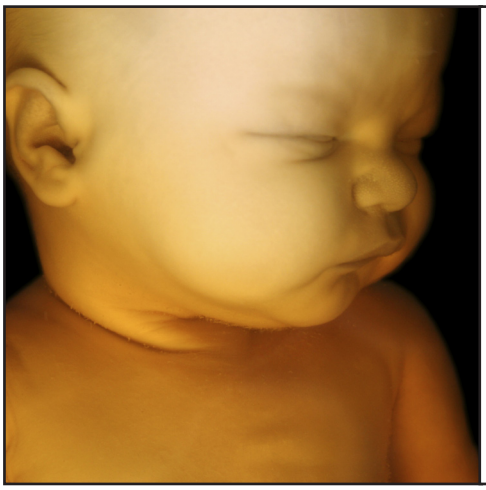
NIEHS
National Institute of
Environmental Health Sciences

Linking Early Environmental Exposures to Adult Diseases



All complex diseases have been shown to have both a genetic and environmental component. A growing body of research is beginning to suggest that many chronic adult diseases and disorders, including asthma, diabetes and obesity, may be traced back to exposures that occur during development. Research supported by the National Institute of Environmental Health Sciences (NIEHS) and others are finding that *in utero* or neonatal exposures to environmental, dietary and behavioral changes may make people more susceptible to diseases later in life.

The Developmental Hypothesis

The reason people think that susceptibility to disease may be established during pre-birth is due to both human and developmental toxicology studies in animals. Researchers like David Barker, for example, put forward the "fetal programming or developmental basis of health and disease" hypothesis, after finding an association between low birth weight and coronary heart disease. Barker found that a malnourished fetus will adapt its metabolism in the womb to survive until birth, but these changes then increase a person's risk of disease later in life, such as heart disease, diabetes and possibly cancer. This idea that the human fetus is vulnerable to outside influences, and that what women eat and perhaps even breathe during pregnancy can impact children into adulthood and possibly even future generations as well, is a growing area of research. Little is currently known about the mechanisms by which fetal insults lead to altered programming and to disease later in life.

RESEARCH FINDINGS

It would be difficult to follow humans for 60 years to see if they develop diseases based on what they were exposed to before birth. For this reason, almost all data showing developmental exposures leading to increased susceptibility to disease later in life have been done in animal models. With the use of new technologies, however, researchers are able to examine gene expression changes in tissues during development and to link them to onset of disease later in life, providing a framework to understand the impact that environmental factors may be having on programming the body for future diseases. Some human studies have corroborated what we have seen in animals, including the long-term effects of Diethylstilbestrol (DES), smoking and some heavy metals like mercury.

Diethylstilbestrol (DES), a medication used from the 1940s–1970s to prevent miscarriages in high risk pregnancies, is the best proof of principle supporting the developmental basis of adult disease hypothesis. DES has been shown to cause an increased risk of vaginal, uterine and breast cancer in humans and animal models. It has also been shown to cause uterine fibroids in mouse models and DES-exposed women. NIEHS researchers also found that the adverse effects of DES in mice can be passed to subsequent generations, even though they were not directly exposed. Researchers have also linked developmental exposures to a variety of environmental chemicals to increased susceptibility to infertility,

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endometriosis, uterine fibroids, obesity, neurodegenerative diseases and cardiovascular and lung diseases. There are also some data suggesting that infertility due to environmental exposures during development can be transmitted up to four generations after exposure. These studies indicate that a person's fertility may even be the result of what her great grandmother was exposed to while she was *in utero*, suggesting again that what a woman may be exposed to during her pregnancy can affect the fertility of her children, grandchildren and great grandchildren. Mechanisms involved in the transmission of the altered programming due to exposures during development have been shown to involve epigenetic events or changes in gene function that occur without a change in the DNA sequence.

Timing and Duration of Exposure

From NIH-supported research we know that there are critical periods of vulnerability in the developmental process. This is when cell growth is occurring, tissues are forming, and the body is still without an immune system, blood brain barrier, DNA repair system or any detoxification system to rid itself of chemicals or to protect itself, making the timing and duration of environmental exposures critical. The developmental period is also the most sensitive time for the development of the epigenetic system. This system controls gene expression in tissues and these changes can be transmitted across generations. Thus, changes in the epigenetic system provide a mechanism for environmental exposures to have effects long after the exposure.

The level of response to a given dose may change dramatically depending on the stage of development at which a fetus is exposed. All of this new research is indicating that a "four-century-old paradigm, which states that 'the dose makes the poison,' needs to be expanded to emphasize that 'the timing makes the poison' as well.

Even seemingly minor exposures during early development can lead to functional deficits and increased disease risks later in life.

Early Prevention is Critical

If the "developmental basis of disease" hypothesis proves true, then there is an even greater need to change our focus from treating diseases after they are detected to prevention. Doctors have long hoped for ways to prevent or reverse health problems before they become chronic diseases. Given that many disorders arise during fetal development from disruptions in the dynamic but still poorly understood interplay of genes, environment and nutrition, prevention may have to occur decades before a symptom even appears.

NIEHS Research Directions

NIEHS is committed to understanding the link between early environmental exposures and adult diseases. To accomplish this, NIEHS will:

- Continue to lead a trans-NIH to determine the factors, such as the environment, that regulate or turn genes on and off. The Roadmap Epigenomic Program will produce a map of the epigenomes of normal human cells, to serve as a reference for diseased cells, allowing us to understand how environmental factors can change patterns related to the link between exposures and disease.
- Encourage the development of more sensitive exposure assessments.
- Encourage the use of stored human samples obtained at birth, to link developmental exposures to diseases in humans later in life.
- Work with others to define biomarkers of exposure and effect in rodent models that can be translated to humans, to indicate potential increase in susceptibility to disease later in life.
- Continue to play a leadership role in promoting partnerships between scientists and community members, to study environmental health concerns, and translate the results to the public, including encouraging more participation by members of the media and communication experts.

For more information on the National Institute of Environmental Health Sciences, please go to our website at :
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