Case 8: Marked for Disease

Session Objectives

Students will be able to:

- Describe epigenetics and how it works
- Discuss evolving concepts of disease causation
- Explain how environmental exposures might cause long-term and even transgenerational changes to the epigenome

In this session students will consider a story, based on historical facts, about DES, disease and epigenetics. Read this scenario, based on a real situation, to the group, or have a student read it out loud.

In his office across from his lab, the tall scientist was bent over his desk, reading the draft manuscript he had prepared with a colleague. Pushing back from the desk with his Birkenstocks, he leaned back in the chair. As it creaked he put his hands behind his head, elbows sticking out, and stared at the ceiling in concentration.

The manuscript described experiments on mice exposed to diethylstilbestrol (DES). This chemical was prescribed to pregnant women for decades before being banned for use when it was linked to rare cancers in the children of mothers who had taken it. The experiments on mice in this scientist’s lab confirmed that exposure in the uterus to DES led to uterine malformations and cancers. But they also showed that the offspring of exposed mice—the “grandchildren” of the mice who were given DES—showed the same kinds of disease. The experiments were repeated, the data incontrovertible.

This result was exciting, but also a little scary. Scary because of its real-world implications for sure, but scary also because there was no known mechanism for how it could occur.

CAPTION: Diethylstilbestrol (DES) is a synthetic chemical that is strongly estrogenic and has been used in humans and livestock  
CREDIT: ChemIDPlus, National Library of Medicine

CAPTION: Genistein is an isoflavone found in high concentrations in soybeans and soy products like tofu and soymilk  
CREDIT: ChemIDPlus, National Library of Medicine
In London during 1854 there was an outbreak of Asiatic Cholera. The prevailing theory of disease at that time, that it was caused by “foul airs” or “unclean living” had changed little for centuries, but was being challenged by discoveries in microbiology led by Pasteur. This new conception of disease was that it was caused by germs—what we now call bacteria or viruses. An analysis of cholera cases by a physician using maps identified a particular pump as key to the outbreak, and strengthened this germ theory, which eventually led to remarkable medical technology like hand washing before surgery.

The re-discovery of Mendel's work, and other breakthroughs in genetics in the early 20th century led to the emphasis of genetics, and eventually the eugenics movement. The discovery of the genetic code strengthened this genetic paradigm, which continues today as the dominant disease concept. The importance given to the human genome project and identification of genes “for cancer” and other diseases exemplifies this.

And yet since the 1960's there have been challenges to this concept of disease. The discovery of teratogens and then DES have brought attention to environmental factors in disease. We may be nearing a time when genetic and environmental disease concepts are synthesized, but while in epidemiology, public health, and other research fields the environmental concept is gaining acceptance, when you go to the doctor with a complaint, she or he is much more likely to take a family history (for genetic purposes) and test for infection (germ theory) than to ask questions about work or lifestyle that might lead to information about exposure to environmental factors.

In agriculture DES was used as a growth promoter, to chemically castrate male chickens, and as birth control for female livestock, until the FDA banned its use in 1972. It was found in tested cattle raised in the U.S. as late as 2000.

The situations and characters in this case are fictionalized, but they represent composites of real people and events.

Continue with the conclusion of the based-upon-fact scenario:

The scientist revised the manuscript, hypothesizing that the exposure to DES caused a mutation in the genome that was passed on to subsequent generations. This idea is dangerously close to the disreputable theories of the inheritance of acquired characteristics known as Lamarckism. Over the next three decades further research supported his discovery of transgenerational effects of exposure in the uterus to some chemicals. Epidemiological studies have found grand-daughters of women who took DES to be more at risk for disease; the phytoestrogen and the plasticizer bisphenol-a have been shown to have similar effects across generations. Some of the research was in his lab, and more was by his colleagues. This further research has not supported the idea that the chemicals are causing a mutation in the genes. Rather, evidence is accumulating that these chemicals change the proteins that wrap up the DNA, and control which genes are available for expression.

This new aspect of gene regulation, termed epigenetics, has become a very active field of research, and holds the promise of being able to unify genetic and environmental concepts of disease. You will now hear a brief explanation of epigenetics and how it works. Answer the questions below as you listen.

What is epigenetics?
What gets methylated or acetylated, and what does this mean for genes?
What normally causes methylation and acetylation?
How is methylation an ordinary part of development?

A recent paper* described the sites in the human genome where the Estrogen receptor binds, and found that the binding site was often very far from the gene it “turned on.” Connect this information to what you have learned about epigenetics. What do you think the estrogen receptor is doing to “turn on” the genes? Why would this be occurring from far away? Use what you have learned in this session and the articles given to you to write brief answers to these questions.

What is the estrogen receptor is doing to “turn on” the genes?
Why would this be occurring from far away?
Case Assignment

Examine the scientific literature on Epigenetics and estrogens and answer the following:

1. What is epigenetics?
2. What gets methylated or acetylated, and what does this mean for genes? What normally causes methylation and acetylation? How is methylation an ordinary part of development?
3. What is the estrogen receptor is doing to "turn on" the genes?
4. Why would this be occurring from far away?

References


Murphy, SK and Jirtle, RL. 2000. Imprinted genes as potential genetic and epigenetic toxicological targets. Environmental Health Perspectives Supplements 108(S1):5-11.


Susiarjo, M., et al. 2007. Bisphenol a exposure in utero disrupts early oogenesis in the mouse. PLOS genetics 3(1)e5.