COMMUNICATION

IN LIFESTYLE MEDICINE

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Epigenetics

Abstract: *The field of Epigenetics represents the science which helps us understand the influence life has on genetic function. Research has shown that what we do, what we are exposed to, and the internal and external environments have significant influence on the output of our genes. In this article, the reader will understand how alterations in the DNA explain how the genetic output was changed as a result of exposures to life.*

Keywords: epigenetics, genetic alterations, methylation

The field of epigenetics is a branch of science that helps us understand the impact life has on the function of genes. We have thought for some time that we were born with a genetic makeup that was fixed, but recent research has proven that what we do, what we are exposed to, and our internal and external environments have tremendous influence on the output of our DNA. The “Aha! Moment” becomes evident when it is realized that clinical outcomes are variable even when the clinical treatment is the same. These situations show that heritable changes in phenotype arise in the absence of alterations in the DNA, and therefore, the explanation is seen in how the genes function as a result of exposures to life.

The field of epigenetics was first proposed by Conrad Waddington in 1940 as he described the interactions between the environment and gene function. He showed that gene activity (and protein

production) changed but the structure of the DNA remained stable. He identified many factors that affected the way genes functioned and described chemical mechanisms for these changes including methylation and histone post-translational modifications. These chemical modifications resulted in a change in the types of proteins the genes produced, and these changes resulted in a change in the phenotype of the organism (how it looked).

To a large degree the story of epigenetics is the story of nutritional deficiency and how these deficiencies affected the DNA, chromosomes, genes, proteins, and enzymes. All of this is the sum total of cellular chemistry. In 1962, Dr Joel Wallach, a veterinary student and comparative pathologist, realized that many diseases thought to be genetically transmitted were in fact caused by nutritional deficiencies. Examples being pellagra (vitamin B₃/niacin deficiency), scurvy (vitamin C deficiency), rickets (vitamin D deficiency), and beriberi (thiamine/B₁ deficiency). There is also some evidence that multiple sclerosis is affected by a deficiency of vitamin D since the incidence of multiple sclerosis is higher in the northern states where there is less sunlight and more vitamin D insufficiency and deficiency.

Between 1995 and 2011, the incidence of rickets increased 400% with the clinical recommendations to avoid sun exposure, the fear of cholesterol in egg yolks, and the widespread use of sunscreen lotions for the fear of skin cancer. In the case of beriberi, supplementing the diet with brown rice, legumes, and other foods high

in thiamine reversed the signs and symptoms of this illness.

Now when we start to compare these nutritional deficiencies of the past, we can start to think about the pathophysiology of diabetes, obesity, cardiovascular disease, and even dementia and consider that these diseases might also be related to nutritional deficiencies. When we consider obesity, we know this is one of the common denominators for diabetes, metabolic syndrome, cardiovascular disease, and more, and in most cases individuals suffering from obesity eat an overabundance of calories but they are nonetheless malnourished. The latter is the result of eating foods high in calories but low in nutritional value. As a result, we know that it is important to provide a diet that is low in calories but high in nutritional value.

The Mediterranean diet is a good example of such a diet, and research has shown that this type of eating affects the pregnancy rates in women. Karayiannis et al¹ showed that women in the lowest tertile (those eating a diet not consistent with the Mediterranean diet) had significantly lower rates of pregnancy and live births. Those with higher MedScores had a 2.7 times higher likelihood of pregnancy and live birth.

Toledo et al² looked at 485 women age 20 to 45 years who reported difficulty getting pregnant and 1669 age-matched controls who had at least one child, and they found that the women in the highest quartile for use of the Mediterranean diet had significantly less difficulty getting pregnant.

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Chavarro et al³ looked at protein intake and infertility and found that the type of protein influenced pregnancy rates. For those eating more animal protein, the relative rate of infertility was 1.39 compared to 0.78 for those eating more vegetable protein.

Goh et al⁴ looked at the use of multivitamin supplementation and found that micronutrients have a positive epigenetic effect resulting in 41% lower rates of infertility, fewer miscarriages, fewer birth defects, less pediatric cancer, and less autism.

Cetin et al⁵ looked at the role of micronutrients in the periconception period. Compared to women who did not take multivitamins, those taking less than 2 tablets per week had a relative rate (RR) of infertility of 0.88. Those taking 3 to 5 tablets per week had a RR of 0.69, and those taking more than 6 tablets per week had a RR of only 0.59. This means the rate of pregnancy was better for those taking more vitamins—more evidence that nutrition make a significant difference.

Scientists at John's Hopkins found that a very low calorie diet can affect the function of the DNA and improve mental function in mice. "Histones" are proteins around which DNA is coiled in order to fit the entire DNA inside. When the DNA is unwound, the genes can be accessed more completely and mental function improved. This type of a diet was thought to alleviate an inherited form of intellectual disability in mice.

It has been known for some time that a ketogenic diet (high-fat diet) improves brain function and symptoms in individuals with chronic seizures (epilepsy).

Chavarro et al⁶ reported that women who took iron supplements had a significantly lower risk of infertility. The adequate dose appeared to be 40 to 80 mg of iron daily.

Studies in epigenetics also reveal that diet in the male partner also affects fertility. Attaman et al,⁷ in the journal *Human Reproduction*, looked at Danish males who ate mostly saturated fat and found 38% lower sperm concentration

and 41% lower sperm counts. Similar studies in the United States found that walnuts improved but alcohol and cannabis impaired male fertility.⁸

Once we realize that external exposures affect genetic function, we start to question when preventive health care should start. The answer seems to be in the preconception period, but it is extremely concerning to know that the average in utero fetus has over 200 chemicals in the cord blood.⁹ This information makes the recommendation for preconception preventive health care even more important. Preconception recommendations should start 4 to 6 months prior to conception and should recommend stopping as many unhealthy foods as possible, avoiding as many environmental chemicals as possible, increasing the consumption of water and cruciferous vegetables, and considering detoxification. Health care providers should also discuss the impact of all the above with couples considering pregnancy. Pediatricians and gynecologists should talk with their patients about the use of vitamins, iron, and so on. The conversation should also review the need to specific vaccinations and any other specifics that would help the individual create a healthy living action plan.

When we consider environmental exposures, pesticides and herbicides appear to be creating a significant risk for Parkinson's disease as well as other neurodegenerative illnesses. In the EARTH study, Chiu et al¹⁰ found that high pesticide residue fruit and vegetable intake was associated with poorer quality semen. The data showed a 49% lower total sperm count and a 32% lower level of normal sperm.

So is life more influential as compared to true heredity? This question is significant especially as we understand that not all individuals with a genetic predisposition actually develop the disease. Research tells us that the genetic potential of an individual is affected by not only the external environment and nutrition but also by all the lifetime experiences of the individual. There is interplay between the DNA, the

environment, and how we view the world and how this affects our internal environment.

Every cell in the body contains the same DNA, but chemical modifications to the DNA create epigenetic "marks," which give an indication of how the genes will function. Jirtle and Skinner¹¹ exposed pregnant rats to high levels of insecticides and documented decreased sperm production and increased infertility. This was the result of methylation of 2 specific genes, and as a result of this, the effects on the genes lasted for 4 subsequent generations in 90% of the males with no further exposure to the pesticides! As a result of this methylation, gene function was altered producing proteins that altered the phenotype of the organism and the function of the cells.

Epigenetics has revealed that gene function is affected by macronutrients and micronutrients, fasting, exercise, stress, sleep deprivation, mental health, purposeful living, toxins, medications, heavy metals, pesticides, hormones, radiation, antibiotics, infections, and even thoughts. All of these exposures influence cellular function and the output from the DNA. In 1983, Feinberg and Vogelstein¹² found that genes of colorectal cancer cells were substantially hypo-methylated compared to normal colon cells. DNA hypo-methylation can activate oncogenes and initiate chromosome instability. Conversely, DNA hyper-methylation initiates silencing of tumor suppressor genes. One important point is to understand that methylation status can be measured and imbalances can be corrected.

Research has uncovered an association between inhalation of diesel fumes and asthma as a result of epigenetic changes to over 400 genes. Maternal exposure to allergens can increase the risk of asthma in the immediate progeny, and even though the effect is not strong there seems to be an increased risk of asthma in grandchildren and great grandchildren. This is what is known as "transgenerational inheritance." Therefore, family history or predispositions may not belong solely to

an individual. As such it is most important to maintain health across the continuum of life.

Substances are not the only source of epigenetic changes. Mother rats groom their pups; and high-quality maternal care results in better health of the offspring.

German occupation of the Netherlands resulted in famine where the average intake of food was about 400 to 800 calories per day. As a result of this the Dutch Hunger Winter Study¹³ was done to look at the effects of food restriction on intrauterine development of the placenta and the fetus. In early gestation, severe calorie restriction resulted in a normal birth weight but elevated rates of adult obesity, hyperlipidemia, and cardiovascular disease. Brain structures develop within the first 3 months of gestation, and food restriction in this period results in decreased mental capacity, altered appetite regulation, and a decline in cognitive function later on in life. Mid- and late-gestation calorie restriction resulted in decreased birth weight as well as adult weight and stature. Exposure to famine during any stage of gestation was associated with glucose intolerance. Human babies in the womb during famine also had higher rates of schizophrenia and clinical depression, and this effect persisted for several generations.

Transgenerational inheritance¹⁴ reveals that mice surviving on a very low calorie diet had underweight offspring prone to diabetes. The males in this litter then fathered another generation of offspring who also developed diabetes even though they consumed a normal diet.

The effects of calorie restriction are also very interesting. Research shows that calorie restriction lowers the level of insulin, which signals the body that food is scarce. When food is scarce this is not a good time to reproduce, and this signals the body to slow the aging process in order for the organism to be alive and youthful and ready for reproduction when food becomes available again.

In 2010, a study¹⁵ looking at prenatal undernutrition and cognitive function in

late adulthood reported that nutritional changes occurring during oocyte development and very early in gestation might permanently alter the methylation status of many genes and subsequent gene expression. This is the reason it is so important to focus on keeping young adults healthy long before they conceive of child. This is the importance of preconception health care.

Although most Americans suffer from diseases that are thought to be genetic but in reality are preventable and curable with simple nutritional support, it still takes years before clinical evidence translates into clinical action in the physician exam room. As an example, it took 200 years of controversy for citrus to be recognized as the prevention and cure for scurvy. In 2018, physicians and other health care providers need to be cognizant of this fact and be diligent to translate clinical research information into effective action that improves the lives of patients.

In preparation for this article, I came across a statement that reported that “farmers are smarter than physicians,” and I wondered if this was true and why this statement was being made. We know that television commercials for healthy food are directed at dogs and cats but not humans. In the last 100 years, the pet and animal industry has spent over \$100 billion on nutritional research, and as a result has significantly decreased birth defects and improved the overall health of domestic and industry animals. We do not see the same research for humans despite knowing that healthy eating saves lives. The commercials we do see for foods eaten by humans is mainly fast foods, which we know create chronic illness, decreases the quality of life, and decreases longevity. As such, we as health care providers need to initially prescribe healthy eating in order to treat, reverse, and prevent disease. Nutritious food must be the foundation of any plan to help an individual become and stay healthy. In addition, the physician/health care provider can encourage meditation, which is known to influence histone genes as well as mediators of cellular

inflammation. Carlson et al,¹⁶ in the journal *Cancer*, looked at telomere length as another marker of cellular aging and reported a slowing of the aging process as a result of healthy eating. Ornish et al¹⁷ showed that an intensive lifestyle and nutrition program resulted in changes in prostate cancer gene expression with up to 500 genes being involved. Similar results have been seen in subsequent research into heart disease. As a result of these studies, it is apparent that lifestyle changes alter the risk and incidence of chronic disease and many cancers.

Additional treatments for the so-called genetic diseases include chromium and vanadium for individuals with diabetes, selenium for those with cystic fibrosis, and copper for individuals with Kawasaki disease. Some of this information is from anecdotal studies, but it is important to understand that randomized control trials are not the only way to collect clinically valid and useful pieces of information.

Research in the *International Journal of Molecular Science*¹⁸ reported on the epigenetic effects of BPA on gene expression. BPA is a chemical found in plastics that is known to have detrimental effects of gene function. BPA exposure alters micro-RNA expression and results in de-methylation of estrogen receptors, the consequences being altered receptor function.

In another research study,¹⁸ while pregnant, certain mice were fed BPA with one diet and other mice were fed BPA but were fed a different diet supplemented with choline, folic acid, betaine, and vitamin B₁₂. The data revealed alterations in phenotypic as well as physiologic changes in the mice including weight and fur color.

Next consider how the age of the father influences gene function and the risk for certain illnesses. D'Onofrio et al¹⁹ looked at the advancing age of the fathers (45 years of age compared to 25) and found a 13 times risk of developing ADHD (attention deficit hyperactivity disorder), a 25 times higher risk of bipolar disorder, twice the risk of developing psychosis or having a substance abuse disorder, and a

60% higher likelihood of failing grades in school.

The question arises as to the ability to measure cellular aging and telomere shortening. Telomeres are the ends of the DNA. Similar to the plastic tips at the end of shoelaces, the telomeres protect the DNA from the effects of aging, and when telomeres shorten, the organism ages. The faster the shortening, the faster the organism ages. Scientists at Duke University analyzed the DNA initially from 5-year-old children and then again when the same children were 10 years of age. The children who experience physical or emotional abuse or other life stressors had shorter telomeres. This study shows that life experiences have a direct influence on the expression of genes. The diagnosis if “psychological Dwarfism” refers to a short stature found in young children raised in an abusive family. The emotional damage results in a physical expression of this stress. The output of the genes is influenced by environmental factors.

The Warburg effect* reveals the epigenetic effects on cancer cells. Depriving rapidly dividing cells of their energy supply influences the growth of these cells. Research has been done using a “ketogenic diet” as part of the treatment for brain tumors. This effect appears to be mediated via calorie restriction and the activation of Sirtuin genes.

In summary, the field of epigenetics is quickly growing with the understanding that the environment and individual lifestyle directly interact with the genome to influence cellular function. Human epidemiological studies have provided evidence that prenatal and postnatal environmental factors influence the adult risk of developing various chronic illnesses as well as mental health disorders.

It has become apparent that epigenetic effects occur not only in the womb but over the full course of a human life span, and these changes can be reversed by controlling lifestyle choices and

environmental exposures. Therefore, genetics may not be the manifest destiny!

Screening for factors likely to create epigenetic marks as time passes includes but is not limited to tobacco, chemicals, chronic stress, physical and emotional abuse, sleep deprivation, and an unhealthy diet. Adding epigenetic considerations to our daily practice includes finding ways to advocate for healthy lifestyles, reaching out to parents regarding lifestyle choices their children make, discussing the data with expecting parents, and getting the obstetrics and gynecologic physicians involved, considering reaching out to teens and those approaching the reproductive years to discuss the implications for the newborn, and participating and energizing a “Culture of Radical Well-being.” The action plan should include the optimization of gene activity, optimizing organ and cellular function, improving energy production and metabolism, and maximizing detoxification. Gene function is also optimized with a positive attitude and optimism, emotional and mental health support, knowledge of the mind-body connection, and practicing healthy lifestyle behaviors such as yoga, meditation, exercise, and more.

The field of epigenetics calls us all to join the revolution in self-care with the initial step being to focus on the basic functions of the cells. Radical well-being requires a conscious choice, so choose wisely and live a long and healthy life!

Senescence (aging) is not just the passage of time. Senescence is an increased chance of dying with the passage of time. The scary part is when we realize that aging is self-imposed!

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Trial Registration

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*The Warburg effect—depriving rapidly dividing cells of their energy supply (cancer cells primarily utilize glucose)—theoretically could be clinically beneficial.

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