 7.4. Environmental causes of congenital heart disease (CHD). Data taken from references 12, 50, 51**

| *Environmental factor* | *CHD* | *% frequency of CHD* |
|---|---|---|
| Rubella virus | PDA, PPS, PS, ASD, VSD | >35 |
| Mumps | Endocardial fibroelastosis | |
| Lithium | Mitral and tricuspid incompetence, Ebstein's anomaly, ASD | |
| Diabetes in pregnancy | Outflow tract lesions, especially TGA, coarctation of the aorta | 3–5 |
| Alcohol | VSD, ASD, ToF | 25–70 |
| Retinoic acid | Conotruncal anomalies | |
| Phenylketonuria | ToF, VSD, coarctation, PDA, SV, ASD | 25–50 |
| Trimethadione | TGA, ToF, HLH | 15–30 |
| Phenytoin | PS, AS, PDA, coarctation of the aorta | 2–3 |
| Systemic lupus erythematosus | Complete heart block | 20–40 |
| Coumadin | PDA, PPS | |
| Thalidomide | Truncus arteriosus, ToF, septal defects, coarctation, PS, TGA, TAPVC | 5–10 |

AS, aortic stenosis; ASD, atrial septal defect (secundum); HLH, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; PS, pulmonary stenosis (valvular); PPS, peripheral pulmonary stenosis; SV, single ventricle; TAPVC, total anomalous pulmonary venous connection; TGA, complete transposition of the great arteries; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

model. With abnormally increased adhesiveness, some of the atrioventricular canals were abnormally formed, just as in an atrioventricular canal defect. What was important in their study was that not all the canals were abnormal. Therefore, the abnormality produced in their model was due to the abnormal adhesiveness, but its expression depended in part upon random events in cell migration. Thus, failure to fit classical Mendelian genetics is not an argument against a genetic cause of CHD.

## Environmental factors

CHD has been associated with several environmental toxic or infectious factors (Table 7.4). We do not know whether most of these act by affecting gene expression directly or by blocking the action of the gene product. None of them are known to affect the genome itself. Phenylketonuria, a genetic defect itself, affects the fetus through the increased maternal blood levels of phenylalanine and phenylpyruvic acid.

There is one clue that links environmental and genetic events, and that concerns retinoic acid and its metabolites. As Kirby first demonstrated,[7,20] the development of the aorticopulmonary and truncal septa depends on the migration into the embryonic heart of cells from the cranial neural crest. If these cells are removed experimentally, there is a high incidence of ventricular septal defect, double outlet right ventricle and truncus arteriosus. Since these neural crest cells also aid in the formation of the pharyngeal arches and pouches (from which the thymus and parathyroid glands are derived) and the aortic arches, this may explain why aortic arch anomalies and truncus arteriosus are so frequently associated with the DiGeorge (CATCH 22) syndrome.[21–24] Certain chemicals are now known to interfere with migration of these neural crest cells. Therefore, giving bis-diamine, isotretoin, or all-*trans*-retinoic acid produces lesions resembling those found in Kirby's experiments.[4] It is thus possible that some outflow tract lesions might be due either to genetically or to environmentally determined defects of neural crest cell migration. Here, the environmental agent, retinoic acid, phenotypically and perhaps genotypically mimics DiGeorge syndrome.

Although dilated cardiomyopathies are not usually congenital cardiovascular defects, about 35% of them are familial and genetically determined, and the majority of hypertrophic cardiomyopathies are also due to isolated gene mutations[25–32] (Table 7.3). Although most of these cardiomyopathies are not present in the fetus or even in the neonate, they do have a genetic origin. A normal echocardiogram in the face of an abnormal family history of one of these diseases does not exclude the genetic defect.

## Incidence of congenital heart disease

To determine the true incidence of CHD there must be a medical system in which pediatric cardiologists can

diagnose CHD accurately and objectively, and in which the whole population has easy access to these cardiologists. These conditions are met in several countries today. One of the changes in recent years is the availability of echocardiography for diagnosis. Not only is this very accurate in experienced hands, but it can be applied to children with minimal heart disease who previously would not have had the diagnosis proven because they would not have been submitted to cardiac catheterization.

Even if the above criteria are met, the incidence of CHD will be determined accurately only if ascertainment of the diseases is complete. Two barriers exist. Some CHD causes death in the first few days after birth. A specific diagnosis might not have been made in these infants by the time of death, and without an autopsy examination the incidence of these serious malformations might be seriously underestimated.[33] Conversely, children with very mild lesions such as minimal pulmonary stenosis or small atrial or ventricular septal defects might never be included in any cardiologist's practice, so that their frequency will also be underestimated. Even though these mild lesions seldom cause clinical problems, failing to include them in a database reduces our ability to study the factors that cause these lesions.

There are several other factors that influence our ability to estimate the true incidence of CHD:

- Patent ductus arteriosus of prematurity, a maturational disorder rather than a cardiovascular anomaly, is very common. An unknown number of these may be included in any collected series, thereby inflating the incidence of the anomaly.[34] Unfortunately, many reports do not specifically exclude this form of patent ductus arteriosus.
- Another major problem is whether or not the bicuspid aortic valve is included in the series. Some data suggest that the bicuspid aortic valve occurs in 1% (possibly more) of the population.[35] If even a few patients with this lesion are included under the title of aortic stenosis, it will alter the apparent incidence of the latter lesion drastically. Alternatively, if subjects with bicuspid valves and small pressure gradients across them are not classified as having aortic stenosis, the incidence of aortic stenosis will appear to be smaller than it should be.
- Mitral valve prolapse is also common, and has been thought to occur in 4–5% of the population.[36] The prolapse does not appear to be present at birth,[37] although this does not exclude a developmental or genetic origin for the prolapse. Most series do not include prolapse as a congenital lesion, but obviously if even a few with mitral valve prolapse and mitral regurgitation are included under the heading of mitral valve lesions, they will inflate their incidence.
- Atrioventricular septal (endocardial cushion canal) defects are disproportionately frequent in children with trisomy 21, and trisomy 21 is more frequent in mothers over 35 years old. The frequency of this lesion in any series, therefore, depends on two factors. One is how many older mothers there are in any series, and this may well differ in different societies. The other is how many pregnancies of fetuses with trisomy 21 will be terminated medically, thus reducing the incidence of this lesion at birth.
- Many serious forms of CHD are now detected by fetal echocardiography, and the parents may choose to abort these fetuses.[38] In some series[39] as many as 50% of pregnancies with fetuses with CHD were electively terminated. In communities where this practice occurs we will have to take account of these aborted fetuses if we wish to determine the true incidence of CHD.
- Recent studies of infants in the newborn nursery have shown that as many as 4–5% of them had tiny muscular ventricular septal defects.[40] Many of these infants had no murmurs. About 95% of these defects close by themselves within 6–12 months after birth. Therefore, the incidence of ventricular septal defects and indeed of all CHD (because ventricular septal defects are the most common forms of CHD) depends upon how many of these trivial defects are included in the series.[41] If they are all included, the incidence of all forms of CHD might be 5–6% of all live births. If they are excluded, the incidence drops to about 1% of live births. In fact, over the past 10 years the incidence of CHD has been rising slowly, not because of a true increase in all congenital heart lesions but because of an increasing number of patients with small ventricular septal defects who are now being included in the series.[42–44]
- In one study, the investigators specified that they did not include mild pulmonary stenosis with systolic gradients across the pulmonary valve of under 25 mmHg.[45] Studies like this will then underestimate the incidence of pulmonary stenosis, since much of it is indeed mild.
- Fetal echocardiography has shown that certain lesions, particularly ventricular septal defects, may be detected in utero but have disappeared at the time of birth. In terms of the need for medical services this is a very desirable outcome, but in terms of understanding frequency and etiology this leads to the underestimation of the incidence of these lesions.

From these caveats it is clear that it is very difficult to achieve an accurate assessment of the incidence of CHD at birth. It should be clear, too, that it might be better to describe the absolute incidence of each specific lesion per 1000 or per 100 000 of the population, rather than to describe its incidence as a proportion of all CHD. For

**Table 7.5. Incidence of congenital heart disease (CHD) in liveborn children**

| | *Percentage of all CHD* | | | | | *Per million liveborn children* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Lesion* | *Lowest* | *25%* | *Median* | *75%* | *Highest* | *Lowest* | *25%* | *Median* | *75%* | *Highest* |
| Ventricular septal defect* | 16.4 | 27.1 | 32.4 | 42.0 | 50.2 | 987 | 1667 | 2267 | 3142 | 6616 |
| Patent ductus arteriosus | 0.8 | 5.3 | 7.1 | 11.0 | 16.0 | 60 | 350 | 471 | 774 | 2108 |
| Atrial septal defect | 3.4 | 6.8 | 7.8 | 11.7 | 14.5 | 135 | 403 | 563 | 910 | 2112 |
| Atrioventricular septal defect | 1.3 | 2.6 | 3.7 | 5.1 | 19.6 | 85 | 213 | 284 | 346 | 791 |
| Pulmonary stenosis | 2.2 | 5.0 | 7.0 | 8.6 | 14.3 | 160 | 280 | 404 | 641 | 1155 |
| Aortic stenosis | 0.3 | 3.3 | 4.1 | 5.9 | 12.0 | 40 | 155 | 283.5 | 339 | 1425 |
| Coarctation of the aorta | 0.0 | 3.8 | 5.0 | 5.8 | 9.8 | 0 | 289 | 332 | 419 | 620 |
| Transposition of the great arteries | 2.1 | 3.5 | 4.5 | 5.3 | 8.4 | 176 | 275 | 327 | 380 | 560 |
| Tetralogy of Fallot | 2.2 | 3.9 | 5.1 | 6.8 | 10.4 | 167 | 261 | 311 | 500 | 633 |
| Persistent truncus arteriosus | 0.0 | 0.7 | 1.4 | 1.7 | 3.8 | 0 | 61 | 86 | 145 | 344 |
| Hypoplastic left heart | 0.0 | 1.6 | 2.8 | 3.4 | 5.7 | 0 | 151.5 | 229.5 | 255 | 347 |
| Hypoplastic right heart | 0.0 | 1.4 | 2.2 | 3.2 | 5.7 | 0 | 105 | 171 | 197.5 | 347 |
| Double inlet left ventricle | 0.0 | 0.7 | 1.4 | 1.7 | 2.7 | 0 | 54 | 87 | 126 | 277 |
| Double outlet right ventricle | 0.6 | 1.0 | 1.2 | 3.9 | 4.3 | 51 | 69 | 79 | 238 | 263 |
| Total anomalous pulmonary venous connection | 0.0 | 0.6 | 1.0 | 1.7 | 2.8 | 0 | 47 | 53 | 93 | 155 |
| Miscellaneous | 2.6 | 8.0 | 11.6 | 14.8 | 23.9 | | | | | |

*Excludes one study in which 5% of all neonates had a small ventricular septal defect, but other forms of CHD were not studied. This study would give a high value for ventricular septal defect of 50 000 per million liveborn children, and about 93% of all CHD.

example, consider that, in a series examined after a year of age that excludes patent ductus arteriosus in premature infants, mitral valve prolapse and bicuspid aortic valves, there are 50 patients with CHD who have tetralogy of Fallot, 400 children with ventricular septal defects and 550 children with all other forms of CHD. From these data, the incidence of tetralogy will be 5% and of ventricular septal defects will be 40% of all CHD. If in that same series the investigators decided to include another 4000 children with small ventricular septal defects present at birth, then the same 50 children with tetralogy of Fallot would be included in a group of 5000 children with CHD (4400 of whom would have ventricular septal defects) for a percentage of 1% tetralogy of Fallot. It would be better to focus on the 50 with tetralogy of Fallot and relate them to the more accurately determined numbers of live births.

Some of the current data on the incidence of CHD are given in Table 7.5, both as percentages of all CHD and as numbers per million live births.[41] Even excluding the studies of neonates with an extremely high percentage of ventricular septal defects, ventricular septal defects are still the most frequent form of CHD. Not only is this true in general, but ventricular septal defects are by and large the most frequently observed congenital cardiac defects in subjects with chromosomal and genetic defects. This probably does not carry any great implications. The ventricular septum is known to be formed from multiple portions of the developing heart,[3] so that it is reasonable that many different ways of interfering with cardiac development will produce a ventricular septal defect.

# Conclusions

Worldwide, CHD is estimated to occur in about 1 500 000 live births annually.[46] Today, because of advances in its treatment, most subjects with CHD survive to become adults and to raise their own families. This progress comes at considerable economic cost; furthermore, CHD remains a major cause of morbidity and premature death. Because the children of these parents have an increased incidence of CHD,[12,16] the total incidence of CHD is likely to increase slowly, generation by generation. Therefore, the ultimate goal should be to prevent CHD or reduce its incidence, and this can be accomplished only after we have a better understanding of its genetic and environmental causes.

# Acknowledgements

I thank Dr Harold Bernstein and Dr James Bristow for valuable advice and criticism.

# References


1. Bristow J. The search for genetic mechanisms of congenital heart disease. Cell Molec Biol Res 1995;41:307–319.
2. Clark EB. Morphogenesis, growth and biomechanics: mechanisms of cardiovascular development. In: Heart Disease in Infants, Children, and Adolescents, Including the Fetus and Young Adult. GCRTA Emmanouilides, HD Allen, HP Gutgesell, eds. Philadelphia: Williams & Wilkins, 1995:1–16.
3. Harvey RP, Rosenthal N. Heart Development. San Diego: Academic Press, 1999.
4. Gittenberger-De Groot AC, Poelmann RE. Normal and abnormal cardiac development. In: Pediatric Cardiovascular Disease. JH Moller, JIE Hoffman, eds. New York: WB Saunders, 2000:3–14.
5. Casey B, Kosaki K. Genetics of human left–right axis malformations. In: Heart Development. RP Harvey, N Rosenthal, eds. San Diego: Academic Press, 1999:479–489.
6. Majumder K, Overbeek PA. Left–right asymmetry and cardiac looping. In: Heart Development. RP Harvey, N Rosenthal, eds. San Diego: Academic Press, 1999:391–402.
7. Kirby ML. Contribution of neural crest to heart and vessel morphology. In: Heart Development. RP Harvey, N Rosenthal, eds. London: Academic Press, 1999:179–193.
8. Mjaadvedt CH, Yamamura H, Wessels A, Ramsdell A, Turner D, Markwald RR. Mechanisms of segmentation, septation, and remodeling of the tubular heart: endocardial cushion fate and cardiac looping. In: Heart Development. RP Harvey, N Rosenthal, eds. San Diego: Academic Press, 1999:159–177.
9. Hoffman JIE. Incidence of congenital heart disease. II. Prenatal incidence. Pediatr Cardiol 1995;16:155–165.
10. Greenwood RD, Rosenthal A, Parisi L, Fyler DC, Nadas AS. Extracardiac abnormalities in infants with congenital heart disease. Pediatrics 1975;55:485–492.
11. Nora JJ, Nora AH. The evolution of specific genetic and environmental counselling in congenital heart diseases. Circulation 1978;57:205–213.
12. Burn J, Goodship J. Congenital heart disease. In: Principles and Practice of Medical Genetics, 3rd edn. AE Emery, DL Rimoin, eds. Edinburgh: Churchill Livingstone, 1997:767–828.
13. Benson DW, Silberbach GM, Kavanaugh-McHugh A et al. Mutation in the cardiac transcription factor *NKX2.5* affect diverse cardiac developmental pathways. J Clin Invest 1999;104:1567–1573.
14. Nora JJ. Multifactorial inheritance hypothesis for the etiology of congenital heart diseases. Circulation 1968;38:604–617.
15. Carter CO. Genetics of common disorders. Br Med Bull 1969;25:52–57.
16. Burn J. The aetiology of congenital heart disease. In: Paediatric Cardiology. RH Anderson, FJ Macartney, EA Chinebourne, M Tynan, eds. London: Churchill Livingstone, 1987:15–63.
17. Bishop DT. Multifactorial inheritance. In: Principles and Practice of Medical Genetics. AE Emery, DL Rimoin, eds. Edinburgh: Churchill Livingstone, 1990:165–174.
18. Kurnit DM, Aldridge JF, Matsuoka R, Matthysse S. Increased adhesiveness of trisomy 21 cells and atrioventricular canal malformations in Down syndrome: a stochastic model. Am J Med Genet 1985;20:385–399.
19. Kurnit DM, Layton WM, Matthysse S. Genetics, chance and morphogenesis. Am J Hum Genet 1987;41:979–995.
20. Kirby ML. Cardiac morphogenesis—recent research advances. Pediatr Res 1987;21:219–224.
21. Lindsay EA, Baldini A. Congenital heart defects and 22q11 deletions: which genes count? Molec Med Today 1998;4:350–357.
22. Wilson DI, Goodship JA, Burn J, Cross IE, Scambler PJ. Deletions within chromosome 22q11 in familial congenital heart disease. Lancet 1992;340:573–575.
23. Wilson D, Goodship J, Takao A et al. Identification of interstitial 22q11 deletion in conotruncal anomaly faces syndrome. Cardiol Young 1993;3 (Suppl 1):86.
24. Lewin MB, Lindsay EA, Jurecic V, Goytia V, Towbin JA, Baldini A. A genetic etiology for interruption of the aortic arch type B. Am J Cardiol 1997;80:493–497.
25. Baty C, Watkins H. Familial hypertrophic cardiomyopathy: man, mouse and cat [editorial]. Q J Med 1998;91:791–793.
26. Burch M, Blair E. The inheritance of hypertrophic cardiomyopathy. Pediatr Cardiol 1999;20:313–316.
27. Fatkin D, MacRae C, Sasaki T et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction system disease. N Engl J Med 1999;341:1715–1724.
28. Mayosi BM, Watkins H. Impact of molecular genetics on clinical cardiology. J R Coll Physicians London 1999;33:124–131.
29. Piano MR. Familial hypertrophic cardiomyopathy. J Cardiovasc Nurs 1999;13:46–58.
30. Seidman CE, Seidman JG. Molecular genetic studies of familial hypertrophic cardiomyopathy. Basic Res Cardiol 1998;93 (Suppl 3):13–16.
31. Towbin JA, Lipshultz SE. Genetics of neonatal cardiomyopathy. Curr Opin Cardiol 1999;14:250–262.
32. Towbin JA. Pediatric myocardial disease. Pediatr Clin North Am 1999;46:289–312, ix.
33. Abu-Harb M, Hey E, Wren C. Death in infancy from unrecognised congenital heart disease. Arch Dis Child 1994;71:3–7.
34. Anderson CE, Edmonds LD, Erickson JD. Patent ductus arteriosus and ventricular septal defect: trends in reported frequency. Am J Epidemiol 1978;107:281–289.
35. Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. Am J Cardiol 1970;26:72–83.
36. Freed LA, Levy D, Levine RA et al. Prevalence and clinical outcome of mitral-valve prolapse [see comments]. N Engl J Med 1999;341:1–7.
37. Nascimento R, Freitas A, Teixeira F et al. Is mitral valve prolapse a congenital or acquired disease? Am J Cardiol 1997;79:226–227.
38. Allan LD, Cook A, Sullivan I, Sharland GK. Hypoplastic left heart syndrome: effects of fetal echocardiography on birth prevalence [see comments]. Lancet 1991;337:959–961.
39. Allan LD, Sharland GK, Milburn A et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol 1994;23:1452–1458.
40. Roguin N, Du Z-D, Barak M, Nasser N, Hershkowitz S, Milgram E. High prevalence of muscular ventricular septal defect in neonates. J Am Coll Cardiol 1995;26:1545–1548.

41. Hoffman JIE. Incidence, mortality, and natural history. In: Paediatric Cardiology. RA Anderson, Baker EJ, Rigby ML, Shinebourne EA, Tynan M, eds. London: Churchill Livingstone, 2000.

42. Fixler DE, Pastor P, Chamberlin M, Sigman E, Eifler CW. Trends in congenital heart disease in Dallas county births 1971–1984. Circulation 1990;81:137–142.

43. Meberg A, Otterstad JE, Frøland G, Sørland S. [Children with congenital heart defects in Vestfold 1982–88. Increase in the incidence resulting from improved diagnostics methods]. Tidsskrift Norske Laegeforening 1990;110:354–357.

44. Spooner EW, Hook EB, Farina MA, Shaher RM. Evaluation of a temporal increase in ventricular septal defects: estimated prevalence and severity in Northeastern New York, 1970–1983. Teratology 1988;37:21–28.

45. Bound JP, Logan WF. Incidence of congenital heart disease in Blackpool 1957–1971. Br Heart J 1977;39:445–450.

46. Hoffman JIE. Reflections on the past, present, and future of paediatric cardiology. Cardiol Young 1994;4:208–223.

47. Marks ML, Keating MT, Familial dysrhythmias. In: Principles and Practice of Medical Genetics, 3rd edn. AE Emergy, DL Rimoin, eds. Edinburgh: Churchill Livingstone, 1997:879–897.

48. Vosberg H-P, McKenna WJ. Cardiomyopathies. In: Principles and Practice of Medical Genetics. AE Emergy, DL Rimoin, eds. Edinburgh: Churchill Livingstone, 1997:843–877.

49. McKusick V. OnLine Mendelian Inheritance in Man; 1999. http://www3.ncbi.nlm.nih.gov/omim.

50. Jackson BT. The pathogenesis of congenital cardiovascular anomalies. N Engl J Med 1968;279:25–29, 80–89.

51. Michels VV, Riccardi VM. Congenital heart defects. In: Principles and Practice of Medical Genetics. AE Emery, DL Rimoin, eds. Edinburgh: Churchill Livingstone, 1990:1207–1237.