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Genetic Basis of Susceptibility to Environmentally Induced Birth Defects

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Exposure of the developing conceptus to selected environmental agents can lead to deleterious and often times, lethal birth defects. These malformations result in serious emotional and financial consequences to families and societies worldwide. As we continue to progress technologically, we face challenges from the introduction of new pharmacological agents and chemical compounds into the environment. This results in a concomitant need to more fully understand the relationship between *in utero* exposure to environmental teratogens and the risk of congenital malformations. Based upon recent experience, it is clear that not all infants exposed at critical periods of development to environmental toxicants are equally susceptible to the induction of birth defects. Understanding the genetic regulation of susceptibility to teratogenesis at the molecular level is an essential first step in reducing the number of infants with environmentally-induced birth defects.
This presentation will review the relationship between environmental exposures to compounds suspected of causing birth defects, and the role of genetic and nutritional modifiers on determining susceptibility to specific toxic agents. A review of the major concepts related to the molecular basis of environmentally-induced birth defects, will include consideration of important fundamental facets of embryonic development, teratology, and gene-environment interactions. Selected environmental compounds will be used to illustrate the limitations of our current understanding. The malformations that will be considered are primarily those that are folic acid responsive, including neural tube defects (NTDs), conotruncal heart defects and craniofacial anomalies. This is because data generated over the past decade demonstrates that periconceptional folic acid supplementation is the greatest environmental modifier of birth defect risk. However, the fact that not all women enjoy the same protective effects from this vitamin supplementation, suggests that underlying modifying genetic factors are involved. The data on the mechanisms underlying

the protective effects of periconceptional folic acid supplementation with respect to birth defects remains unfortunately inconclusive. This may be the result of the inherent complexity involved in trying to unravel the complex gene-environment interactions underlying the development of selected birth defects, which to date have progressed rather slowly. Current hypotheses on how modifiers may interact with genetic susceptibility will be the focus of the final portion of the presentation. Understanding the genetic pathways regulating susceptibility may lead to the development of intervention strategies and the prevention of preventable birth defects.

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