From a public health standpoint, epidemiologic research is essential to better understand the conditions under which birth defects occur, how they affect different human populations, and for generating hypotheses about associated risk factors. However, other scientific disciplines bring essential and complementary information to the table, for example by testing hypotheses generated by epidemiological studies. This is particularly effective when using models like Xenopus (a genus of frogs), where the specific gene variant observed risk factors in humans can be functionally and rapidly tested. At the recent Texas Birth Defects Research Symposium (October 2010), three sessions highlighted the importance of conducting research using animal models to understand the underlying mechanistic causes of human birth defects. Ultimately, the goal is to employ this understanding in the development of effective interventions.

Much of the birth defects research has been conducted using mice as these animals share key genetic characteristics to humans and can be genetically manipulated at the molecular level. The International Knockout Mouse Consortium collaborates on projects which mutate all protein-coding genes in the mouse using a combination of gene trapping and gene targeting in mouse embryonic stem cells. This creates a library of genetic resources for investigators with a wide range of scientific interests—from finding disease genes to identifying targets for drug development. To do this, embryonic stem cell clones with genes of interest, in this case those that have been associated with certain birth defects, are inactivated and then injected into early stage mouse embryos. To date, over 5000 genes have been

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FROM THE REGISTRY
FOCUS ON: GASTROSCHISIS

Gastroschisis is an important birth defect targeted for future research. With many current studies pointing to an increasing prevalence of gastroschisis worldwide, concern has been raised as to what may be accounting for these changes. Gastroschisis is generally categorized as an abdominal wall defect located on either side of the umbilicus. Consequently, with no membranes covering the viscera, abdominal organs develop outside of the body wall and are allowed to float freely in the amniotic fluid. Gastroschisis differs from omphalocele (another abdominal wall defect) which is characterized as abdominal organs herniated into the base of the umbilicus and covered by a sac or skin. Infants with gastroschisis tend to have fewer additional birth defects, including chromosomal abnormalities, and a higher survival rate compared to omphalocele cases.

Risk Factors
A variety of risk factors have been found to be linked to a greater chance of having a baby with gastroschisis. The strength of the associations between gastroschisis and each of these risk factors varies. These factors include:

- Younger maternal age (with particularly high rates among teenage mothers)
- Low prepregnancy body mass index (BMI); unlike most other defects, prepregnancy obesity appears to be protective against having a baby with gastroschisis.
- Oral contraceptive use
- Sex of the fetus (males are more likely than females to have gastroschisis)
- Low maternal socioeconomic status
- Maternal occupation related to commercial and sales work
- Maternal exposure to solvents and colorants
- Inadequacies in mother’s diet
- Maternal tobacco, alcohol, and recreational drug use
- Low parity (nulliparous mothers—those who have not given birth before—are found to be at increased risk)
- Periconceptional (occurring around the time of conception) genitourinary tract infection
- Maternal ethnicity (When comparing to non-Hispanic whites, gastroschisis appears to be more common in Hispanics and less common in blacks. However, when adjusted for other factors, these differences were not observed.)
- Geographic area (some regions of Texas, for instance, such as locations around the Mexican border and Panhandle, appear to have a higher prevalence of gastroschisis compared to other regions)

Outcomes
Gastroschisis is amenable to surgical repair; in 2008, 191 such surgeries were performed in Texas (roughly equivalent to the number of live born infants with this condition). However, survival rates have been noted to vary by ethnicity with white infants more likely to survive than black infants.

Among cases of gastroschisis in the Texas Birth Defects Registry delivered between 1999-2007, 92% were live born, while 6% were stillborn and fewer than 4% were electively terminated.

Patterns in Texas
In Texas, gastroschisis occurs in about 5 pregnancies for every 10,000 live births, which is higher than national estimates (approximately 4 cases per 10,000 live births). As noted, younger mothers in Texas are more likely to have a baby affected by gastroschisis, and this pattern is statistically significant between the youngest mothers (under age 20) compared to older mothers (Figure 1). These maternal age patterns are quite distinct from many other types of birth defects.

Black mothers in Texas are significantly less likely than either non-Hispanic white or Hispanic mothers to have a baby with gastroschisis (Figure 2). Rates of this defect vary by geographic region, with higher rates noted in both the north and south central portions of the state (Figure 3).

In line with these observations, a recent study examining gastroschisis prevalence trends in Texas between 1999 and 2003, found that even after adjustment for maternal age, race/ethnicity, education, parity, and residence, young mothers and nulliparous mothers were at a higher risk of having an infant with gastroschisis, while black mothers were at a reduced risk. Additionally, some indication of a regional increase was noted for the Austin/Waco region compared to other state regions; while a county examination showed a particularly high prevalence of gastroschisis among those inhabiting Nueces County — pointing to areas for future research.

Research Center News

Recent Publications from Texas Collaborators

‘knocked out’ and these genetically altered mice are being used in laboratories worldwide for numerous investigations. Since most genes are essential, knocking out both copies of a functional gene will result in embryonic lethality. This means that scientists must work within the embryonic period to characterize the impact of the gene inactivation.

Animal model research has been particularly helpful in researching neural tube defects, including spina bifida and anencephaly, which in Texas occur at a rate of 3.7 and 2.6 per 10,000 live births, respectively. Using model systems such as mice and chicks provides researchers with a better understanding of the expression of genes that are important for normal development. For example, it has been discovered that specific mutations in genes IRF6, MSX1, and FGFR1 explain up to 15% of oral clefts. Animal studies are also valuable in understanding more about how genes and environmental toxicants interact to contribute to the development of birth defects. By selecting animal subjects with specific mutations (e.g. those leading to disruptions in the folate biosynthetic pathway), and carefully administering environmental exposures (e.g. cigarette smoke, environmental arsenic), much has been learned about the development of orofacial clefts. In another study, mice were found to be useful in studying cleft lip with or without cleft palate. Mice have also been utilized to measure the effect of environmental teratogens that may be risk factors for defects such as holoprosencephaly.

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For some study questions, large animal subjects are preferred as they have larger fetal sizes and longer survival, allowing for the study of cellular and molecular mechanisms which may aid not only in discovery of preventative strategies, but also in novel treatments.

FOR FURTHER READING

PREVENTION
INTERNATIONAL RECOGNITION OF NEED FOR BIRTH DEFECTS PREVENTION AND RESEARCH: THE WHO’S 63RD WORLD HEALTH ASSEMBLY

The World Health Organization’s World Health Assembly came together from May 17th to May 21st 2010 in Geneva, Switzerland to discuss a variety of issues relevant to child and adolescent health, one being birth defects. A total of ten resolutions were made to urge member states to take a more active role in preventing and managing birth defects. Some of these items include stressing the significance of birth defects as a cause for child illness and death, building capacity for prevention of birth defects and care for children with birth defects, and strengthening research on the etiology, diagnosis, and prevention of major birth defects. A full list of the resolutions addressed at the assembly can be found at http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_10-en.pdf

Furthermore, the World Health Assembly made requests to the Director-General of the World Health Organization, including:

- To promote the collection of data on the global burden of mortality and morbidity due to birth defects
- To continue to collaborate with the ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research) in order to improve collection of data on the global burden of mortality and morbidity due to birth defects
- To support the member states in developing national plans for implementation of effective interventions to prevent and manage birth defects

Additionally, the assembly compiled interventions to prevent or treat birth defects. Strategies for pre-conception care, pregnancy care, and newborn infant and child care were addressed. The resolution, including a table summarizing recommended interventions can be found at http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_10-en.pdf.

By highlighting the importance of birth defects as a serious public health problem on the global stage, researchers and practitioners from around the world can continue to grow and work together to prevent and improve outcomes related to birth defects.

ANNOUNCEMENTS
NATIONAL BIRTH DEFECTS PREVENTION MONTH

January 2011 is National Birth Defects Prevention Month, sponsored by the National Birth Defects Prevention Network (NBDPN). This year’s theme is “Medication Use Before, During and After Pregnancy” and promotes the message that women of childbearing age should talk with their doctor about which medications are safe to take while pregnant. The NBDPN web site includes resources for promoting the month, including pamphlets, posters, fact sheets, and a sample news release. Access the site at www.nbdpn.org/bdpm2011.php.

PREMATURE BIRTH REPORT CARD FROM MARCH OF DIMES

The March of Dimes announced the results of its 2010 Premature Birth Report Card, which grades the nation and the states on their preterm birth rates, and shows how the states compare from 2009 to 2010. The Report Card is based on indicators including 1) the rate of preterm infants; 2) late preterm infants (born between 34 and 36 weeks); 3) women smoking; and 4) uninsured women. Overall, the US received a “D” on the report card which measures national preterm birth rates

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against the Healthy People 2010 goals. However, after three decades of increases, in 2008 there began a two-year decline in the preterm birth rates (a 4% drop from 2006). For more information, go to http://www.marchofdimes.com/9214.html. To view state-by-state rankings and download your state’s report card, go to http://www.marchofdimes.com/padmap.html.

**CONTRACEPTIVE MAY RAISE FOLATE LEVELS**

The Food and Drug Administration (FDA) recently approved an oral contraceptive that contains folic acid. In addition to being utilized for pregnancy prevention, the new contraceptive, Beyaz, is the first to be approved by the FDA for the secondary indication of raising folic acid levels in order to reduce the risks of a neural tube defect.

"Combining an oral contraceptive with folic acid is important, because women may become pregnant during OC use or shortly after discontinuation, possibly before seeking preconception counseling from their healthcare provider," said Dr. Anita Nelson, Professor of Obstetrics and Gynecology at the Harbor-UCLA Medical Center, Torrance."

Beyaz is the first and only birth control pill approved by the FDA for four indications:

- Prevention of pregnancy
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD)
- Treatment of moderate acne for women at least 14 years of age
- To raise folic acid levels in women for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing it

For more information, review the FDA announcement at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227237.htm.

**HEALTHY PEOPLE 2020 LAUNCHED**

On December 2, 2010, the U.S. Department of Health and Human Services unveiled Healthy People 2020, the nation’s new 10-year goals and objectives for health promotion and disease prevention. The Healthy People initiative is grounded in the principle that setting national objectives and monitoring progress can motivate action. In just the last decade, preliminary analyses indicate that the country has either progressed toward or met 71% of its Healthy People targets. Based on extensive stakeholder feedback, a number of new topic areas are included in the new initiative, including:

- Adolescent Health
- Early and Middle Childhood
- Genomics
- Global Health
- Health-Related Quality of Life and Well-Being
- Sleep Health
- Social Determinants of Health

For more information, visit www.healthypeople.gov.

In related news, the Healthy People Curriculum Task Force has revised the Clinical Prevention and Population Health Curriculum Framework, which integrates clinical prevention and population health into the education of students across the health professions disciplines.

More information can be found at www.aptrweb.org/about/taskforce.html.
CALENDAR

2011

- January 2-8: National Folic Acid Awareness Week. Contact: ncfa@sbaa.org, www.folicacidinfo.org
- February: International Prenatal Infection Prevention Month. Contact: Marti Perhach, info@gbs-intl.org, www.groupbstrepinternational.org
- February 27-March 1: Texas Advanced Leadership and Advocacy Conference. Contact: Jamie Duran 979-845-1884, talac@tamu.edu

Contact: Cara Mai, cmai@cdc.gov
- April 13-15: Texas Public Health Association 87th Annual Education Conference. Houston, TX. Contact: (512) 336-2520, txpha@aol.com
- June 25-29: 51st Annual Meeting of the Teratology Society. Coronado, CA. Contact: (703) 438-3104, tshq@teratology.org
- September 24-27: 5th International Conference on Birth Defects and Disabilities in the Developing World. Poland. Contact: icbd2011@firstclass.com.pl

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