Image Awareness Wellness Institute

Autism: Epigenetic Involvement?

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Epigenetics Case Study

Epigenetics is a new branch of genetic research which suggests that expression of the DNA can be altered by environmental factors. The underlying DNA does not change. This study is known as epigenetics from "epi" meaning "on top of" and "genetics" or "genes."

A number of factors have been observed to alter the manner in which DNA expresses itself including stress, toxin exposure, and nutrient intake. Alterations in DNA expression can be temporary lasting mere hours or they can last for generations.

The cause of autism is a mystery to most of the medical profession. This newsletter will discuss a theory which relates autism to epigenetic changes to the DNA while the infant is still in the womb. While only theory, the hypothesis explains many of the peculiarities of autism.

The theory does not explain what environmental factors are responsible for the changes we shall discuss. It is not impossible that a variety of factors could play a role including heavy metal poisoning, exposure to pesticides and herbicides, and estrogenic pollutants in the environment including plastics and birth control pills.

Epigenetic alterations in the manner in which genes are expressed are much more likely to take place during periods of rapid growth and development. The time from conception to birth, the early years of life and puberty are periods associated with epigenetic alterations.

The Condition

Autism is an abnormality of brain function which affects boys five times more often than girls. The latest research by the CDC on March 29, 2012 has reported an incidence of 1 in 54 boys. The latest data suggest 1 in 88 American children suffer with autism spectrum disorder. This is a 78% increase over a ten year period.

It is unclear how much of the increase is due to improved identification of the problem. There is little doubt that doctors are getting better at early recognition of the disorder characterized by impaired language, communication and social skills.

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A Clue

Male and female brains are generally wired differently. The female brain is built around empathizing or the ability to predict and respond to behavior of people (most often) by inferring their mental state and responding with the appropriate emotion.

Male brains are quite different. The male brain systemizes. It analytically evaluates relationships and applies the rules that govern systems.

Bill and Pam Farrel have put together a seminar entitled "Men Are Like Waffles Women Are Like Spaghetti." Men organize everything like the boxes in a waffle. They tend to lock themselves into one box at a time and can have difficulty moving to another.

By contrast, women are more like a plate of pasta. Their minds are conected to a lot of other noodles. As they follow one noodle they can easily switch and follow another noodle. This makes women much better at multitasking than men.

Simon Baron-Cohen and his associates suggest that autism is an extreme of the male pattern characterized by difficulty in empathizing and augmented systematizing. He suggests that "'Empathising' is the drive to identify another person's emotions and thoughts, and to respond to these with an appropriate emotion. Empathising allows you to predict a person's behavior, and to care about how others feel." He observes that epathising is more a characteristic of the female brain than of the male brain.

By contrast, the male brain is characterized by systemising. "'Systemising' is the drive to analyse the variables in a system, to derive the underlying rules that govern the behaviour of a system. Systemising also refers to the drive to construct systems. Systemising allows you to predict the behaviour of a system, and to control it."

Simon Baron-Cohen has suggested that autism is a result of the extreme development of the male brain. Baron-Cohen argues that autistic individuals, both male and female, provide evidence of an over-masculinized brain. Autistic individuals have a preference for rule-based, structured, factual information, they prefer constructional and vehicle toys, they engage in collecting, and are obsessed with closed systems such as computers. Fathers and grandfathers of autistic children are overrepresented in the fields of mathematics, physics and engineering. Autistic males show precocious puberty and have a longer ring finger than their second finger, a male trait, in exaggerated form. He provides other evidence of his theory as well.

The distinction between the functioning of the male and female brain is not politically correct, but it is based in physiological differences and may help researchers unravel the mystery of autism.

Boys generally do better with mental rotation tests, spatial navigation (eg. map reading) and working with figures. Girls are generally more efficient at verbal fluency, social sensitivity, and emotional recognition.

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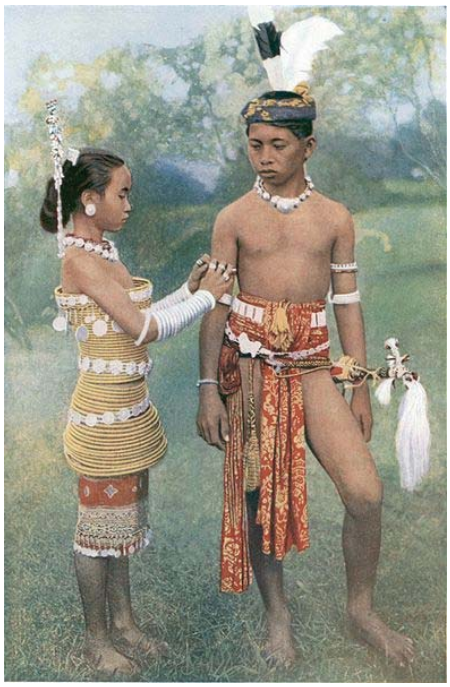
RORA

The androgen theory of autism is supported by the recent discovery of a gene that regulates the conversion of testosterone to estrogen in the brain. The gene, RORA, has been linked to autism by the study of identical twins. Rora activates other genes that are key players in neurodevelopment. Estrogen enhances activity of RORA while testosterone decreases activity. RORA also regulates the aromatase enzyme which converts testosterone to estrogen in the brain.



RORA stands for "retinoic acid-related orphan receptor alpha." Autistic brains exhibit decreased expression of this gene and the BCL-2 gene. The methylation status of these genes revealed that the genes were being influenced by environmental factors sitting on top of the genes and changing the way they function.

Nguyen and associates recently found decreased expression of RORA and BCL-2 proteins in autistic brains. The study focused on examination of identical twins with the same DNA. One of the twins was autistic while the other was not suggesting that the DNA code itself was not a causative factor in autism, but rather alterations in the manner in which genes are expressed (epigenetic factors).

Nguyen's research is of interest because RORA regulates levels of the enzyme aromatase which controls expression of estrogen and testosterone. RORA regulates the conversion of testosterone to estrogen. Underexpression of the RORA gene during development due to epigenetic factors would rob the developing brain of an infant of estrogen leading to extreme development of a male brain.

RORA has been shown to protect neurons from oxidative stress and inflammation. It also helps maintain circadian rhythm. RORA has an impact on at least 300 other genes.

Estrogen enhances the expression of RORA which may explain why women are less susceptible to autism than are men. Estrogen also turns on some of the same genes as RORA providing women double protection.

Valerie Hu, professor of biochemistry and molecular biology at George Washington University, is a lead investigator on the impact of hormones on the RORA gene. Hu began work-

ing on autism because she has a son affected by the disorder.

Those who hold to the androgen theory of autism suggest that estrogen is not functioning normally at the time of brain development. There are a number of possibilities as to why this would be the case including excess androgen, estrogen deficiency, inability to synthesize estrogen in the brain, or exposure to pollutants which block the beneficial effects of estrogen on brain development.

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Understanding Hormones

Hormones are very powerful chemicals that organize or program cells, tissues, organs, the brain and behavior before birth. They can set the course for an individual's entire lifetime. Hormones switch genes on and off while the baby is still in the womb.

Hormone chemistry is a fine tuned mechanism to an astonishing degree. Hormones like estradiol alter physiology at parts per trillion or one thousand times lower than parts per billion. Striking differences can result from a difference of only 35 parts per trillion in estradiol circulation or one part per billion difference in testosterone circulation.

In 1987 Ana Soto and Carlos Sonnenschein were conducting tests to find a natural inhibitor to growth of breast cancer cells. They were working with a strain of breast cancer which multiplies in the presence of estrogen. They feel that estrogen overrides this natural inhibitor to cancer growth.

Overnight their estrogen-sensitive breast cancer cells began multiplying wildly. Some mysterious contamination affected the entire lab. It took them four long months of sleuthing to identify a phantom estrogen and two years to put a name to it. They discovered that the plastic tubes supplied by Corning were exhibiting powerful estrogenic properties. In 1988 they learned that Coring had changed the plastic resin to make the tubes less brittle without changing the catalog number. In 1989 Soto and Sonnenschein were able to put a name to the chemical, p-nonylphenol, a chemical added to plastics as an antioxidant to make them more stable and less breakable.

A similar drama was playing out at Stanford University at the same time, but it was a little different. At Stanford the suspect chemical proved to be bisphenol-A. BPA is a chemical used in the production of polycarbonate plastic. It has been associated with higher body weight, increased breast and prostate cancer, and altered reproductive function. The chemical is found in almost everyone since it is used in many plastics including the lining inside metal cans to prevent the leaching of metals into foods.

The implications were enormous because in the modern world plastics are encountered at every turn. Now we have learned that these chemicals have both hormonal effects and epigenetic effects. The hormonal effects include the ability to trigger explosive growth in cancer cells!

Many xenobiotics have estrogenic properties and function as endocrine disrupters. Their ability to modify gene expression is largely unexplored. Genes can be altered throughout life, but they are particularly susceptible to alteration during pregnancy, early development, puberty, and old age.

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Methylation

Hypomethylation of DNA has been observed and commented upon in the medical literature. What remains to be learned is what factors may be causing hypomethylation of the RORA gene in autism.

Methylation is the addition of a methyl group to DNA. The addition of the methyl group can turn a gene on or off. One compound which has been shown to induce decreased methylation of DNA is bisphenol A (BPA).

One way of studying methylation is by observing the yellow agouti mouse. Low methylation turns these mice yellow while adequate methylation turns the animals brown. Expo-

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sure to bisphenol A moves the mice toward a yellow color.

Yellow agouti mice have an increased tendency to become obese and also manifest an increased risk of degenerative conditions such as heart disease and cancer.

A highly significant discovery suggests that nutrients may prevent BPA from causing hypomethylation. Dolinoy induced hypomethylation of the Agouti gene by exposure to bisphenol A during the pregnancy of a mouse. The research also demonstrated that supplementation with either methyl donors like folic acid or the phytoestrogen genistein negated the DNA hypomethylating effects of BPA. Methyl donors would include not only folic acid, but also vitamin B12, choline, betaine, dimethyl glycine, and vitamin B6. Nutrients tested and shown to change coat color of agouti mice include folic acid, B12, choline and betaine.

Dolinoy concluded her article by saying, "Thus, we present compelling evidence that early developmental exposure to BPA can change offspring phenotype by stably altering the epigenome, an effect that can be counteracted by maternal dietary supplements."

It is of interest that while exogenous estrogens like BPA causes hypomethylation of genes the plant phytoestrogen genistein has the opposite effect.

Xenoestrogens tend to increase weight and risk of cancer. Genistein appeared to do the opposite in this experiment.

Dolinoy writes, "Thus, the ability to counteract negative environmental toxicant effects, such as DNA hypomethylation, via in utero or possibly even adult nutritional supplementation, has the potential to protect human health in the present and future generations; however, the effectiveness of this preventative approach would be expected to be inversely related to the level of toxicant exposure."

We are far from knowing all the factors which could play a role in the hypomethylation of the RORA gene in autism. The insights provided by the new science of epigenetics may lead to a better understanding of the disease.

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