Thursday, January 22, 8:00AM-12:00PM
Plenary Session

Congenital Heart Defects
Moderator: Marcia Feldkamp, Utah Birth Defect Network, Salt Lake City, UT

Embryology
Thomas Sadler (retired), University of North Carolina, School of Medicine Cell and Developmental Biology, Chapel Hill, NC

Heart development begins in the 3rd week of gestation (post fertilization) as a collection of cells in front of the cranial neural folds that will form the brain. Gradually, these cells coalesce to form a horseshoe shaped tube. Then, during the 4th week, as the embryo folds into the fetal position, the sides of the horseshoe are brought together in the midline where they fuse into a single tube. The caudal end is for venous blood return, while the cranial end grows vessels that will form the arteries to the head and neck and to the rest of the body via the aorta. By the end of the 4th week, the tube begins to beat, blood begins to flow, and various regions differentiate into an atrium, ventricle, and outflow tract. Now the tube lengthens and folds on itself (a process called looping), and together these phenomena create the basic shape of the heart. However, there are no divisions between the prospective atria, ventricles, or outflow tract, such that the heart still remains in a tube-like form, albeit a folded one. During the 5th and 6th weeks, septation occurs. In the common atrium a septum (septum primum) grows down from the roof toward the atrioventricular canal where two other septa(formed by endocardial cushion tissue) grow together to create 2 separate atrioventricular openings (The atrial septum and the atrioventricular septum are at right angles to each other, like an upside down 'T'). Before the septum primum contacts the atrioventricular canal septum, a hole appears in its dorsal portion. Then a second septum (septum secundum) grows down from the atrial roof toward the atrioventricular canal septum and overlaps septum primum. Septum secundum never reaches the atrioventricular canal septum, and this results in a hole at the bottom of septum secundum. Thus, there is an opening at the bottom of septum secundum and one at the top of septum primum. In this manner, an overlapping valve is created as an atrial septum. This valve is important because, during fetal life, the baby does not use its lungs to provide oxygen in the blood. Instead, the placenta handles this function and returns oxygenated blood to the right atrium via the umbilical vein. This blood then gets shunted across the valve-like atrial septum to the left atrium, then to the left ventricle and out to the body. Later, at birth, when the baby breathes, this valve is pressed closed and the normal postnatal blood flow is established. The ventricular septum forms when muscle tissue grows up toward the atrioventricular canal septa and septation of the ventricles is completed when tissue from the atrioventricular canal septa grows down to fuse with this muscle tissue. Finally, the outflow tract is septated into the aorta and pulmonary vessels. This septum is unique in that as it grows together it spirals 180º. If it fails to do so, then transposition of the great vessels occurs. If, on the other hand, it is displaced anteriorly, then the pulmonary channel is too narrow. Also, the ventricular septum fails to form properly resulting in a ventricular septal defect that is overridden by the aorta. Finally, the right ventricle hypertrophies because of the resultant altered blood flow. These 4 abnormalities are called the tetralogy of Fallot. Atrial septal defects occur when there are abnormalities in formation of either septum primum or septum secundum and almost all ventricular septal defects are due to a failure of the atrioventricular canal septa to grow down and fuse with the muscular portion of this septum. If this sounds complicated it is, but heart defects are the most common type of birth defect and so are very important to understand. It is possible and easier with pictures so we can be like the tinman in the *Wizard of Oz* and find our heart at this meeting (Interestingly, the master gene for heart development is called the tinman gene).

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Preventing Disease, Improving Outcomes: Epidemiologic Challenges and Opportunities for Congenital Heart Defects
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The burden of congenital heart anomalies is ancient but not inevitable, and can be decreased through primary prevention (removing causes) and improved survival of those affected. Epidemiologist, now more than ever, can help gauge and accelerate progress in that direction, by working closely with other medical and public health professionals and by leveraging the ongoing progress in morphologic diagnostics, genetic technology, and database integration.

What follows is a personal selection of current challenges of cardiac epidemiology, many of which can translate into opportunities for joint studies within NBDPN. They are here presented to stimulate discussion and collaboration.

1. What is the current impact and what are its components?
Major heart defects are currently diagnosed in 1 in 110 newborns. Several factors contribute to uncertainty and heterogeneity. Challenges include a) monitoring occurrence of specific entities (‘pure’ diagnoses) or child-based diagnoses rather than solely defect codes; a) using fairly flexible approaches that allow interchange of data; a) leveraging the increasing use of fetal echocardiography to get earlier diagnoses without missing the attending increase in pregnancy terminations

2. What is the evolving morbidity of heart defects?
It is difficult to capture morbidity on a population basis in the US, but it is invaluable to evaluate progress, identify gaps in services, and suggest opportunities for improvement. Challenges include capturing a) novel aspects of morbidity including developmental outcomes; b) quality of life; c) issues related to adults with congenital heart disease. Developmental outcomes can be a by-product of the cause (eg, 22q11 deletion), of postnatal physiology (eg, prolonged cyanosis), or of therapy (eg, bypass time at surgery), and will be increasingly important as more children survive undergo surgical treatment, live longer, and expect normal or near normal life.

3. What is the mortality for heart defects and how is it changing?
Heart defects account for at least 1 in 3 infant deaths due to congenital anomalies. Mortality for US children with heart defects has improved in the last decades, declining 40% since 1979. However, studies suggest that mortality is higher among blacks than among whites, suggesting a gap that should be further documented and understood. An assessment of the types of heart defects that contribute most to early mortality (conotruncal defects, hypoplastic left heart) can also help direct research and prevention efforts.

4. Is the science of fully translating into prevention?
Although they are few, some causes of heart defects are known and can be managed, including uncontrolled diabetes, vaccine-preventable infections, and teratogenic drugs. One important challenge is monitoring whether cases associated with these exposures continue to occur (eg, by including specific variables in registry forms) and acting, or promoting action, on such information.

5. What is the genetic contribution to heart defects in the population?

Research into the genetic and environment determinants of heart defects is also urgently needed because most cases of heart defects still remain without a known cause. With the growth of genetic technology and the increasing the possibility of collecting and storing blood spots, there are increasing opportunities for registries to contribute significantly to population-based surveys of genes of clinical and public health importance. Such studies can greatly expand the knowledge gained in the laboratory or specialty clinic.

6. To what extent can folic acid and other vitamins prevent heart defects?

Several independent studies suggest that the risk for some heart defects is reduced among mothers who used a multivitamin containing folic acid during the periconceptional period. The risk reduction varies by type of heart defect but can be considerable (~30-50%) for some severe defects such as transposition of the great arteries and tetralogy of Fallot. Contributions to this line of investigation to confirm, qualify, and quantify these findings can provide an unprecedented opportunity for population-wide primary prevention of heart defects.

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Prenatal Diagnosis of Congenital Heart Defects
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Congenital heart defects (CHD) are common birth defects, occurring in approximately 7-8 per 1000 livebirths. Autopsy series suggest the incidence may be as high as 30/1000 in stillbirths. In association with other abnormalities, the heart defect is often the life-limiting lesion, predicting the overall prognosis for the condition. Approximately 25% of all infant deaths are due to congenital malformations, one-third of which are due to congenital heart disease. Although many risk factors related to an increased risk for CHD are known including diabetes, PKU and alcohol, most infants with CHD are born to mothers without specifically defined risk factors. It for this reason, that the emphasis on fetal evaluation has evolved to screening both low and high-risk pregnancies for the presence of CHD.

While ultrasound has been used as an imaging tool in obstetrics for nearly 30 years, only the development of high resolution, real time ultrasonography has enabled the detailed evaluation of the fetal heart. Even so, the screening ultrasound (4- chamber view) may detect less than 50% of all defects. Conotruncal abnormalities in particular are often not detected on the 4-chamber view. Addition of the evaluation of the outflow tracts, as well as doppler, not considered part of the standard screening fetal ultrasound, may allow the identification of approximately two-thirds of cardiac lesions in the setting of a comprehensive fetal evaluation. The development of fetal echocardiography, practiced by individuals specializing in the fetal (and often the pediatric) heart has enabled even more advanced antenatal diagnostic evaluation, with a higher detection rate. Antenatal diagnosis of CHD not only permits appropriate genetic counseling and testing, but may also alter recommendations regarding timing and location of the delivery.

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Coding and Classification of Cardiovascular Malformations
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"Heart defect" is a broad term which can refer to an entity which is not a structure (eg. tachycardia), not a malformation (eg. cardiomyopathy), or may be a functional (eg. valve regurgitation) or physiologic (eg. PFO, ventricular hypertrophy) mechanism. A cardiovascular malformation (CVM) is a congenital structural anomaly of the heart and/or great vessels. CVMs challenge surveillance programs because of their frequent occurrence, complexity, public health importance and time investment, i.e. so many hearts, so many component defects, so little time.

Medical record abstraction and **Coding** are the initial hurdles that surveillance programs encounter. The anatomic details found in the autopsy and/or echocardiographic examination are generally superior. When several diagnostic tests are available, they must be serially compared. The newborn echocardiogram may differ from the final operative report which is usually more reliable. Often, test information is complementary rather than hierarchical. Some programs accept the fetal echocardiogram obtained by a pediatric cardiologist in the absence of postnatal confirmation. Clinically diagnosed CVMs are generally deemed unacceptable.

Most US programs such as the Metropolitan Atlanta Congenital Defects Program use a modified British Pediatric Association (BPA) six-digit code that is more detailed than the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM codes) (Correa-Villaseñor et al., 2003), cardiac codes included. The universality of the ICD system is its greatest strength. For CVMs, weaknesses include codes which are archaic, or inadequate for assorted levels of right and left heart obstruction, rare CVMs and complex hearts.

Beyond description and coding, cases with CVMs can be classified. At a minimum, **Classification** implies organization. At a higher level, it increases homogeneity which will hopefully provide insight into pathogenesis, similar to the process of classifying other birth defects (Rasmussen et al., 2003). The mechanistic classification system of CVMs based on postulated embryologic errors has intuitive appeal, but is incomplete. Recent systems are more accurately viewed as coding databases, eg. the Association of European Pediatric Cardiologists codes. In addition to classifying the heart, additional analysis involves the patient as a whole, distinguishing "isolated" and "complex" forms (ie. associated with extracardiac defects).

For the National Birth Defects Prevention Study (NBDPS), a novel frequency-based classification was designed. After reviewing a subset of existing cases from the database, frequency tables were created. The most common groupings were retained, and uncommon or unique ones set aside. Key to NBDPS methodology is that the cardiac diagnosis in the patient is a unified "patient diagnosis"; individual CVMs are not tallied. Hearts with more than one CVM are "collapsed", necessitating priority assignment. Using conotruncal hearts as an example, most cases were classified "Single or Essentially single" defects (Lin et al, 2003). Cases which could not be further reduced were pragmatically assigned to "Association" or "Complex" groups.

Counting unified heart diagnoses rather than individual CVMs is not unique and has been used by other researchers. In the future, state surveillance programs might consider adopting this approach. This would require additional analysis of CVM cases, but has great potential for more meaningful data collection and interpretation.