LIFE AND HEALTH
IT'S YOUR CHOICE

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DOES LIFESTYLE IMPACT OUR OFFSPRING?

In February 2001 a draft sequence of the human genome was published, bringing great hope that this would usher in a new era for medicine. But in the past few years, the predicted life expectancy of babies born in developed countries is reduced compared to those born the first 15 years of this century.[1] How can this be? Could our lifestyle have anything to do with it?

The first hints came from a study carried out by Bygren, Kaati and Edvinsson.[2] They used records from Överkalix, Sweden, an area quite isolated from the outside world in the 19th century. Therefore, the inhabitants had to get by almost exclusively with the food produced locally. Using the food supply and death records, researchers found that if the grandfather did not have an abundance of food between his ninth and 12th years of life, the grandsons had a health advantage. On the contrary, an excess of food during that period reduced the life expectancy of his male grandchildren

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between 6 and 32 years. In the case of women, a key timepoint was pregnancy. The grandchildren of expectant mothers who had an adequate supply of nutrients fared better.

Now, think about the abundance of food and quality to which youngsters have access these days, and draw your conclusions. Numerous medical advances and new therapies are developed each year. Nevertheless, in developed countries, life expectancy has begun to decrease. Could this have something to do with our lifestyle? Or with Exodus 34:7: The Lord "'punishes the children and their children for the sins of the fathers to the third and the fourth generation'" (NIV).[3]

Well, maybe we have a clue here. The Creator knew that our decisions impact not only our health, but also that of our descendants. And He shared this explicitly with us to make us conscious of the responsibility we have. It is our life, our freedom, our choices—but they have an impact on others.

Ellen White stated: "Many are suffering in consequence of the transgression of their parents. They cannot be censured for their parents' sin. . . . [W]herein their parents' habits were wrong, they should change their course, and place themselves by correct habits in a better relation to health."[4] But, how do choices impact our lives and our descendants?

EPIGENETICS—THE BRIDGE BETWEEN LIFESTYLE AND HEALTH

Conrad Hal Waddington was the first to recognize in 1942 that to function, cells not only need genes, which can be compared to the hardware of a computer, but also specific "software" to function properly. To describe this concept, he coined the term *epigenetics*. *Epi* indicating that there is information "on top of" the genes, which is essential to control and regulate which of the 22,000 genes found in each of our cells will be accessible for use. There isn't a single cell that uses the information contained in all these genes; thus, it is important that only those genes that are needed can be accessed and are "readable." All others must remain "muted" or inaccesible.

In contrast to the fixed "letters" of the DNA sequence that conform our genes, most epigenetic marks can be changed during our life in response to environment and lifestyle. And this regulation can be just as or even more important for our health than the quality of the genes we have inherited! To date, three epigenetic processes are known to act as the bridge between lifestyle and cellular processes:

- ***The first epigenetic mechanism: methylation.*** The first way to "shut down" a gene is to put a mark on the cytosine, one of the four "letters" of the DNA. For this, it is necessary to have enough "ink" and the associated enzymes to accomplish the marking. When an "ink blot" (a methyl group) is placed on a gene, the information contained in this gene cannot be read, copied, or used to produce the encoded protein. Diet plays a major role in methylation, as a sufficient supply of certain nutrients is needed to produce the "ink." On the other hand, drinking alcohol perturbs the correct functioning and leads to suboptimal functioning. Recent studies support the idea that for optimum health, it is better not to drink any alcohol at all.[5]

Studies in humans have shown that diet is just one of multiple factors—from exercise, to the seasons, to fresh air—that lead to changes in methylation. For example, a study of healthy people showed that cycling for 45 minutes four times a week for three months resulted in a significant change in the activity of more than 800 sites and and significant differential expression of approximately 4,000 genes in the leg muscles by modifying the methylation.

Everyday products can lead to abnormal methylation. An example of this is Bisphenol A (BPA), which is used in the manufacture of many plastics. It is also found in thermal cash receipts, inside the lining of some metal cans, and produced when the dental composite resins used to treat caries hardens. Studies show that 93 percent of us eliminate BPA in urine, which means that we have absorbed it orally or through the skin. This estrogen-similar molecule is an endocrine disruptor and leads to changes in methylation of key processes. It increases the risk of type 2 diabetes, cardiovascular disease, some types of cancer, polycystic ovary syndrome, and it alters thyroid function and sex hormone concentrations. It also reduces male sexual function and sperm quality. BPA exposure during pregnancy and in childhood is associated with neurodevelopmental problems and correlates with higher levels of anxiety, depression, hyperactivity, inattention, and conduct problems.[6] Its effects are not limited to the person exposed, but may also affect descendants. For example, exposure of male mice to BPA disrupted the production of sperm and led to a decline in sperm count, not only in the exposed generation, but also in sons, grandsons, and to some degree in great-grandsons.

Recognizing this health threat, some countries have banned BPA from specific products, but generally only those used by babies. Because of potential risks, it is recommended to buy food products packed in BPA-free materials, and one should be careful not to store, heat, or cool food in plastic containers, and avoid handling receipts, in order to limit exposure to this substance.

As in most areas of medical research, the majority of studies related to epigenetics are done in animal models because of the ease of manipulation, shorter lifespans, and the possiblility to control test conditions. Most of the time, results observed in animal studies translate to observations in humans.

One such animal model, the agouti mouse, was used to study the effect of diet during pregnancy on methylation.[7] The study showed that an abundance of methyl donors in the maternal diet is needed to methylate the agouti gene in the pup. If there are not sufficient nutrients for optimal methylation of this gene during pregnancy, the gene is not turned "off" as it should during development and the mice have yellow fur and a predisposition to obesity, diabetes, and cancer. On the

other hand, a maternal diet rich in folic acid, betaine, choline, and vitamin B_{12} resulted in healthy pups with normal fur color even though the mother had the described symptoms. Pups of pregnant mothers that did not receive sufficient nutrients had the described health problems and yellow fur.

Even social contacts influence the expression of genes. In this case, using rats that experienced different maternal care behaviors are impressive.[8] Offspring that received the necessary attention grew up as confident animals, while neglected animals had a changed response to stress stimuli. Investigations on humans corroborate that what they experience leaves an epigenetic imprint and can influence their mental well-being and behavior. For example, there are measurable epigenetic differences in the blood cells of people who have suffered childhood abuse, even when measured 40 years after the episode.[9]

Constant stress can lead to depression. However, studies show that physical activity lessens depression risk by removing methylation marks from a gene in muscle cells. The now active gene encodes an enzyme that adds an acid group to kynurenine, a molecule generated when people experience stress. As the resulting kynurenic acid is too large, it is no longer able to migrate from the blood into the brain, and therefore stress will have a smaller impact on the mental well-being.[10]

In a study of rats, an enriched environment that included exposure to novel objects and voluntary exercise during adolescence improved memory not only in the mouse experiencing it, but also in its future offspring, even if the offspring never experienced the brain-stimulating environment.[11] Such studies are difficult to do on humans, but they hint that enhanced enviroments and activities that influence neural plasticity positively are not only beneficial for us but might might contribute to a more positive development in our descendants—as the epigenetic changes in the animal model occur not only in the brain of the animal experiencing it but also in his sperm or her eggs.

• ***Second epigenetic mechanism: histone changes.*** Whether a cell can use the information contained in a gene is also regulated by controlling the accessibility to the genes that need to be "read" and copied in order to make the proteins. Due to the limited space in the cell nucleus, only some segments of chromosomes are loose and legible at a given timepoint. Vast stretches of the approximately 2 meters of DNA typically found within human cells are not needed most of the time. These unused stretches of DNA are therefore packaged to prevent tangling and other problems and to allow room for those segments of DNA containing genes that are in use to be expressed. This packaging state can be modified by making chemical changes to the histones, the protein "bobbins" around which the DNA is wrapped. It has been shown that not only good nutrition, but also a few minutes of meditation and many other factors contribute to the optimal functioning of the histone-changing enzymes.

• ***Third epigenetic mechanism: microRNA.*** When a gene has been read and copied in the so-called messenger RNA, it is used as a blueprint to produce the encoded protein as long as it is intact. This "instruction" can be destroyed by the action of microRNAs (abbreviated miRNAs). As the name implies, miRNAs are very short. As soon as a miRNA finds a stretch of letters that mirrors its sequence in a messenger RNA, it will bind to it, and the messenger RNA is rendered unusable—thus halting the corresponding protein synthesis. While most miRNAs are active in the cell that produced them, a significant number of miRNAs are exported and circulate in the blood. As food consists of cells, a portion of the miRNAs found in food, especially animal products, are absorbed in the human digestive tract and may affect gene expression. For example, if the concentration of a certain miRNA found in broccoli, spinach, cabbage, carrot and onion is low in blood, women have a higher risk of breast cancer. If tumor cells are treated with this miRNA, tumor growth slows down.[12]

Epigenetics also plays a key role in addictions.[13] Researcher Eric Nestler explains that stable changes in gene activity in nerves of the reward system are based, at least partially, on epigenetic changes. For instance, cocaine use leads to histone changes and causes the cells to switch on a different "program." This happens not only with substance-related addictions (drugs and alcohol), but also with substance-independent addictions such as compulsive computer game playing. The latter leads to measurable changes in the concentration of some miRNAs in the blood. These miRNAs can, in turn, influence the activity of 1,300 genes, some of which are involved in various diseases such as schizophrenia or severe depression.[14]

EPIGENETICS THROUGHOUT LIFE

The first hours after fertilization, witness key epigenetic changes. Environmental and lifestyle factors during this time and throughout pregnancy, as well as childhood-related circumstances, lead to long-term changes that can not only predispose to disease decades later, but also affect the well-being of children and grandchildren. Thus, these may be considered critical periods. Recent studies show that early-life environments increased risk of type 2 diabetes later in life.[15]

RESPONSIBLE ONLY FOR YOURSELF?

Certain life experiences and environmental cues are "memorized" in sperm and eggs. Research from various laboratories have demonstrated that maternal and paternal characteristics, acquired even years before conception, can be passed on to the descendants.[16] These include, among others, a high-fat diet, a low-protein diet, mental stresses, and odor sensitivity to specific chemicals.

Here are a few examples of multigenerational effects of lifestyle choices:

- In a study on mice, saccharin exposure produced locomotor hyperactivity and working memory deficit not only in the saccharin-exposed males but also in their offspring.[17] Sperm DNA was hypermethylated in the saccharin-exposed fathers, especially at dopamine receptors, suggesting that epigenetic modification of germ cell DNA may mediate transmission of behavioral phenotypes.
- In another study, the offspring of stressed mice fathers exhibited hyperglycemia due to reduced production of a microRNA.[18]
- A Western-like diet (high fat and/or high sugar) increases the likelihood of obesity and diabetes in descendants. Recently, it was determined that a microRNA in the sperm leads to predisposition in the next generation. The injection of this microRNA into one-cell embryos is enough to induce metabolic alterations similar to the diet-induced phenotype.[19]
- Mice pups of fathers that inhaled nicotine before conception had attention deficit and fewer dopamine receptors.[20]
- Increased risk of asthma due to lowered global methylation of sperm in children of parents and grandparents who smoked.

CONCLUSION

We began this article with a biblical reference to the multigenerational effects of sin (Exodus 34:7). We now conclude with the promise from verse 6: "'The Lord, the Lord, the compassionate and gracious God, slow to anger, abounding in love and faithfulness, maintaining love to thousands, and forgiving wickedness, rebellion and sin.'"

Most health outcomes depend on our small, everyday decisions. As in retrieving wood blocks in a game of Jenga, the results will not be immediately visible in most cases, but a healthy lifestyle increases the probability of plentiful health not just for us but also our offspring. As Ellen White shared with us: "The use of natural remedies requires an amount of care and effort that many are not willing to give. Nature's process of healing and upbuilding is gradual, and to the impatient it seems slow. The surrender of hurtful indulgences requires sacrifice. But in the end it will be found that nature, untrammeled, does her work wisely and well. Those who persevere in obedience to her laws will reap the reward in health of body and health of mind."[21]

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