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Transgenerational Epigenetic Inheritance

Clayton D. Carlson

Recent findings in the emerging field of transgenerational epigenetic inheritance suggest that the lifestyle choices and experiences of an individual have biological implications for offspring not yet conceived. Studies show that diet, drugs, and even social experiences can lead to life-long changes in gene expression. Some changes in gene expression are passed down to future generations. These conclusions deserve careful analysis from Christians trained in science who should teach freedom from epigenetic determinism, the fallenness and blessing displayed in the results, and the limits of the new field. Christian communities generally should show special grace to those that are epigenetically burdened, work to liberate victims from destructive epigenetic cycles, and prepare a healthful epigenetic inheritance for their children.

ew revelations from the rapidly expanding field of epigenetics show that lifestyle decisions made by individuals could have biological consequences for future generations. Epigenetics studies chemical modifications to the chromatin of our genome that influence gene expression. These modifications are established by the cellular or organismal environment and are passed down during cell division in order to maintain cellular identity. Transgenerational epigenetic inheritance is the handing down of these epigenetic marks across generations resulting in changes in gene expression.

The purpose of this article is to explain the basic science of transgenerational epigenetic inheritance, highlighting particularly intriguing examples from human beings and rodent models, and to suggest that these discoveries require appropriate responses from Christian educators in science and from Christian communities in general.

Genetics and Epigenetics

In 1809, Jean Baptiste de Lamarck published his theory that changes acquired

over a lifetime's effort can be passed on to successive generations.1 His example explaining the development of the giraffe's long neck through generations of giraffes stretching for the highest leaves is still shared and corrected in numerous introductory-level biology textbooks.2 His theory lacks a mechanism that would explain the inheritance of these earned traits. The later theory of evolution by natural selection proposed by Charles Darwin and Alfred Wallace rejected the concept of use versus disuse. Their theory, combined with genetics in the modern synthesis, provides a better understanding of how genes are passed from parent to offspring.

As an example of the modern explanation of inheritance, consider the mutation of a gene that codes for a protein responsible for regulating gene expression. If this mutation led to a slight change in the affinity of this protein for its typical

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binding partners in the cell, it could orchestrate a broad change in gene expression in the organism. If the mutation in a certain environment is detrimental to survival or procreation, perhaps by leading to severe cognitive defects, then this mutation would be less common in the next generation than it is in the current. On the other hand, if the mutation were beneficial, perhaps by leading to an ability to better tolerate cold temperatures, and thereby increasing the probability of having children, the mutation would be expected to be more common in the next generation than the current.

The genetic code of higher organisms is written in chromosomes made up of DNA wound around histone proteins in the form of nucleosomes. Each nucleosome contains two copies of four different histone proteins (H2A, H2B, H3, and H4) as well as around 141 base pairs of DNA.³ Each histone protein has flexible tails that extend out past the wrapped DNA. These tails are made of amino acids that are able to accept numerous chemical modifications. Histone tails can be methylated, acetylated, phosphorylated, and much more. These modifications help regulate the expression of genes wrapped on the nucleosome. Histone modifications can precondition the DNA to be very easily read into RNA or, conversely, they can effectively shut down gene expression. Histone modifications are required for a cell to maintain its identity.4 Epigenetic marks such as histone modifications will prevent heart-specific genes from being expressed in the liver or retina-specific genes from being read in bone. For the integrity of the tissues, these marks are passed down during mitotic cell division. The epi-genetic inheritance of a daughter cell prepares it for the kinds of gene expression that will be needed in its cellular environment.

There are many types of epigenetic modifications. Acetylation of lysines of the histone tails often correlates with increased levels of gene expression, and the enzymes that add these modifications are often found bound to DNA with the machinery responsible for reading DNA into RNA.⁵ Removal of these acetyl groups can lead to inhibition of gene expression. Methylation of histone tails can have varying effects, depending on the level of methylation (single, double, or triple) and on which lysine is being methylated.⁶ Another important epigenetic modification is methylation of the DNA itself. DNA methyltransferases can add a methyl group to the nucleotide cytosine. The methylation typically occurs in the context of the

short DNA sequence cytosine-guanine or CG. This sequence is a palindrome in DNA and will read CG on both strands (because C binds with G and G binds with C). The cytosines on both strands will be methylated. DNA methylation can inhibit transcription in a number of ways.⁷ It can prevent appropriate binding of a transcriptional activator that promotes gene expression. It can recruit proteins that specifically bind methylated DNA and then actively inhibit gene expression. Some methyl DNA-binding proteins will recruit enzymes that remove the acetyl groups of histones in the region, further suppressing gene expression.

Maintenance of Epigenetic Marks

The maintenance of these modifications during DNA replication and cell division is not yet fully understood. An overview of the current understanding is as follows.⁸ During DNA replication, the nucleosomes are unwound and partially disassembled. Each daughter strand of DNA, after replication, will be rewound on nucleosomes made of some recycled histone proteins from the DNA mother strand and of histones that are freshly made. Since reused histones are thought to be incorporated into new DNA within just hundreds of base pairs of their original location, the inherited histones will include the modifications that are relevant for the current stretch of DNA.⁹ The freshly produced histone proteins will require appropriate modification.

As for the inheritance of DNA methylation, the processes of semiconservative DNA replication will produce two daughter strands of DNA that will each be hemimethylated, with the inherited strand methylated and the recently synthesized strands unmethylated. Cells contain regulatory proteins that identify hemimethylated DNA and recruit the DNA methyltransferases that will methylate the other strand, restoring the parental methylation state.¹⁰

Transmission of epigenetic information across generations is even less well understood. At or just after conception, DNA methylation is dramatically reduced. Early in development, the few cells of an organism require the flexibility to express genes appropriate for whatever kinds of tissue they differentiate into. These early cells have much less DNA fully shut down from gene expression than do mature tissues. Therefore, only very few DNA methylation patterns are passed directly from one generation to the next. Similarly, during formation of mature sperm cells, more than 85% of the histone proteins are removed, and DNA is compacted by forming a complex with proteins called protamines. The small number of histones donated to the offspring could carry some epigenetic information, but this may not be the dominant means of conveying this regulatory information.¹¹

Another possible way that epigenetic information could be passed down across generations is in the form of regulatory RNA. Regulatory RNAs are known to have roles in controlling the epigenetic landscape of the genome.¹² Regulatory RNA is required for proper maintenance of DNA methylation and some histone modifications. Additionally, both male and female sex cells carry active RNA molecules. The RNA packaged with a sex cell will have developmental, and potentially epigenetic, consequences, some of which may be passed on to generations yet to come.

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In the winter of 1944–1945, the Western Netherlands experienced a season of extreme cold, devastation from years of war, and a food embargo enforced by German forces still in control of the area.¹³ The resulting famine, called the Dutch Hunger Winter, decreased average caloric intake for residents to a low of about five hundred Calories a day and killed an estimated twenty thousand people. The human tragedy created a group of survivors that, because of the organized and meticulous records of the Dutch medical system, could be studied for effects on later generations. Females that experienced the famine in the earliest stages of fetal development were born at average birth weights; however, their offspring have a higher-than-average birth weight. Additionally, victims of the famine that were in the first weeks of fetal development during the famine had changes in the DNA methylation patterns of a gene, IGF2, even six decades after the Dutch Hunger Winter.

Famines experienced at other stages of development beyond birth also have transgenerational epigenetic consequences. Marcus Pembrey and others have studied the historical records, including harvest records and food prices, of the remote Swedish community of Överkalix.¹⁴ They find that food supply during the

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slow growth period of late childhood has biological consequences for future generations. Intriguingly, the effect is strongest for the grandparent on the father's side that shares the same sex as the grand-child. For example, low food availability during the slow growth period in a female leads to a statistically significant decrease in the mortality rate of her son's female offspring. Likewise, abundant food availability during the slow growth period in a male correlates with increased mortality in his son's male offspring. These results, and others like it,¹⁵ that show a clear transgenerational effect through the male lineage, offer clues as to the mechanism of how this occurs, but currently the exact answers are not yet known.

The effects of parental diet on future generations can be more carefully studied in rodents. A study published in Nature in 2010 determined the effect of a paternal high-fat diet on the regulation of gene expression in the pancreases of their offspring.¹⁶ The male rats with this high-fat diet showed an increase in body weight and body fat, and showed symptoms of diabetes, including decreased glucose tolerance and insulin insensitivity. Although these male rats were almost identical genetically to the control males that were fed a standard diet, their daughters showed a significant difference in the expression of hundreds of genes in the cells responsible for regulating glucose. Of the hundreds of genes that showed a significant change in gene expression dependent on the diet of the father, the gene most disturbed (Il13ra2, 1.75-fold increase in expression) had less DNA methylation, which could explain the increase in gene expression. In human beings, paternal diabetes increases the risk of diabetes in offspring.¹⁷ While this increased risk could certainly be genetically and/ or environmentally transmitted, this study in rodents indicates that transgenerational epigenetic inheritance may also be involved.

Another study, published in *Cell* that same year, reports the effect on offspring of feeding male mice a low-protein diet.¹⁸ This group found hundreds of genes involved in lipid and cholesterol synthesis with changed levels of expression in the next generation. Numerous genes in the offspring, which were fed a standard diet, showed slight changes in the level of DNA methylation, including the regulatory region of one of the key genes that oversees the lipid biosynthesis (*Ppar*). Interestingly, the sperm showed normal methylation levels in this gene, ruling out a direct transmission of the methylation pattern but

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leaving room for transmission of the signal via an RNA molecule.

Other reports indicate that parental diet or caloric restriction at specific times in development, from embryo to adolescent, may have ties to heart disease, psychological disorders, and more.¹⁹ Though the mechanisms are not yet fully understood, the dietary choices of one generation seem to have potential lifelong consequences for the next and perhaps even for generations yet to come.

Unfortunately, there is also evidence that some molecules and environmental toxins can cause epigenetic changes. The most widely reported example comes from the fungicide vinclozolin.²⁰ Vinclozolin is a hormone disrupter that is able to decrease sperm production, reduce sperm motility, and increase cell death in the testes of male rodents whose mothers were exposed to the molecule. In the key study, pregnant rats were injected with high doses (100mg/kg/day) of the fungicide throughout pregnancy. In addition to affecting fertility of the male rats exposed in utero, *their* male offspring also showed reduced fertility through four generations.²¹ These descendants also showed changes in DNA methylation patterns in fifty-two different genes.²²

A human example showing the potential consequence of transgenerational inheritance of environmentally induced epigenetic changes comes from the drug diethylstilbestrol (DES), once given to prevent miscarriage. DES is an estrogen disrupter that is able to cross the placenta and cause developmental changes in the fetus. Now known to cause birth defects and to increase the risk of cancer of the reproductive system in those exposed in utero, it is possible that even granddaughters of women that took this drug may pay a biological price for this decision. In mice fed doses of DES similar to what was given to pregnant women, granddaughters of mice given the molecule still show increased rates of uterine cancer when compared to a control group.23 The mechanism of this transmission is not yet known, but changes in DNA methylation patterns of important estrogendependent genes have been reported in response to DES treatment.24

There is evidence that not only diet and toxins, but also social experiences, can cause epigenetic changes that are passed on to future generations. Signs of good mothering in rats include licking, grooming, and arched-back nursing. Rats that receive this caring nurture in their first weeks of infancy are less fearful as adults and have a more moderate hormonal response to stress.²⁵ Michael Meaney and others reported a possible epigenetic explanation for this result in 2004.²⁶ They found that mice which are raised by mothers that provide attentive licking, grooming, and arched-back nursing have decreased methylation patterns in the regulatory region of the glucocorticoid receptor in the hippocampus of the brain. Methylation of this region was later shown to disrupt an interaction between the regulatory DNA of the glucocorticoid receptor gene and a protein that controls transcription of the gene.²⁷ Decreased methylation permits increased expression of the receptor and could explain the lifelong decrease in stress response these rats experience. These experiments indicate that, in rats, the attentiveness given by a mother in the first weeks of her offspring's life leads to a permanent change in how that youth will respond to stress throughout its life.

Conversely, the data also suggest that harsh treatment in early infancy has lifelong and even transgenerational consequences. A study published in Biological Psychiatry in 2010 showed that newborn mice exposed to chronic unpredictable maternal separation for the first two weeks of life show depressive-like behaviors and have a reduced response to novel environments as adults.²⁸ Offspring of males that experienced this maternal separation show the same psychological consequences as their fathers. This is a complex behavior and could have many explanations, but the researchers did find changes in DNA methylation patterns that affected gene expression in the deprived males and their offspring. Another study exposed rats in infancy to caregivers that were under substantial stress.²⁹ These rat pups experienced "significant amounts of abusive maternal behaviors." Victims of this abuse showed DNA methylation and reduced expression of the gene BDNF in the prefrontal cortex of the brain. Additionally, offspring of females that experienced the abuse also show these changes in gene expression in the brain. Female mice that suffered abuse as pups were more likely to treat their own offspring abusively, explaining some of the transgenerational response. However, even if young rats were removed from the abused mother at birth and given nurturing, adoptive mothers, they still showed some of the changes in BDNF methylation and gene expression.

Whether these results directly transfer to human beings is not yet understood, but there is evidence that human child abuse causes epigenetic changes in the brain. Michael Meaney and others compared DNA methylation patterns and gene expression of the glucocorticoid receptor in brains of suicide victims who had suffered abuse as children, and compared them to other suicide victims who had not been abused.³⁰ They found increased methylation and decreased gene expression, which may have caused an increased stress response in suicide victims who had been abused. While this is a complicated study, it at least suggests that some of what has been learned about the transgenerational epigenetic inheritance of traits acquired by the social experiences in rodents may be true in humans as well. The social choices and experiences of one generation have biological consequences for the next generation and potentially for generations yet to come.

Christian Responsibilities

Christian Educators in Science

The provocative conclusions coming from this field have ramifications for Christian educators of science. Scientists should emphasize that there is freedom from epigenetic determinism.³¹ A simple reading of the work summarized above may suggest that how an individual responds to stressful situations and to sugars may already be determined by the DNA and histone methylation patterns that they inherited. That deterministic understanding could lead to incredibly damaging decisions. Students with anger issues could feel that their outbursts were justified and feel no need to change because their response is predetermined by how they were raised as infants. Overweight students may feel no personal responsibility for their health because they are already predetermined to suffer from diabetes due to their father's dietary choices. Educators in science should remind students of their relative autonomy as adults, of the probabilistic nature of genetics generally and epigenetics specifically, and of their freedom in Christ. DNA methylation patterns may increase the likelihood of contracting a certain disease or responding in a certain way, but persons are still responsible for their own actions. We are to remind them that while they may be predisposed to alcoholism, no histone modification makes anyone open an alcoholic beverage. We are to show them that while their probability of struggling with diabetes may be higher than

the student in the next row, it is the responsibility of each of us to eat well and exercise. Human health is a complex outcome of environment, genetics, sociology, psychology, faith, and epigenetics.³² By the grace of God, each of us can overcome epigenetic burdens that would predispose us toward crime, sickness, or sin.

Another responsibility of Christian educators in science is to highlight not just the fallenness revealed in this new field, but the grace it shows as well. The examples discussed above, particularly regarding the epigenetic inheritance of poor parenting and violent behavior that could be a factor in generational cycles of abuse, clearly demonstrate the fallenness of transgenerational epigenetic inheritance. But I would like to suggest that this is only a twisted version of how good, or even holy, transgenerational epigenetic inheritance can be. Transgenerational epigenetic inheritance is a mechanism by which wisdom from one generation can have positive implications for the next. There are undoubtedly numerous examples of inheritance of DNA methylation patterns that are beneficial for the offspring. One example from plants bears mentioning. Campanulastrum americanum is a small plant that produces lovely purple flowers. It grows both in the deep shade of forests and in broken light under thinner tree growth. A study published in Science in 2007 shows that, even for genetically identical plants, seeds that land in the same light conditions as their parent have 3.4 times greater fitness than those that are moved to different light conditions.³³ What this means is that the experience of the paternal generation, the gene expression decisions that a certain plant finds are most successful for the environment in which it lives, can be shared with its offspring. If this is true in humans, then by God's grace, children have an opportunity to learn from their parents even if the children and their parents had never met.

Further, Christian educators in science should teach students the limits of this work. The study of transgenerational epigenetic inheritance is still a very new field. There is certainly a chance that many of the modifications to DNA and histones that have been discussed here are effects instead of causes. It may be that proteins that regulate gene expression determine the biological response of a cell (or an organism) to a certain environment. The epigenetic marks could be put in place once the cellular response has already begun. While the results that have been discovered

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so far are exciting, huge numbers of experiments have been disappointing. One researcher, Steve Cole, who studied changes in human epigenetic marks in response to socio-economic status, is reported to have said, "Lots of people have spent lots of time and money and are now a little grumpy about this."³⁴

Which choices, experiences, or molecules lead to an epigenetic response are not yet known. There is certainly no reason to avoid any medication, food, or experience until it has been proven to cause detrimental epigenetic consequences. The exact means of transmission of epigenetic marks is not yet understood, and until it is, it will remain difficult to make predictions about transmission. The conditions that maintain or disrupt inherited epigenetic marks are also not yet known, which means that it is still impossible to predict gene expression in the offspring even if the epigenetic landscape of the parent is fully known. With the incredible amount of work being done in this area, answers to these questions are likely to be the headlines of scientific articles in the near future. In the meantime, Christian educators should highlight the exciting conclusions this field is producing while explaining the limits of what is, so far, known.

Christian Communities Generally

One responsibility for followers of Christ in light of the findings in epigenetics is to show special grace to those who might be biologically disadvantaged in their struggles against sin and disease. While on Earth, our King showed special grace, love, and respect to someone caught in adultery and to others sick or impoverished. As followers of Christ, we are expected to show love and grace to those whose decisions lead to destruction and sin. Of course, as modern readers, we know nothing of the circumstances that led to these displays of brokenness and, as yet, there is no definitive evidence that a cycle of broken relationships will result in epigenetic changes that are able to perpetuate the destructive cycle. However, I suspect that, knowing that there is a possibility that poor decisions regarding relationships, drugs, or health may be made as a product of the cycle of brokenness and epigenetic consequences, this knowledge could offer some comfort for those left in the destruction of a loved one's choices. As it is easier to show patience and grace in the face of the difficulties in learning to read when we know the student struggles with dyslexia (which may have a

genetic component³⁵), so perhaps we can better love like our Lord when we understand that a potential epigenetic change has occurred in a person's brain that could make it biologically more difficult to make good decisions. Dyslexia and a predisposition toward poor decisions can be overcome, but it may take grace, love, and assistance from a community.

Another obligation of Christian communities that deserves emphasis, given what epigenetics is suggesting, is that we are called to liberate people from destructive cycles. As mentioned above, some part of the destruction caused by cycles of poverty, violence, or abuse could come from epigenetic changes in the brains of those raised within the cycle. Fortunately, the field of epigenetics has provided evidence that breaking the destructive cycle can also have lasting consequences for generations. James Curley and others published a study in 2009 that analyzed maternal BALB/c mice.³⁶ The BALB/c mouse strain displays significant deficiencies in social interactions including parenting.37 The 2009 study found that the BALB/c mothers who raise their pups in isolation show increased levels of aggression (such as biting) and reduced displays of maternal care (such as licking, grooming, or arched-back nursing). However, they found that when BALB/c mice with brand new pups raise their young in community, they display reduced stress response, reduced aggressive behaviors, and increases in maternal care. The pups (which still bear the BALB/c genetics that predispose them to antisocial behavior), once grown, show many of these same increases in maternal care to their offspring even if they raise them in isolation. These changes may be explained by changes in gene expression in the brains of these mice as a result of the nurturing parenting they received as pups. Some of the beneficial physiological and social consequences were still present when the granddaughters of the females that had reared their young in community became mothers themselves. These results imply that, at least in this example from rodents, epigenetic changes that result from positive social experiences can break a cycle of abusive parenting.

Even the possibility that such results could occur in humans demands that followers of Christ begin to break these destructive cycles. This could mean that cycles of alcoholism, abuse, sexual sin, poverty, or poor decisions in relationships could be broken in ways that change the brain chemistry of not only those freed from the cycle, but also of their children and their children's children. Churches and Christian communities can help those trapped in destructive cycles to find freedom in the body of Christ. By teaching one young mother how to care for her daughter with love and compassion, we may be influencing the hardwiring of her daughter to be a better mother herself one day.

Another responsibility of Christian communities is to foster lives that provide a healthful epigenetic inheritance. In addition to breaking cycles of abuse, Christian communities should encourage those within and around their community to make epigenetically healthful decisions regarding food and relationships. The effects of male rats' diet on the insulin response of their daughters should demand that we are conscious of the epigenetic legacy we will pass on to our children. If a young father made a habit of filling bottles for his six-month-old daughter with cola, a mentor could teach, in love, the possible detrimental health consequences that that decision could have for his daughter. Perhaps we should make similar interventions to young men (and women) who will one day be parents. If a young person is making poor decisions about friends or romantic interests, a loving member of their Christian community could try to help them learn to make God-honoring decisions. Perhaps we should actively train young parents in what God-honoring relationships look like in order to change the environment (and possibly the epigenetic state) of their children. Most Christian communities take leaving a healthy spiritual legacy for the next generation very seriously. I suggest that we should also work to leave a healthy epigenetic inheritance for them as well.

The discoveries being made in epigenetics suggest a new and exciting meaning to the question asked by the righteous in Matthew 25:37.

Lord, when did we see you hungry and feed you, or thirsty and give you something to drink? When did we see you a stranger and invite you in, or needing clothes and clothe you? When did we see you sick or in prison and go to visit you?

We know that when we do these things for the least among us, we do it for Christ. However, we now know that when we care for the least among us, we are not only helping them and honoring our Savior, we may also be helping their children down through the generations.

Conclusions

Like so much else in our time between Calvary and the new creation, transgenerational epigenetic inheritance shows evidence of the brokenness of our world while still displaying the overwhelming goodness of God's creation. Transgenerational epigenetic inheritance could increase an infant's risks for disease, sin, and death in response to decisions, actions, foods, chemicals, and experiences from earlier generations. However, transgenerational epigenetic inheritance also gives us another way to prepare our offspring to thrive in the world, even if we never meet one another. While we wait and see what this exciting field will finally offer, I suggest that we seek transgenerational justice, love epigenetic mercy, and walk humbly in our God's creation. ð

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SCIENCE AND RELIGION: AN INTRODUCTION

Denis O. Lamoureux, PhD (Theology) PhD (Biology) Associate Professor of Science & Religion St. Joseph's College, University of Alberta

Blended (Flip) Classroom Format

Before arriving in Hamilton, students will examine all the class audio-slide lectures, class notes, and class handouts. For the best learning experience, students should also have a rough draft of the 12 written assignments (see http://www.ualberta.ca/~dlamoure/2dhomepage.html). Over the two days in Hamilton, there will be lecture summaries and class discussions on all the assignment topics. All the materials are online. Students can start the course right now! No prerequisites required.

Credit or Noncredit Students

This course can be taken as an audit course without exams or assignments or as a 3-credit undergraduate course (40 hours) that is an arts elective in all undergraduate programs. This course is listed as **CHRTC 350: Science & Religion** in the University of Alberta calendar. Students may also make an arrangement at their own college/university to take this course for credit.

NOTE: It is possible to take this course for **Graduate School Credit**. Contact Professor Lamoureux for details: dlamoure@ualberta.ca

To register, contact the assistant to the Academic Dean: sjcdean@ualberta.ca