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Epigenetics: Blurring the Line Between Nature and Nurture

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EPIGENETICS: BLURRING THE LINE BETWEEN NATURE AND NURTURE

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Chapter 1: *History of Epigenetics*

One of the longest and most intriguing psychological debates is that of the effects of nature verse nurture. This debate can be traced back to Sir Francis Galton's *English Men of Science: Their Nature and Nurture*, published in 1874. In this publication Galton defines nature as the characteristics a man brings with him into the world, and nurture as what influences and affects this man after his birth (Groff & McRae, 1998).

This long-standing nature versus nurture debate is cited in behavioral and physical expressions of disease dysfunctions, resiliencies, and recovery. Their purposes are noted both in scientific pursuits as well as literature. This discourse has been particularly intense in the fields of psychology, psychiatry, and biology where there is a long history of scientists' attempts to disprove or discredit others' intellectual and professional measures. Interestingly, recent advances in the neurosciences and genetic technologies have brought these fields closer together with a new focus – the interactional relationship between nature and nurture – epigenetics.

Epigenetics is the study of how individual experiences affect genetic expression and translation of genes from one generation to the next (Jeanteur, 2005). This relatively new field of scientific study, which has emerged in the last 10 years, provides a way of analyzing the underlying processes by which environmental events or conditions are transmitted genetically. Genetics is the study of the ways in which information is

inherited, or passed, from parents to their offspring through genes (sequences of DNA) in the sperm and egg cells. *Epi* is a Greek word meaning "on, upon, at, by, near, over, on top of, toward, against, among" (Medicine Net, Inc., 2003). Therefore epigenetics, as defined by Jeanteur, is "the pattern of successive gene expressions that govern how an organism's cellular material will function" (2005, pg. 222).

Environmental stimulus experienced by an organism that alters the expression of an organism's gene in one generation may have an impact on the expression of behaviors in current and future generations. Gene expression is the process by which a gene is switched on or off. On a biological level, this process will produce proteins within the altered cell that will modify how the cellular material will function (Cloud, 2010). The ramification of epigenetic changes potentially could be quite serious as they can lead to diseases or chronic conditions or perhaps be beneficial as they may increase resistence or decrease vulnerability depending on the meaning of the event to the organism and the translation of the event genetically from generation to generation.

Joseph Ecker, a Salk Institute biologist and leading epigenetic scientist, provided an analogy to better understand the mechanism of how experiences are translated differently based on the genetic blueprint of the individual. "I can load Windows, if I want, on my Mac. You're going to have the same chip in there, the same genome, but different software. And the outcome is a different cell type" (Cloud, 2010, pg. 3). In this statement, Ecker describes genes as the hardware, the basic structure of the computer that physically stays the same, but operates differently depending on the compatibility of the software that is being installed. The compatibility of the software does not only affect the efficiency of the current operating system, but also may impact the future generation of

computers. Wrong information produced in one generation may have a lasting impact on successive generations. And conversely, well matched software may allow successive generations to operate more efficiently.

It would have been difficult for Sir Francis Galton to predict that 125 years after publishing his novel *English Men of Science: Their Nature and Nurture*, psychologists and biologists would still be interested in the difference between nature and nurture. In recent years advances in technology have allowed for biologists to better understand and explain how genes are transferred and altered during their passage from one generation to the next. These biological perspectives, in conjunction with psychological understanding of behavior, have shown that both nature and nurture can affect the development of a fetus. These breakthroughs in understanding have assisted psychologists in researching the effects of environmental changes on a developing fetus. Some of the most influential and harmful environmental variations include: maternal depression, anxiety, stress, smoking, alcohol, lead, dioxin, and other environmental toxins.

Chapter 2: Biology

Epigenetics is the study of how the environment can impact the replication of genes that are passed from parents to their offspring. Central to the study of epigenetics is an understanding of what makes up an organism's genetic blueprint, what alters the blueprint, and the impact of those changes. In order to fully understand this concept, it is important to know the biological systems behind this theory. This chapter will explore the biological systems that are involved in the replication and mutation of an organism's genes.

Human Genome

Humans have approximately 25,000 different genes that shape the physical and operating structure of a cell (Bygren, 2010). Deoxyribonucleic Acid (DNA) carries the genetic information that informs each cell in an organism how to operate. In 2003 the Department of Energy and the National Institutes of Health completed the U.S. Human Genome Project. The main goal of this project was to identify and map the genome, the collection of the 25,000 genes in human DNA, and to determine the sequence of the 3 billion chemical base pairs that make up DNA.

The goal of the project was to store this information in a database, improve tools for data analysis, transfer related technologies to the private sector, and address the

ethical, legal and social issues that may arise with this project (U.S. Department of Energy, Office of Science, 2008). The knowledge and scientific advances that resulted from the Human Genome Project sparked great interest in the study of gene replication and mutation.

Simple causal models of gene structure and disease have yet to be discovered based on the results of the Human Genome Project. For example, scientists had hoped to discover the cause of a known mutation for Tuberous Sclerosis. It had been previously identified that the disease was caused by a mutation in the TSC1 or TSC2 gene. This gene is responsible for preventing cells from growing too fast or in an uncontrolled manner. A mutation to this gene can cause cells to divide excessively, which leads to numerous tumors throughout the body, called Tuberous Sclerosis (Mayo Clinic Staff, 2010). To identify the cause and the specific gene mutation that causes every disease will take a great amount of time and resources, making this an extremely complex task.

Rather than simplifying the extremely complex process of genetic transmision, the Human Genome Project enhanced the knowledge and understanding of this process. This project defines genetic transmission as the process by which information is translated from generation to generation. It appears that every gene may have a specific set of instructions and a correlating function that can be altered in a variety of ways by the experience of the gene and the instructions during development.

Gene Sequence

The role of a gene is to define the function and purpose of a cell. Each of the trillions of cells in the human body has a specific order of genes within a nucleus – the

cell's control center. Within the nucleus is tightly coiled DNA, a specific gene sequence, which surrounds the cell's proteins (Cloud, 2010). The gene sequence is a code to instruct the cell to produce specific proteins that are required by the organism to function properly (Bygren, 2010). For example, the code tells liver cells to behave differently than brain cells.

Some diseases are produced by predictable mutations in the gene sequence. Lynch Syndrome is an inherited pattern of gene mutations in the liver. The inheritance of the abnormal liver gene sequence is harmful to the individual because this gene is responsible for correcting mistakes in the genetic code. Individuals who inherit a gene associated with Lynch Syndrome lack the ability to repair minor mistakes in their liver. An accumulation of these mistakes will increase the risk of damage to the cells, which can eventually lead to cancer (Mayo Clinic Staff, 2010).

However, according to the knowledge gained through the Human Genome Project, there appear to be genes that are present, but never activated within some cells or genes that behave differently than expected (U.S. Department of Energy, Office of Science, 2008). One discovery is that it appears that genetic redirection can be the result of variations to how the epigenome is packed within the nucleus of the cell. The epigenome is responsible for interpreting environmental signals received by the cells instructing what DNA should and should not be active in the cell. This layer will uncoil around to expose active genes and will wrap tightly around the histones to hide inactive genes. This makes the inactive genes unreadable and the active genes easily accessible (Genetic Science Learning Center, 2010).

Gene Expression

Every sequence of DNA has a genotypic and phenotypic expression. The genotype expression will determine the internally coded and inheritable information of a cell. On the other hand, the phenotype will have an outward, physical manifestation (Jablonka & Lamb, 1995). Therefore, every phenotypic expression of an organism's genetic information is a function of the imprinted gene of past generations. An imprinted gene can be turned on or off, which will impact the phenotypic expression of any gene sequence.

Epigenome

The epigenome shapes the physical structure of the genome. It is extremely flexible, which helps it to maintain and adjust the physical structure of the genome to the environmental demands relayed by the cell's proteins. The cell's DNA is surrounded and protected by proteins called histones. These proteins are responsible for passing information signals from outside the cell to the cell's DNA control center. Signals are received by the epigenome from inside the cell, from neighboring cells, or from the cell's environment. This information will adjust specific genes in the cell to the demands of an organism's rapidly changing environment (Genetic Science Learning Center, 2010).

Epigenetic Marks & Epigenesis

Through the developmental process a cell will change its gene expression to that of a specialized cell, which is responsible for a specific organ, such as the liver. This cell will record its experiences on its DNA through epigenetic tags. Epigenetic tags change a

cell's gene expression by telling an organism's cell to switch on or off particular genes in the epigenome (Jablonka & Lamb, 1995). These tags also stabilize the gene expression and identify a specialized function for each of the hundreds of cell types (Genetic Science Learning Center, 2010).

Epigenetic marks, connected to the organism's DNA, assist in passing specific traits from parent to offspring. The parents' DNA will imprint their genes on the forming genome of the offspring (Jeanteur, 2005). Once the parental genome is imprinted on the offspring, their genes are reprogrammed to allow the new unidentified cell to develop into any specialized cell (Genetic Science Learning Center, 2010). These cells are re-established according to the sex of the individual in order to be imprinted correctly on the offspring (Jeanteur, 2005).

The process by which the epigenetic marker communicates with the cell's DNA is called epigenesis. Epigenesis occurs during the developmental process of cell differentiation. Cell differentiation occurs when a less specialized cell becomes a more specialized cell, a cell with a specific responsibility (Genetic Science Learning Center, 2010). During epigenesis, epigenetic markers silence certain gene sequences and activate others (Bygren, 2010). Most often these marks are signaled by environmental stimuli to imprint on genes. This will signal the newly activated or silenced trait to be expressed in the specialized cell (Cloud, 2010).

DNA Methylation

The genotypic expression of a gene can be turned on or off through the process of DNA methylation. This biological process will change the phenotypic expression of the

altered cell's gene sequence. DNA methylation, which is also known as DNA replication, is one of the key mechanisms involved in regulating the expression of a gene in differentiated cells. DNA methylation does not change the sequence of DNA; rather, it changes the expression of a cell's DNA sequence (Jeanteur, 2005). DNA methylation occurs within the epigenome when an organism's cell receives a signal from a surrounding stimulant (Genetic Science Learning Center, 2010).

DNA methylation is the process by which a methyl group attaches to a specific spot on a gene (Cloud, 2010). A methyl group is repsonsible for signaling the location of a cell; for example, this chemical chain would tell a liver cell to remain in the liver for the entire lifetime of the organism. The methyl group also supresses the expression of viral genes and forms the basis for all chromatin structures (Jablonka & Lamb, 1995).

DNA methylation is an important cellular process as a large number of genetic diseases occur when there are complications (Jeanteur, 2005). One disease that comes from a disruption in DNA methylation is Rett Syndrome. Rett's patients initially demonstrate typical development, but begin to show signs of mental retardation, autism, and movement disorders later in life. This syndrome occurs from a mutation in the gene for the methyl-binding protein MeCP2. This protein is important because it silences the expression of genes binding tightly to methylated DNA (Geiman & Robertson, 2010). Without DNA methylation, genes are left to randomly replicate during the developmental process of a new organism.

To demonstrate the importance of DNA methylation, Jirtle, an oncologist at Duke University, and Waterland, a postdoctoral student at Duke, conducted a study to show how controlling an organism's environment can alter the phenotype, the physical

characteristics, of an organism's gene. The researchers used mice with a uniquely regulated agouti gene as their subjects. When this gene is continuously expressed, mice have a yellow coat, propensity for obesity, and diabetes.

Jirtle and Waterland fed one group of pregnant agouti mice a diet rich in B vitamins. The control group of genetically identical mice received no prenatal care or special diet. They found the mice that were fed a diet rich in vitamin B gave birth to healthy brown pups that were of normal weight and were not prone to diabetes. These results concluded that the B vitamins acted as a methyl donor, which caused methyl groups to attach more frequently to the agouti genes in utero, thereby altering their expression and genomic structure of the mice's DNA (Waterland & Jirtle, 2003). This study shows how DNA methylation worked in favor of the mice by altering the imprinting of their genes to express more favorable phenotypes.

Environmental Factors

Changes to the epigenome of a cell occur when chemicals accumulate in, on, or around a cell. These chemicals will eventually trigger a response from the epigenome, sending a signal to turn on or off specific genes (Issa, 2007). Some of the most influential chemical factors are diet, stress levels, and prenatal nutrition or care (Cloud, 2010). For instance, a rich diet high in fat can have harmful effects on the passage of genes from one generation to the next.

The influence of environmental factors, such as a rich diet, has been shown to activate epigenetic marks that modify the production of proteins (Bygren, 2010). Biologists have also shown that environmental stimuli can affect how tightly the

epigenome is wrapped around the cell's proteins and DNA. If the cell's proteins are wrapped too tightly the DNA will be hidden in the cell and therefore cannot be utilized (Issa, 2007).

The effect of a mother's rich diet was explored further by Raz, Tel Aviv University, and Jablonka, an epigenetic pioneer, in 2009. Raz and Jablonka fed roundworms a strand of bacteria that left the offspring with an altered appearance and a switched off green florescent protein. This epigenetic change lasted for over forty generations of roundworms. Their paper cataloged over 100 forms of epigenetic inheritance (Cloud, 2010). Their study was able to show the power of environmental toxins on the development of roundworms, a conclusion that suggests an application to more complex organisms.

Summary

The Human Genome Project was groundbreaking, mapping the 25,000 genes and 3 billion chemical base pairs of the human genome. This project paved the way for the hundreds of studies on gene replication and mutation which followed and will come. Studies have already helped determine the role and structure of DNA, the instructions that allow for an organism to function properly.

DNA has a flexable and maliable covering, called the epigenome. This structure surrounds each and every sequence of genes. The proper replication and expression of this sequence is crucial for an organism's survival.

Genes within each gene sequence can be altered through DNA methylation or epigenesis. Most often epigenesis will activate an epigenetic mark, triggered by an

environmental stimuli. This activation of this mark will turn on or off the expression of certain genes, which will alter the genotypic and phenotypic expression of the organism's gene sequence.

Chapter 3: The Foundation of Epigenetic Theory

The most commonly used definition of epigenetic changes in eggs and sperm cells is gene activity that does not involve alterations to the genetic code, but nevertheless still gets passed down to at least one successive generation (Cloud, 2010). Scientists have begun to amass historical data to determine both if and what environmental conditions can leave imprints on the genetic material of egg and sperm cells. These scientific investigations have foundations in the theories of one of the first genetic scientists, Charles Darwin.

Charles Darwin

Charles Darwin, one of the earliest and most renowned scientists, who concluded that evolutionary changes occur over many generations and through millions of years of natural selection (Darwin, 1872). While Darwin's work focused on environmental change and adaptations that occurred over extended periods of time, the main theories of epigenetics have a foundation in his work.

During the late 1800s, Darwin was concerned with the environmental factors that were causing variations within a species' environment. He looked at how the variations can cause modifications to an animal's organs or physical structure. These changes may have been a response to needs changing in a group, or a species response to survive in an

altered environment. For example, Darwin examined the adaptation of the length of a giraffe's neck. He postulated that the giraffes with the longest necks were able to survive by reaching the vegetation that was out of reach from other herbivores, including the giraffes with shorter necks. Darwin called this process of elimination of the less desirable traits "natural selection" (Darwin, 1872).

From a genetic point of view, Darwin's theory of natural selection explained that the replication of the gene sequence for a long neck giraffe was passed on from one generation to the next through survival of the fittest. Over time the sequence for a shorter neck was extinguished because it was harder for these giraffes to survive on the limited vegetation of the lower branches. Conversely, too long of a neck may have made it difficult for these giraffes to drink water or move efficiently. Darwin postulated that the preferred genes for a long neck are passed through selective mating, as long necks decided to mate with other long neck giraffes. This strengthened the adaptive advantage of offspring in regards to locating and consuming adequate nutrition (Holdrege, 2003). The long neck allowed for the giraffe to reach the food on the tops of trees, to run quickly from predators, and to make it harder for predators to attack them. This change in the giraffe's gene sequence took many generations to show (Darwin, 1872).

Evolutionary Theory

Most often natural selection happens through synthetic gradual changes, such as mutation, recombination, and selection. Natural selection is an unconscious choice by mammals to combine their most important and beneficial survival features with others of their species. Oftentimes the animal's mating partner will also have desirable traits that

will increase the chance of passing on the most functional physical and genetic makeup to their offspring.

The adaptation in the length of the giraffe's neck is an example of an unconscious natural selection. After many generations the gene had manifested in the physical appearance of the giraffe that occupies the interior of Africa today (Lonnig, 2006). In fact, the giraffe ancestry can be traced back millions of years to the shorter necked deer, Eumeryx (Holdrege, 2003).

Darwin's theory sought to explain that every species will make an appearance in the form of a single species, exhibiting no diversity until it has been in existence for a long period of time. Present day giraffes are characterized by longer forelegs than hind-legs and extremely long necks. To determine this species anatomical and physiological history it is important to trace the giraffe ancestor's fossils and explore their botany, climatology, and migration patterns. The generations of species' fossils can be arranged in a chronological order to map their ancestry and physical changes over time (Lonnig, 2006). Most importantly, the earliest fossils of each group will be distinguishable from the new fossils, hence the length of the present day giraffe's neck and his ancestor's short neck.

DNA Expression

Darwin's theories were correct in stating that genes take many generations, through natural selection, to alter the phenotypic expression of a mammal's genetic composition. With recent technological advances, researchers have been able to show how genes are manipulated. DNA methylation, a chemical process, and epigenesis, the

theory of this process, have been identified as the processes that alter the expression and regulation of human genes. These evolutionary processes will most often change the expression of genes from one generation to the next.

Epigenesis research has recently been focused on discovering what affects the expression of DNA. The process of epigenesis occurs most often during the DNA replication and development of embryo and fetal cells. DNA replication alters the histones that form the core of the nucleosome. The nucleosome contains DNA packed tightly around the histone; this forms the nucleus of the cell. This DNA modification can change the surrounding chromatin to influence the expression of the gene sequence, but this will not change the genetic composition of the organism (McCarthy et al., 2009).

Human Fetus

In order to determine how the environment is affecting the replication of DNA, a researcher needs to consider the environment in which the fetus is developing. In general, the fetus' environment has little variation. The fetus' environment is fairly standardized and anatomical within the shell of the woman's uterus (Kuo, 1967). The standardization of the utero environment allows for the fetus to develop with stability and reliability.

The one component of the uterus that can vary from one woman to another is the chemical components contained within the uterus. These chemicals can influence the development of the fetus as the fetus is surrounded by the chemicals in the womb. These chemicals play an important role in the behavior of the developing fetus (Kuo, 1967). The sensitivity of the chemicals' components can affect how the genetic information is passed on to the embryo. This in turn can affect the phenotypic expression of the offspring's

genes by altering the genetic expression of a gene sequence. These characteristics can be altered by even slight changes in the fetus' sensitive environment (Jablonka & Lamb, 1995).

Agricultural Impact

One of the earliest epigenetic studies to examine the effect of the environment on the developing fetus was conducted by Lars Olov Bygren in the 1980s. Bygren's study examined the long-term effects of feast and famine on children growing up in Norrbotten, Sweden during the 19th century (Bygren, Kaati, & Edvinsson, 2001).

Bygren examined Norbotten's population because of their geographic isolation. The citizens of Norrbotten starved in times of bad harvest, and gorged when crops were in abundance. In addition to the isolation of Norrbotten, this sample was used because of the extremely accurate and extensive records kept by the Swedish government (Bygren et al., 2001). These records allowed Bygren to draw a random sample of individuals whose ancestors experienced environmental fluctuations. These fluctuations can be pinpointed to a few powerful factors because of Norbotten's isolated environment.

Bygren compared a random sample of 99 individuals born in the Overkalix parish of Norrbotten in 1905. He used Sweden's historical records to trace this sample's parents and grandparents back to their births (Bygren et al., 2001). The parents' and grandparents' records were also examined to determine the effect of each successive generation's pattern of longevity of their grandchildren. This data was compared with the environmental changes the participants' ancestors lived through in early 1900s Norrbotten.

The agricultural records at the time of the participants' ancestors' birth were designated as the environmental stimuli in Bygren's study. These records were used to compare, and hopefully prove, that the environment has an effect on successive generations' gene expression (Bygren et al., 2001). The agriculture records were consulted to determine how much food was available to the parents and grandparents when they were in their youth.

The two types of harvest that were considered in this study were overabundant and poor harvests. An overabundant harvest was defined as a period of time when the citizens of Overkalix would go from typical eating to gluttony eating in a single season, drastically changing their diet (Bygren et al., 2001). An overabundant harvest was rare and seldom lasted for more than one season. More often than not, these children typically ate small amounts of food that were provided by the poor harvest.

Bygren hypothesized that the inconsistency of the mother's diet could have harmful effects on the health of her fetus. He believed that these changes in the environment could affect the expression of the genes passed down to Overkalix citizens born in 1905. In addition, he proposed that the variation in diet would affect the offspring well into their adult life (Bygren et al., 2001).

Dr. Bygren tested his hypothesis by comparing the age at death of his 99 participants with the length of their ancestors' lives and the agricultural records from their ancestors' childhood. The results of this sample were compared to citizens who were also born in Overkalix, but whose ancestors lived through only poor harvests (Bygren et al., 2001).

The results of Bygren's study were groundbreaking. He found that both diet and the environment can affect successive generations, proving his theory correct. One of the results of his study was that the male grandparents who enjoyed the rare overabundant winter produced sons and grandsons who lived shorter lives. The overabundant winter occurred during the grandfathers 9-12 years of life. On average, the sons and grandsons of these men lived six years less than the sons and grandsons of those who lived through all moderate harvests. Individuals who experienced a stable diet, defined by a moderate availability of food throughout their lifetime, on average lived longer. When the same group of males was controlled for socioeconomic differences, the average lifetime of the males was 32 years less than the males of poor harvest ancestors (Bygren et al., 2001).

Sweden's Norrbotten data have been used in several other studies, as it is one of the best kept records of multiple generations of a population. Later papers using the citizens of Norrbotten as their participants found a decrease in the longevity of the female line in addition to the male line. It can be concluded that the daughters and granddaughters of girls whose eating patterns went from normal to gluttonous in their childhood gave birth to girls and boys who lived significantly shorter lives (Bygren et al., 2001). The results of these studies suggest that a single winter of overeating as a child can activate a biological sequence of events that will change the average lifespan of one's children and grandchildren.

Bygren's study showed how environmental conditions, such as starvation, can have a serious effect on a developing organism, in this case the development of a human fetus. The environment can leave an imprint on the genetic material of the eggs and sperm cells (Bygren et al., 2001). This genetic imprint short-circuits Darwin's process of

evolution and natural selection by passing new traits in a single generation, through altering the gene expression of the still intact gene sequence.

This study has given psychologists and scientists great insight into the field of epigentics, although it is not the capstone. There are a few major limitations, including: sample size, the use of only three generations of data, and the inability to replicate this study. Therefore, the full impact of the epigenetic change from variations in diet cannot be determined from this study alone. Although, there are limitations to this study, it does provide a solid foundation for future epigenetic research.

Conclusions

The research and experimental results produced by epigenetic studies have laid the groundwork for the biological processes involved in the epigenetic replication, modification and mutation. Epigenetics can be described as the developmental process of life that emerges from an interaction of genetic, phenotypic, and environmental variables. Increased knowledge and scientific advances have sparked great interest in determining what factors contribute to the expression and silencing of certain genes within the genome and more specifically a gene sequence. Through epigenetic research a better understanding is possible concerning how the genetic propensity (nature) and the environmental factors (nurture) that surround a developing fetus affects the birth of a child (Thomason, 2004).

This knowledge and understanding allows psychologists to define epigenetics on a less molecular level as the study of a transformation by means of new relations that become the basis for subsequent restructuring. In fact, epigensis can be simply defined as

"construction" (Morra et al., 2008). By combining the biological and psychological definition of epigenetics, researchers in both fields are able to better define this process of genetic change.

Chapter 4: Maternal Depression and Stress

A woman experiences a wide range of emotions when she first discovers she is pregnant. Pregnant women often experience feelings of excitement, fearfulness, anxiety and isolation. These emotions are often associated with how the mother feels about the environment into which she is bringing her child. The impact of atypical maternal emotions on the developing fetus has recently become a hot topic for epigenetic researchers. Most often the focus of these epigenetic studies are on maternal depression and stress.

Maternal Depression & Anxiety

Psychologists are particularly interested in the impact of maternal depression on the development of the fetus and the fetus's developing genes. In fact, maternal depression has been found to affect almost 18% of pregnant women in the United States (Diego et al., 2009). The number of depressed pregnant women in the U.S. is most likely higher than the reported number, as this figure only accounts for the women who have reported symptoms and been formally diagnosed. The most common symptoms of maternal depression are very similar to typical depressive symptoms. They include: "crying, sleep problems, fatigue, appetite changes, disinterest in daily activities, difficulty

concentrating, irritability, apathy or heightened anxiety, obsessive thoughts or worries, and feelings of guilt or hopelessness" (ACOG Office of Communications, 2007). Many pregnant women, as well as their doctors, may ignore or misidentify these symptoms. Often these symptoms are blamed on the natural fluctuations of hormones during pregnancy.

The hormones most often blamed for mood fluctuations during pregnancy are estrogen and progesterone. In fact, a pregnant woman has 10 times more progesterone than a non-pregnant woman. These hormones are responsible for almost all of the depression-like symptoms pregnant women experience during gestation. Some of the most common hormonal symptoms are breast soreness and sensitivity, a heightened sense of smell, irritability, anxiety, and fatigue (Jocoy, 2009). The symptoms themselves can cause mild mood fluctuations in the pregnant woman, while they are also vital for the survival and development of her fetus.

Ignoring or misidentifying maternal depression as the symptoms of hormone fluctuations can be extremely harmful to a pregnant woman. Maternal depression is a chemical imbalance in the brain that can limit a woman's ability to function from day to day. The symptoms of maternal depression can last for several weeks at a time (ACOG Office of Communications, 2007). If this period of depression is left untreated it can lead to significant ramifications on the development of the fetus.

The implications of maternal depression on the developing fetus are particularly important to understand and manage, as the number of women who suffer from this chemical imbalance is rapidly increasing. Prolonged periods of maternal depression that are left untreated have been linked to many developmental restrictions. One of the most

common consequences is a constraint on the growth of the fetus. Fetal growth restrictions are the leading cause of infant morbidity and mortality. Additionally, these restrictions have been shown to be associated with adverse neurodevelopmental outcomes, cardiovascular diseases and an increased risk for diabetes throughout the offspring's life (Diego et al., 2009). The developmental restrictions initiated by maternal depression and anxiety are one of the most recent and significant findings of epigenetics. The influence a mother's emotional health and well-being can have on her child's adult life is a powerful conclusion to come from these studies.

Effect of Excess Cortisol

Cortisol is a hormone that helps the body properly respond to a stressful stimulus. A wide range of animal research has found that excess cortisol is associated with hyper-activation of the pregnant female's Hypothalamic Pituitary Adrenal axis (HPA axis). This axis is responsible for the body's response to stressful stimuli—too much stress leads to too much cortisol which has been shown to restrict fetal growth (Diego et al., 2009). The HPA axis is a loop of communication in the brain between the hypothalamus, pituitary gland, and adrenal glands.

In regards to depression, the hypothalamus is responsible for regulating emotions. The pituitary gland secretes hormones that help maintain stability in the body and the adrenal gland secretes hormones in response to a stressful stimulus (Bowen, 2001). During emotional or physical stress, this axis is activated by the adrenal gland release of cortisol (Varghese & Brown, 2001). During a period of depression, the hyper-activated HPA axis will produce an abundant amount of cortisol. Prolonged increases in the body's

level of cortisol are particularly dangerous as it can suppress the immune-system and accelerate bone loss (Talbott, 2002).

A study by Diego and her fellow researchers (2009) was conducted to determine the effect of depression on the growth and development of a fetus. They also hoped to determine the risk factors to the fetus that are a consequence of maternal depression. Forty depressed and forty non-depressed pregnant women participated in their study. Each of these women was in the second trimester of pregnancy, meaning their fetuses were 18-20 weeks old. The researchers estimated fetal weight, urine cortisol level, and birth weight. The data from the depressed women were compared to the non-depressed women to determine the effect of depression on the developing fetus (Diego et al., 2009).

The study reported that depressed women had a 13% greater incidence of premature labor and a 15% greater incidence of low birth-weight compared to non-depressed women. Depressed women also had higher prenatal cortisol levels during midgestation, which is believed to be a factor in their babies having lower fetal weights (Diego et al., 2009). This study underscores the importance of maintaining chemical balance during the gestational period and the adverse physiological impact of depression on the developing fetus.

Effect of Anxiety on Fetal Heart Rate

In addition to maternal depression, anxiety has been a topic of interest for epigenetic researchers. One study examined differences in fetal heart rate associated with a mother's psychiatric status, in particular anxiety. Highly anxious pregnant women in general have faster resting heart rates, which is believed to delay the maturation of the

fetus (Monk et al., 2004) The participants were 57 pregnant women in their third trimester of pregnancy, between 33 and 39 weeks (Monk et al., 2004).

Participants completed the self-report measure of anxiety using the Spielberger State-Train Anxiety Inventory (STAI). The women also completed the Trait Anxiety scale of the STAI to measure their predisposition to feeling anxious. These measures were used to assess the participants' daily levels of and exposure to anxiety (Monk et al., 2004). These measurements were used as a control factor for later comparisons of the level of anxiety the mother experienced during the research task and the effect of the anxiety on her fetus.

The mother's anxiety was measured by monitoring her heart rate and blood pressure, as well as the respirations and fetal heart rate, during and after a stressful situation. The stressful situation considered in this experiment was a task consisting of a 5 minute resting period of complete silence, a 5 minute psychological challenge, and a 5 minute recovery period. The 5 minute psychological challenge was the Stroop color-word matching task. Subjects were asked to press a key corresponding to the color of the word, which was either congruent or incongruent with the name presented. If the participant answered incorrectly she received a message indicating she had answered incorrectly. Additionally, the participants were given verbal prompts at minute intervals, which needed to be promptly and accurately completed (Monk, et al., 2004).

The results of this study indicated different responses for fetuses of anxious and non-anxious mothers. The fetuses of highly anxious mothers had an increased heart rate during and after the challenge. The physiological changes associated with stress altered the fetus's utero environment, while the fetuses of mothers displaying low and middle

levels of anxiety showed no response to the challenge (Monk et al., 2004). This biopsychological study demonstrated how a pregnant woman's emotional state can alter the development and well being of her fetus.

Ethnic and Socio-Economic Effect

Numerous studies have come to similar conclusions on the adverse consequences and effects of maternal depression on a developing fetus. Previous research has noted that at birth newborns born to depressed mothers are notably different than newborns of non-depressed mothers. These differences have included how the brain sends signals (through neurotransmitters), EEG patterns (heart rate), and behavior (Field et al., 2002). These patterns are believed to be related to elevated stress hormones in the mothers prenatally, which is believed to subsequently elevate fetal activity.

Field (2002) led a cross-cultural study to determine if there are differences in the orientation and early behavior of newborns born into different cultures. The study conducted by Field et al. was designed to determine if the effects of prenatal depression varied by ethnicity. This study compared the development of fetuses and newborns of depressed mothers with those of non-depressed mothers from two different ethnic groups. The fetuses were tested at periodic stages of development as well as two days after their birth.

The participants were 86 pregnant women from two Miami cultures: Hispanic and African-American. In addition, the participants from each culture were either in the lower or middle socioeconomic status group. This study predicted that the fetuses and newborns would have different consequences of maternal depression based on their mother's

ethnicity. It was hypothesized that this variation would be a result of how the mothers differed prenatally by their cultural groups.

Field et al. (2002) found that during the postnatal period, there were differences between the Hispanic and African-American mothers reported levels of anger on the POMS Scale and levels of serotonin. The Profile of Mood States (POMS) scale measures six bipolar subjective mood states: composed–anxious, agreeable–hostile, elated–depressed, confident–unsure, energetic–tired and clearheaded–confused (Sanders & Bruce, 1999). The neurotransmitter Serotonin influences a variety of psychological and bodily functions, which include: mood, sexual desire and function, appetite, sleep, memory and learning, temperature regulation, and some social behavior. Many researchers believe that an imbalance in serotonin levels may influence mood in a way that leads to depression (Bouchez, 2009).

The Hispanic mothers reported higher levels of anger on the POMS Scale compared to the African-American population. The effect of an increased level of anger, based on POMS, and a noticeably higher serotonin level in the newborns of the Hispanic women, confirmed Field et al.'s theory that prenatal depression has different effects on newborns of different cultures. Hispanic newborns had higher dopamine and lower cortisol levels. Dopamine is the chemical in the brain responsible for the pleasure/reward pathways, memory, and motor control. Hispanic newborns spent less time in deep and indeterminate sleep (Field et al., 2002). These babies also spent more time in a quite alert state.

The results of this study are consistent with other epigenetic research as it demonstrates how fetal reactivity is related to the mother's mood during pregnancy,

while it also shows how various cultures may respond to pregnancy in a different manner. The differences in Hispanic and African-American mothers and their fetuses were believed to have been a by-product of an increased number of diagnosed phobias and higher levels of intermittent anxiety. This study highlights how culture is another variable that can have an influence on the environment in which a fetus is developing. The emotion-based changes in the maternal physiological environment has a significant effect on a developing fetus, and may be specific on the newborn of any particular culture.

Maternal Stress

In addition to maternal depression, psychologists are also extremely interested in the role psychological and emotional factors, such as stress, play during the course of pregnancy and childbirth. New research has suggested that stress may be the strongest emotion-related risk factor for a pregnant woman and her developing child. Most commonly stress is associated with anxiety, sorrow, and worry. Previous research has demonstrated that these symptoms can disturb the fetus and even cause the fetus physical harm (Project ABC, 2004).

Stress is a complex emotion as the human body needs a moderate amount of stress to maintain its internal balance. Stress outside of pregnancy triggers the brain to produce two hormones, corticotrophin (CRH) and adrenocorticotrophine (ACTH). These stress hormones will travel through the blood stream to activate the hypothalamic-pituitary-adrenal (HPA) axis and specifically the adrenal gland (Project ABC, 2004). The adrenal gland will produce cortisol and adrenaline, hormones that will help the body properly respond to the stressful situation. Common responses to stress are an increased rate and force of contraction of the heart muscles, constriction of blood vessels, dilation of the

bronchioles, increased metabolic rate, and dilated pupils (Bowen, 1998). The response of the adrenal gland helps return the body to an internally balanced state of homeostasis.

In a non-pregnant state the cortisol will reach the brain through the blood stream, inhibiting the future release of CRH and ACTH. During pregnancy, cortisol will also stimulate the release of placental CRH. Excessive placental CRH has been shown to cause potentially detrimental complications with pregnancy. Most often excess CRH will cause preterm labor and early delivery (Project ABC, 2004).

Pregnant women often feel stressed and fearful about the outcome of the pregnancy, the experience of labor, their ability to care for a new baby, and the health and well-being of their child. The factors that can influence how a woman responds to maternal stress include the nature of the stressful experience, the timing of stress during gestation, and the availability of a support system to mediate the stress. Additionally, the CRH hormone makes stressful experiences even more potent when its increase is accompanied by an infection, work strain, nutritional deficiency, financial stress, or substance abuse (Project ABC, 2004).

Effect of Synthetic Stress Hormones

Chronic maternal stress has been shown to compromise the normal regulation of a woman's hormonal activity during pregnancy. Excess levels of corticotrophin (CRH), a stress hormone, can cause preterm labor, reduce birth weight, and slow fetal growth rates.

Schneider et al. (1992) conducted a study on two groups of pregnant rhesus monkeys to simulate and help determine the effect of stress hormones on the fetus. The first group of monkeys was a control group, who were left alone during their gestational

period. The second group of rhesus monkeys was injected with adrenocorticotropic hormone (ACTH) every day for a two week period (Schneider, Coe, & Lubach, 1992).

The researchers injected ACTH into the rhesus mothers because it is a hormone that is normally produced in response to a stressful situation. This drug was used to help determine whether stress and ACTH affect the early neuromotor development of the mother's fetus. The hypothesis was that these infant monkeys would experience responses similar to those whose mothers experienced natural prolonged psychological stress during their pregnancy (Schneider et al., 1992).

After the birth of the rhesus monkey, during the first month of the infants' lives, the researchers measured their development using a modified version of the Brazelton Newborn Behavioral Assessment Scale (Schneider et al., 1992). The Brazelton scale assesses a wide range of behaviors which describe the baby's strengths, adaptive responses, and possible vulnerabilities (Brazelton Institute, 2008). The rhesus infants who had the ACTH treatment during gestation experienced impaired motor coordination and muscle tonicity. These infants also had shorter attention spans, were more irritable, and more difficult to console than was the control group (Schneider et al., 1992). The findings in this study indicate that even a short period of stress during pregnancy can have an adverse effect on an infant's neurobehavioral development.

Effect of Long-Term Stress

There is a significant amount of animal research suggesting an association between prenatal stress and cortisol production during the offspring's teenage years. As noted previously, cortisol is a hormone produced by the hypothalamic-pituitary-adrenal

(HPA), which is responsible for helping the body respond to stress. A study conducted in 2005 was the first to test these results on human participants (O'Connor et al., 2005).

O'Connor et al. (2005) hoped to determine the relationship between prenatal stress and the child's future production of cortisol. The researchers first measured the mother's level of stress, anxiety, and depression during her pregnancy and postpartum period. These measurements were a combination of the results from the mother's scores on the Crown-Crisp Index, Spielberger Sate-Trait Anxiety Inventory, and Edinburgh Postnatal Depression Scale. Multiple measures were used to help support the hypothesis that stress during the prenatal period has a lasting effect on the child (O'Connor et al., 2005).

When these children celebrated their 10th birthday, researchers measured their cortisol levels through saliva samples. Saliva samples were taken 30 minutes after the child awoke, at 4:00 P.M., and at 9:00 P.M. on three consecutive days. These samples were examined to determine if there was a link between cortisol production, an indicator of HPA axis functioning, and the mother's level of prenatal stress (O'Connor et al., 2005).

The results indicated an association between prenatal stress and the level of cortisol during the awakening and afternoon time periods. This result held true when the numbers were controlled for obstetric and sociodemographic risks. Even after controlling for multiple postnatal assessments of maternal anxiety and depression, results were still attributed to a significant difference in cortisol levels (O'Connor et al., 2005).

This study gives human evidence to support the animal studies regarding the effect of a mother's stress on her developing fetus. It also concluded that prenatal stress

may have a lasting effect on the functioning of the HPA axis in children (O'Connor, et al., 2005).

Summary

In recent years epigenetic biopsychological research has produced numerous studies showing the negative impact of maternal stress and anxiety on a developing fetus. These studies have indicated how the variations in prenatal emotion-based physiological activity can affect the fetus's behavior and development.

The study on maternal depression conducted by Bowen (1998) found that a biological imbalance, specifically the excess production of cortisol, restricted the growth of the developing fetus. Fields research team (2002) took this idea a step further to determine if there was a socioeconomic affect on the newborn's orientation and early behavior. Field et al. found that the depressed pregnant Hispanic women experienced higher levels of anger and a higher level of serotonin, compared to the depressed pregnant African-American mothers, resulting in different restrictions on their developing fetuses.

The studies profiled on maternal anxiety and stress demonstrated the effect a short period of heightened stress can have on the fetus's development. Long-term prenatal stress was found to have a lasting effect on the HPA axis functioning in children who participated in the O'Connor et al. (2005) study. This effect may increase their risk for psychopathology in their childhood and adolescents. Monk's et al. (2004) study on the effect of maternal anxiety on fetal heart rate found that the changes in a mother's mood have a direct and sometimes detrimental effect on the fetus.

These studies illustrate how the variations in emotional regulation can be linked to physiology, behavior, and future psychopathology. Additionally, there is evidence to suggest that characteristics of children's regulation systems are likely to form and be identified at the earliest stages of their development.

Chapter 5: Environmental Toxins

Maternal depression and anxiety are two of the most common contributing factors to epigenetic changes that occur as a result of changes in the neurochemistry and behaviors of the mother prenatally and postnatally. However, these are not the only factors that contribute to atypical changes in fetal development. Powerful environmental conditions that can affect a fetus's development in utero are classified as environmental toxins, most commonly known as teratogens.

Teratogens are substances in the environment that can increase the chances of birth defects. The birth defects could be a result of numerous environmental substances, the most common being: bacteria, viruses, various recreational and prescription drugs, chemicals, and radiation (Schneider, 2006). The US Environmental Protection Agency has identified known substances that have teratogenic effects on fetal development. The most harmful are: lead, mercury, cocaine, alcohol, tobacco, heroin, iodized radiation, and dioxin (Kellerman, 2006).

Teratogens have been shown to cause mutations in the DNA expression of a gene sequence. These mutations change the neural chemistry in a developing fetus, resulting in the disruption of cellular migration and DNA replication. A fetus responds to these teratogens, often causing permanent epigenetic changes in the structure and physiology of the genes (Schneider, 2006).

Although some teratogenic agents can be effectively avoided by pregnant women, for example alcohol, exposure can occur prior to knowledge of the pregnancy or without knowledge of the exposures. A woman who is pregnant may not know she has exposed her unborn child to teratogenic drugs or environmental chemicals, such as lead, until they are several months old. Most commonly the effects of the teratogen will reveal itself within nine months of the child's birth (Schneider, 2006).

Effect of Alcohol Exposure

Alcohol was first recognized as a teratogen in the 1970's. At that time, children of mothers who drank throughout their pregnancy were diagnosed with Fetal Alcohol Syndrom (FAS). When this syndrome was first identified the focus was on heavy drinkers. FAS was identified by significant changes in facial features as well as changes in the cognitive abilities of the children. In the 1970's social drinking by pregnant women was acceptable and intravenous alcohol was a common treatment for pre-term labor.

Today, the Center for Disease Control (2010) estimates that 0.5 to 2.0 cases of FAS per every 1,000 live births occur every year, emphasizing the importance and relevance of research on alcohol exposure. Research indicates that alcohol impacts embryonic and fetal development and that no amount of alcohol has been deemed safe for a developing fetus. A wider range of insults to the developing fetus and to the subsequent child is diagnosed as Fetal Alcohol Effects (FAE) (Schneider, 2006). In fact, it has been shown that children of mothers who binge drink are often born with greater physical and mental deformities.

FAE occurs when a mother drinks alcohol. The alcohol enters her bloodstream and eventually reaches the fetus by crossing the placenta threshold. The fetus' blood alcohol concentration is much higher than the mother's since the fetus metabolizes alcohol extremely slowly (Mayo Clinic Staff, 2009). The extended presence of alcohol alters fetal development by disrupting cellular differentiation and growth, DNA and proetin synthesis, and inhibiting cell migration. Additionally, the alcohol modifies the cellular metabolism of carbohydrates, proteins, and fats, as well as the transfer of amino acids, glucose, folic acid, zinc, and other essential nutrients. The nutrient deprivation and metabolic modifications alter the cellular division and cellular replication of the fetuses' genes (Vaux & Chambers, 2010).

Alcohol has been shown to inhibit the normal development and growth of a fetus. Every year over 40,000 children born in the United States are diagnosed with some type of alcohol related damage, although this number is most likely an underestimation (Marshall et al., 2009). Although, the risk of FAE is present during the entire pregnancy, consuming alcohol during the first trimester, when a woman may be unaware of her pregnancy, is extremely hazardous to the embryo's development. Consumption during this period of time can cause impairment to facial features, the heart and other organs, bones, and the central nervous system, and in extreme cases can eliminate the corpus callosum – the connection between the right and left hemispheres of the brain (Mayo Clinic Staff, 2009).

The effects associated with FAE are irreversible and are classified along a spectrum of deformities including physical, learning, and memory problems (Marshall et al., 2009). Some of the most prominent symptoms of FAE include: distinctive facial

features, heart defects, slow physical growth, vision difficulties, hearing problems, small head circumference and brain size, poor coordination, learning disorders, and abnormal behavior (Mayo Clinic Staff, 2009). In addition to these symptoms FAE can also cause mental retardation, although the severity of mental retardation is variable.

Alcohol may be the most identifiable toxin to affect a developing fetus as the effects are often physically apparent and present themselves within the child's early years. The consequences of fetal alcohol exposure are long lasting and irreversible, which has been shown through generations of alcohol abuse. As alcoholism has the genetic component of addiction, this exposure has caused an increase in alcohol related societal problems. The research around fetal alcohol syndrome has inspired numerous other toxic exposure studies.

Effect of Lead Exposure

There is substantial evidence indicating that lead is an extremely hazardous teratogen. Lead is another significant teratogen that is known to pass from the mother to her unborn child through the placenta. Lead poisoning occurs when a substantial amount of lead is ingested through breathing or swallowing of the chemical compound. Most often the lead is ingested from sources such as food, dust, paint, and water (Golonka, 2008). Lead is a particularly dangerous substance, as a substantial blood lead level has been shown to cause deficits in children's learning, hearing, and behavior.

Epigenetic researchers are also interested in the impact of lead poisoning, although instead of focusing on the child ingesting lead, they consider the effect of the mother ingesting lead. After lead is ingested, it will bind tightly to the mothers' red blood

cells, transferring to the fetus through the placental membrane. The fetus has an extremely sensitive environment that is compromised by a low level of bone tissue to assist in sequestering the lead. In addition, the fetal blood-brain barrier is more permeable, which allows for the lead to enter and affect the development of the fetus's central nervous system (Public Health Services, 2003).

A study published by The New England Journal of Medicine assessed the relationship between prenatal and postnatal lead exposure and early cognitive development (Bellinger et al., 1987). This research was a longitudinal study of 249 children born in the Brigham and Women's Hospital in Boston. Children were assessed from birth to two years of age. Each child was assigned to one of three subgroups based on the lead levels in their umbilical-cord blood: low (> 3 micrograms per deciliter), medium (6 to 7 micrograms per deciliter), and high (≥ 10 micrograms per deciliter) (Bellinger et al., 1987). The children's development was measured semiannually starting at six months of age. The researchers used the Mental Development Index of the Bayley Scales of Infant Development (BSID) to measure the child's cognitive development (Bellinger et al., 1987). The BSID is a standardized assessment tool designed to measure the mental cognitive, motor, and behavioral domains of infants from one to 42 months of age.

The 249 children were evaluated to determine the association between the infant's umbilical-cord blood lead level and their development score on the BSID. Results indicated that those infants who were in the high-prenatal-exposure group scored significantly lower on the BSID than the two other groups of infants, at all points between 6 months and two years of age. At the time this study was conducted the Center

for Disease Control (CDC) defined the highest acceptable level of lead for young children to be 25 micrograms per deciliter. It appears that the fetuses in the high group already demonstrated adverse affects, even though their lead concentrations were well below the current acceptable level (Bellinger et al., 1987). This speaks to how any amount of lead exposure can have a severe impact on the growth and development of children.

The performance deficits observed in this study are consistent with previous studies on primates. Previous research on primate prenatal lead exposure has found an association with learning deficits in primates. This information was the background for the study conducted on infants born in the Brigham and Women's Hospital in Boston (Bayley, 1993). Lead exposure has been shown to have a serious impact on the development of children, although it is not the only chemical compound to affect the fetus in utero.

Effect of Dioxin Exposure

Many epidemiological studies have suggested that prenatal exposure to dioxin may also have a serious and detrimental effect on a developing fetus. Dioxin is a general term used to describe a group of hundreds of chemicals in our environment. This chemical compound is one of the most toxic substances that have been identified by scientists to date. These chemicals are the unintentional by-product of industrial processes involving chlorine, such as chemical and pesticide manufacturing, and pulp and paper bleaching (Environmental Protection Agency, 2010).

Epidemiological studies examine the distribution and determinants of health-related events, such as epigenetic diseases and abnormalities (WHO, 2010). Most commonly, dioxin is believed to cause reproductive and developmental abnormalities. Although the abnormalities have been identified, few studies have been able to explain the mechanisms of dioxin that stimulate these epigenetic changes (Takeda et al., 2009).

The last several decades have been marked by several incidents of dioxin contamination. In 1976 inhabitants of Seveso, Italy were exposed to large amounts of dioxin, a result of a chemical factory accident. This accident contaminated 15 square kilometers of land, involving the lives of 37,000 people. Subsequent studies on this population have found an increase in certain cancers as well as effects on reproduction. In 1997, the United States found chicken, eggs, and catfish to have been contaminated by dioxin. This contamination originated from tainted clay that was manufactured to feed farm animals. It was speculated that the dioxin might have been released from the clay through natural forest fires (WHO Media Centre, 2010).

A study conducted by Takeda et al. (2009) was designed to test the effects of exposure to dioxin, specifically Tetrachlorodibenxo-*p*-dioxin (TCDD). These researchers exposed pregnant Wistar rats to TCDD in order to test their hypothesis. Their hypothesis was that TCDD would damage the gonadotropin-regulation of protein production in fetal gonads. This damage was hypothesized to imprint defects in sexual behavior as well as affect the maturation of gonadal tissue (Takeda et al., 2009).

To test their hypothesis, the researchers orally administered one dose of TCDD to the pregnant Wistar rats on their 15th day of gestation. The TCDD was found to reduce the fetal expression of testicular and ovarian proteins. The maternal exposure to TCDD

delayed the development of gonadal tissue in both male and female pups. This exposure also impaired the pup's sexual behavior. The results of this study demonstrate how maternal exposure to dioxins can disrupt the gonotropin production, causing demasculinization of males and defeminzation of females.

Effect of Smoking

One of the most prevalent and powerful toxin in the environment today is cigarette smoke. Both first- and second-hand cigarette smoke have been shown to negatively affect a developing fetus. Epidemiological studies have found a relationship between maternal smoking during pregnancy and adverse neurobehavioral effects later in life. This toxic exposure has also been linked to an increased risk for cognitive deficits, attention deficit/hyperactivity disorder, conduct disorder, and a predisposition in the offspring to start smoking and abuse alcohol (Jauniaux & Greenough, 2007).

The adverse effects of cigarette smoke on fetal and placental development are due to nicotine and cadmium, the major toxic elements in cigarette smoke (Jauniaux & Greenough, 2007). Cadmium and nicotine reduce the amount of oxygen available to the fetus by restricting the utero-placental blood flow. The reduction of oxygen can negatively affect the central nervous system through cellular damage and reduction, and produce a premature change from cellular replication to cellular differentiation (Alexandra et al., 2007).

Most epigenetic studies have focused on the effect of a mother who smokes during pregnancy. Instead of questioning the mother's impact, a study conducted in 2006 questioned the effect on the offspring of a father's choice to smoke. These researchers hypothesized that fathers could have a cigarette-induced transgenerational effect on the

growth of their offspring. They believed that smoking before puberty would be associated with deficiencies in the offspring's growth patterns (Pembrey et al., 2006). The sample was 9,886 men from Bristol, United Kingdom, and the Avon Longitudinal Study of Parents and Children. These fathers reported on a standardized questionnaire that they had smoked at some point during their lifetime. Of these 9,886 participants, 166 reported that they had started smoking before the age of 11 (Pembrey et al., 2006).

The age of 11 was used as the critical point because this is the period in which a male body is preparing to enter puberty. During this period boys are genetically isolated as they cannot produce sperm. Since boys cannot produce sperm before puberty, this period of time creates a rich environment for epigenetic changes (Pembrey et al., 2006).

Comparisons were performed on the effect of the onset of paternal smoking at five different time periods: < 11 years, 11-12 years, 13-14 years, > 14 years, and never smoked. These groups were then compared with their children's body mass index (BMI) at 7 and 9 years of age. In the original regression analysis paternal smoking was found to be associated with an increased BMI in both girls and boys at age 9. When these results were controlled for variables, most importantly being if the fathers had continued smoking up to the child's conception, the results showed that paternal smoking only had an effect on the 9-year-old male offspring (Pembrey et al., 2006).

Results of this research highlight a higher risk for obesity and other health-related problems in adulthood for those males whose fathers started smoking before they reached puberty. These results, along with other epigenetic transgenerational studies, demonstrate the importance of the exposure-sensitive period and sex specificity of toxic exposure (Pembrey et al., 2006).

Summary

Recent epidemiological studies have shown the impact of teratogens on a developing fetus. These studies have indicated that a mother's exposure to teratogens during pregnancy can be extremely hazardous to the development and growth of the fetus.

The information profiled on Fetal Alcohol Syndrome and Fetal Alcohol Effects showed the effect of any amount of alcohol exposure on a fetus's development. Specifically, the study conducted by Marshal et al. (2009) was able to show the irreversible and extremely serious deformities associated with alcohol exposure.

The study on lead exposure conducted by Bellinger et al. (1987) found that children who were exposed to higher prenatal levels of lead, levels lower than the CDC's current acceptable level, displayed decreased mental development. The Takeda et al. (2009) study also considered the effect of limited exposure to hazardous chemicals on a developing fetus. Their research found a single dose of dioxin to reduce the fetal development of sex related organs and behaviors.

The dioxin produced by cigarette smoke is known to increase a fetus's risk for cognitive deficits. Jauniaux and Greenough's (2007) study was conducted to determine the effect of a father who started smoking before he entered into puberty. They found that paternal smoking was associated with an increased childhood BMI, which is known to increase the risk for obesity and health-related problems in a child's adult life.

These highlighted studies have shown how a parent's exposure to teratogens is linked to the development of the fetus, as well as the health and well-being of the child.

Overall results indicate that teratogenic exposure during gestation is likely to increase the risk of irreversible damage to the fetus in the earliest stages of development.

Chapter 6: Where Do We Go From Here?

Epigenetics is paving a new pathway of scientific understanding in which the long-standing issue in the dichotomous debate on nature vs. nurture may no longer be relevant. And neither may the independent study of psychology or biology. In fact, there is clear evidence confirming a complex interplay between the experiences that occur throughout the lifespan of an individual and the environmental factors that contribute to development. These developmental experiences have consequences for the individual, his or her offspring, and generations of relations to come.

Environmental and physiological events influence the genotypes and phenotypes in complicated chemical interactions. These interactions have both protective and destructive features and possibilities. Epigenetic research points to these powerful interactions as overlapping factors that have contributed to a new understanding of development and pathology. This understanding comes from the growing number of studies implicating that early adversity has a long-term effect on the behavioral development of humans.

Findings from several human studies, which included infants, children and pregnant women, suggest there are a variety of environmental factors that change the inter-uterine environment and affect the development of the children throughout the lifecycle. Some of the best documented environmental agents include: diet, maternal

depression & anxiety, maternal stress, alcohol, lead, dioxins, and tobacco. An example of one of the first comprehensive epigenetic study was conducted in Norrbotten, Sweden. Using agricultural and birth and mortality data, the researchers discovered that the diets of grandparents and parents can decrease the average lifespan of their offspring (Bygren et al., 2001).

Studies on maternal depression and anxiety have found that depressed women, who have higher prenatal cortisol level, will have a greater chance of premature labor and low birth-weights (Diego et al., 2009), both of which increase risk in the child of learning and developmental delays. Field et al. (2002) alter the physiological responses of pregnant women to anxiety inducing situations. Much like maternal depression and anxiety, maternal stress produces physiological responses that affect the development of the fetus. When a pregnant women experiences high level of stress she will produces adrenocorticotropic, a stress hormone, which has been shown to affect the fetuses motor coordination, muscle tonicity (Schneider et al., 1992), shorten attention spans, increase irritability, and make these infants harder to console (O'Connor et al., 2005). It appears that culture can moderate experiences of pregnant mothers, thereby influencing the impact of epigenetic affects on the fetus.

Another growing area of epigenetics is the study of teratogens, which are powerful environmental substances that are ingested by the mother and passed through her placenta to the developing fetus, increasing the chance of birth defects. Some of the most powerful environmental toxins include alcohol, lead, dioxin, and smoking. These toxins have been shown to cause irreversible physical, learning, and memory problems (Marshall et al., 2009), cause deficits in learning, hearing, and behavior (Bellinger et al.,

1987), cause demasculinization of males and defeminzation of females (Takeda et al., 2009), and increase the risk for cognitive deficits, attention deficit/hyperactivity disorder, body mass index, increase the risk for obesity, and other health-related problems in adulthood (Pembrey et al., 2006). The one connecting thread between all of these environmental factors is that each variable can cause irreversible and often devastating effects on the development of the fetus.

These studies have shown that the gestation period is an extremely vulnerable period of time in the human lifecycle and the experiences of the mother have significant impact on the development of the fetus and child. There are powerful symbiotic relationships between the cellular worlds of the mother, fetus, and placenta, which all affect the development of the fetus. Each of these cellular worlds has its own set of environmental hazards and stimuli that can deter or enhance the fetus's overall risk for genetic malformations. Therefore, it is important to understand and observe the interaction between all of these environments on the development of the fetus.

While humans have developed to protect and reproduce with the greatest efficiency, it is remarkable to think of the vulnerability a fetus faces during gestation that are related to untreated illness in the mother or unpredictable environmental events. Before this new human being has a chance to take his or her first breath the environment has already played a role in his or her life. Both the mother's external environment and the intrauterine environment, as impacted by the mother's physiology, have had significant influence on the development of the fetus. These implications are often extremely serious and detrimental to the child's life. Therefore, the best support that can

be given to pregnant women is to support healthy and informed choices by the mother, choices that will encourage healthy development of her vulnerable fetus.

Although there is substantial evidence demonstrating the effect of intrauterine and external environmental stimuli on the epigenome of a developing fetus, there are still many questions unanswered and knowledge yet to be discovered. The search for more information was expressed by the National Institute of Health (NIH) in 2008 through their funding of a nationwide initiative, the NIH Roadmap Epigenomics Program. This initiative was funded by a $180 million multilab grant. By October 2010, NIH had produced the first detailed map of an epigenome. The NIH successfully mapped the embryonic and fibroblast epigenome. Zerhouni, the director of the NIH and this project, has said that this research project will produce a "deeper understanding of how DNA information is dynamically regulated through DNA histone modifications as well as the emerging role of micro RNAs and other factors" (NIH, 2008).

Epigenetic studies, like the NIH Roadmap, have laid the foundation for scientists to manipulate the expression of epigenetic marks through chemical additions to the genetic sequence. The ability to manipulate the epigenome has allowed for new treatments of genetic illnesses that would not have been possible without this understanding. These drugs are extremely powerful, as they are able to silence bad genes and turn on the expression of good genes. In fact, the first epigenetic drug was approved by the U.S. Food and Drug Administration (FDA) in 2004. This drug, Azacitidine, is used to treat patients with Myelodysplastic syndrome, a rare and deadly blood disease. The drug uses epigenetic marks to suppress genes in blood precursor cells that have become over-expressed (Cloud, 2010). This epigenetic success gives hope that someday

research will develop drugs to turn off the genes that play a role in cancer, schizophrenia, autism, diabetes, and many more diseases.

Over the last decade there have been important medical advances that have allowed for the identification of the epigenetic mechanisms that play a role in gene regulation. This information has been essential to the understanding of epigenetic systems, their replication, and subsequent mutations. However, there are still several questions yet to be answered. In an evaluation of epigenetic research, DeAngelis et al. (2008) found two powerful questions that have yet to be answered. These questions concerned the events that have led to the deregulation of epigenetic systems and the ability of one epigenetic change to regulate the appearance of another irregular epigenetic change. The answers to these questions may lead to one of the greatest scientific discoveries in this lifetime, discoveries that will forever change the way humans survive in this world.

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