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Article

The Genetics of Addiction

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Abuse of alcohol and other substances has been with humanity for millennia, and the devastating effects of addiction to any substance are painful and costly to society, families, and individuals. Addiction disorders are complex behaviors driven by a combination of environmental factors, neurological changes stemming from long-term exposure to the addictive substances, and genetic predisposition to addiction. Recent advances in genomic analysis and gene expression profiling are beginning to advance our knowledge about the contributions of genetics to addiction. The data thus far indicate that the genetic contribution involves a multifaceted interaction among many different genes, with a significant epigenetic component to the final outcome.

It was the time of year for the regional middle school music festival in my corner of the Midwest. In the era long before helicopter parents were invented, I caught a ride with my best friend and her mom to the host town, about 30 minutes from home. As we rode down the dark two-lane blacktop, the topic of drinking came up. My friend's mom matter-of-factly stated that the chance of a daughter of two alcoholics herself becoming an addict was very high, so my friend should never risk taking even one drink. Both of my friend's parents were sober, but the path to sobriety had not been easy for anyone in the family—which was no secret in our town. Were my friend and her brother doomed because of the home life during their childhood? Was the family's sin being punished through subsequent generations? Were they destined to fight the same demons as their parents because of a genetic roll of the dice? Would one drink destine them to scheduling their lives around Alcoholics Anonymous meetings?

Her mom did not have the answers that night, and as with most things in life that involve the brain and human behavior, the answer is tremendously complicated and still incompletely understood. This article will describe the current state of knowledge regarding the contribution of genetics to addictive disorders. Unlike the classic examples of genetic disease, substance dependence is caused by a strong environmental component paired with inherited risk factors and acquired genetic changes. The mechanisms behind these genetic changes, examples of genes that have been identified as candidates for genetic change in addictive disorders, and potential targets for new addiction treatments will be discussed. Finally, this article will make suggestions for church communities in support for addicts and their families.

Addiction, or substance dependence, is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5*, the standard for mental health classifications in the United States, as compulsive drug-seeking and use, despite harmful consequences.[1] By far the most common addictive substances used in our society are nicotine and alcohol. Along with the other commonly abused substances of marijuana, opium derivatives, and cocaine, there is a long history of human use and abuse of these drugs. As far back as the ancient Greeks, people noticed that alcoholism tended to run in families.[2] Twin and sibling studies over

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the years have consistently confirmed this informal observation, and several studies showed that the addiction was specific to alcohol versus other addictive substances or mental illnesses in general.[3] However, commonly described patterns of inheritance associated with single-gene phenotypes are not observed for addictive disorders. In fact, only a few alleles of specific Mendelian-inherited genes are associated with changes in risk of developing an addiction.

Classic Mendelian Genetics and Addictions

The best examples of single-gene variants that influence addiction are the inheritance of genes encoding inactive enzymes for alcohol and aldehyde metabolism. These inactive alleles make consuming ethanol physiologically unpleasant, and thus are clearly protective against alcohol abuse.[4] Figure 1 shows that alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) act in series to metabolize ethanol in humans. The first enzyme oxidizes ethanol to acetaldehyde, which is then further oxidized by ALDH to acetic acid. Acetic acid can be converted to acetyl coenzyme A (Acetyl-CoA) which either enters the Krebs cycle to release stored chemical energy for ATP production, or alternatively uses fatty acid production pathways to synthesize fats for later use.[5] A variant in ADH1B that changes a single amino acid in the protein reduces risk for alcoholism in Asians, Native Americans, European Americans, and African Americans.[6] Acetaldehyde buildup accounts for many of the unpleasant side effects associated with hangovers, and thus individuals with low ALDH levels generally find consuming ethanol unpleasant. The drug Antabuse (disulfiram) has been used since the 1940s to inhibit ALDH activity and thus to disincentivize drinking and alcohol abuse by exacerbating the unpleasant after effects of alcohol consumption.[7]

The clear association between ALDH and ADH genetic variants and protection against addiction to ethanol is the exception, and those genes are specific to alcohol. Almost all of the remaining literature regarding genetics and addiction falls into one of two types of investigations: (1) studies of differences in the relative risk of suffering from addiction disorders due to genetic differences between individuals, or (2) epigenetic changes in the genome that, during development or the individual's lifespan, result in daughter cells expressing the same changes in gene expression that were found in the progenitor cell. A small number of studies show germline transmission

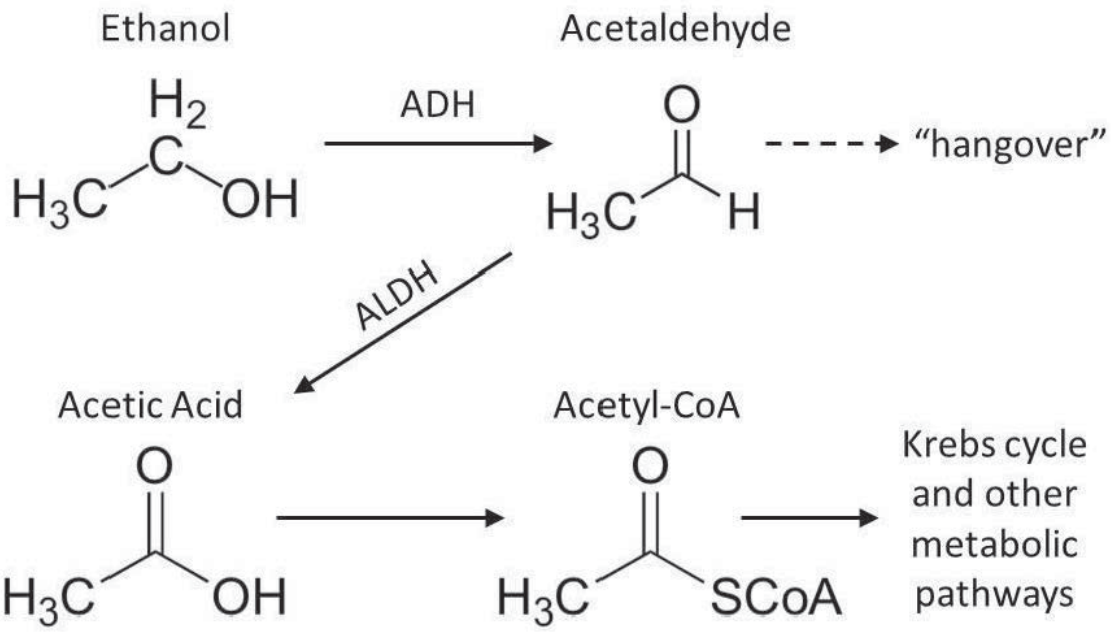

Figure 1. Biochemical Pathway for Ethanol Metabolism. Ethanol is oxidized by alcohol dehydrogenase (ADH) to acetaldehyde, which produces the unpleasant symptoms associated with "hangover." Acetaldehyde is further oxidized to acetic acid by the enzyme aldehyde dehydrogenase (ALDH), and acetic acid can be joined to coenzyme A (CoA) whereby it enters the Krebs cycle, fatty acid metabolism, or other pathways. Chemical structures from Wikipedia commons.

of those changes through sperm or egg DNA modifications. It is important to note that neither of these categories of studies will identify anything resembling popular conceptions of an "addiction gene," relative to any abusable substance or behavior.

Beyond the Punnett Square

A primer on genetics that goes beyond the Punnett square is useful at this point. Punnett square exercises in high school lead people to believe that genetic risk determination can be made very precisely for a given trait, and for the example traits used, this is true. Even more complicated calculations for polygenic trait inheritance in university-level genetics classes suggest that a firm probability of having a trait can be calculated. While this is a very useful foundation to start from, many human traits, including susceptibilities to most common diseases, must take more factors into account. Two key concepts, heritability and relative risks, are important to understand in complicated traits such as addiction.

Phenotypes are determined by both environmental and DNA-based factors. "Heritability" is defined as the proportion of the variation of a trait in a population that is due to genetic factors. Note that this is a measure for a group of people, in contrast to calculating odds for a particular person or couple in the classic genetics problems. In practice, heritability is very difficult to quantify because families share both genetic and social/environmental factors.[8] My son received both his genetics and his childhood environment and social setting from my husband and me. Furthermore, heritability is not fixed for a given trait. In different environments, the heritability of a trait will differ. For example, in a society in which all children have plenty to eat, enriching experiences, and strong loving families, the differences in their intelligence/IQ will be largely due to genetics. In the reality of life in the city of Chicago, the differences in IQ between children have far less to do with genetics and are largely determined by factors in each child's environment.[9]

The heritability, or "genetic component," of addiction disorders ranges broadly in different studies, from 0.3 to 0.7, in part because of the differences in environmental variation.[10] Taking an intermediate value of a heritability of 0.5 means that genes would be responsible for half of the variability in risk for addiction in the whole group of people. To further complicate things, many different genes are likely to cooperate in contributing to that heritability. One given allele, or variant, of a gene may be responsible for only a small portion of the final outcome.

Practically, genetic studies do not attempt to parse out the fraction of responsibility, but are more frequently reported as changes to the relative risk of developing an addiction by observing an appropriately chosen sample of the population. Relative risk is the ratio of the risk of having the trait under two different conditions. For example, in relation to addictions, it would be the risk of becoming addicted for individuals who have a specific allele of a gene divided by the risk of becoming addicted if you do not have that allele.[11]

Relative risk is not trivial to calculate, as all other factors leading into addiction (or whatever trait is under investigation) should be as equal as possible between the two comparison groups.[12] Thus, a fivefold increased risk of addiction for individuals with a specific allele of a specific gene could still mean a very low risk of addiction, or it could mean a quite high risk for each person carrying that allele. It all depends on the starting risk point. Generally, the relative risks for addiction in carriers of one specific allele that are reported in the literature are not impressive—for example, there is a relative risk of only 1.11–1.15 for alcohol dependence in individuals carrying a variation in a gene for the α2 subunit of the $GABA_A$ neurotransmitter receptor, *GABRA2*.[13]

Finding Candidates for Genes That Contribute to Addictions

Our understanding of the biology of response to addictive chemicals and the neurobiology of pleasure and reward has identified several important molecular components as good genetic candidates for influencing addiction. For example, alleles of genes coding for monoamine oxidases (MAOs) play a central role in balancing neurotransmitter levels in the brain and, as such, set a level of sensitivity to the environment that may make an individual more or less susceptible to those influences on addiction and other psychiatric conditions such as depression or anxiety.[14] A great deal of attention has focused on the dopaminergic system because of its role in mediating pleasure and reward. Several studies showed a link between drug abuse (of various substances) and a genetic variation in a noncoding region of a gene adjacent to one of the dopamine receptors, *DRD2*.[15]

While this "Taq1A" polymorphism was initially promising and associated with decreased dopamine-receptor levels and responsiveness, subsequent work did not show correlation with drug abuse.[16] Later studies zeroed in on the *DRD2* gene itself, and have shown more reliable linkage to addictions for a specific variant of the gene.[17] It is important to note that these are correlational studies, and a specific mechanism for driving the increase in drug abuse should be demonstrated experimentally before claiming a cause-effect relationship between an allele of a gene and addiction.

Genetic investigations that seek to associate particular alleles of genes with increased or decreased risk for addictions need a way to identify the candidate genes. With the advent of genomics, the most common tool used to find candidate genes is Genome-Wide Association Studies (GWAS). Single-nucleotide differences (polymorphisms) at millions of different sites throughout the human genome are recorded for groups of affected and unaffected people. On occasion, a DNA variant at one site will be much more prevalent in the genomes of one group or the other, making it a candidate region for a gene controlling that trait. Theoretically, this approach will be powerful in its "blind" identification of undiscovered genes involved in these addiction syndromes, as the experiments are inherently unbiased toward one genetic region versus another.[18]

The results from GWAS studies, however, have been inconsistent, and thus quite disappointing in finding variants associated with alcohol dependence,[19] other than the previously identified ADH and ALDH genes.[20] The inconsistent results suggest that for the very complex trait of addiction, there are many genes that make small contributions to the phenotype, and thus much larger samples of affected and unaffected people are needed to detect the small effects of risk loci.[21] While some authors predict that larger meta-analyses of GWAS studies may be fruitful, others propose that whole-genome sequencing is the most likely approach to moving forward with identifying genes that make small contributions to alcohol use disorder and other addictions.[22] Indeed, some whole-genome studies are already entering the literature.[23] As the cost of whole-genome sequencing continues to drop, and as more whole human genomes (and the associated medical records) can be entered into publicly available databases, this area of study has high potential for extending our knowledge of the many genetic loci that contribute to addictions.

Epigenetics: Changing Inheritance without Changing the DNA Sequence

The second category of genetic studies investigates epigenetics, or inheritance of phenotypic changes that are not caused by changes in the DNA sequence. Almost all examples of epigenetic inheritance involve passing on a pattern of gene expression from an altered parent cell to the daughter cells during cell division—within a single organism, not from parent to child. Notably, the sequence of nucleotides on the DNA strands does not change during epigenetic inheritance, but the phenotype of the offspring cells reflects the altered phenotype of the parent. These changes can be thought of as the genetics underlying the *development* of addictions, rather than the *inheritance* of increased risk for addictions.

There are several different mechanisms for changing gene expression that can be passed to offspring cells during mitosis, or cell division. DNA methylation (fig. 2) was discovered in the 1970s as a process used by bacteria to regulate gene expression, and subsequent studies showed that eukaryotes, including mammals, use differential methylation of cytosine to control levels of transcription for a range of genes.[24] Cytosine is "C" in the "ACGT" abbreviations for nucleotides. DNA sequences are conventionally written by the order of nucleotides on a directional DNA strand, starting with the end with a phosphate group, notated as the "5' end." The opposite end terminates with a hydroxyl group on the deoxyribose, and is termed the "3' end." The two strands of a DNA double helix are antiparallel to each other, such that the 5' end of one strand is attached to the 3' end of its complementary strand. In vertebrates, methylated cytosines are almost always found before, or 5' to, a guanosine residue, and are sometimes referred to as "CpGs." A CG sequence is base paired with a

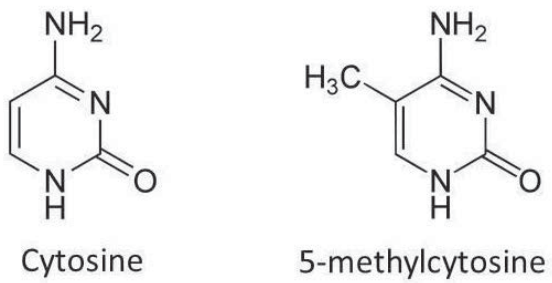

Figure 2. Structures of 5-methylcytosine. The unmethylated pyrimidine base cytosine is shown on the left, next to 5-methylcytosine on the right. Chemical structures from Wikipedia commons.

CG sequence (in the opposite orientation) on the complementary DNA strand, and the enzymes that methylate cytosines recognize CpG sequences that are base paired with methylated CpGs on the partner strand. Thus, after DNA is copied during replication, the newly formed double helix will have one original, methylated strand that helps the methylating enzymes find the nucleotides on the newly synthesized strand for modification, propagating this pattern of methylation through cell divisions.[25]

Methylation influences interaction with many DNA-binding proteins that are important for turning on or turning off transcription in that region. The most important family of these DNA-binding proteins are the histones. Histones are the oft-forgotten foundation of eukaryotic chromosomes. While the classic diagrams of DNA structure evoke a helical staircase model (fig. 3, panel 1), DNA inside cells is found associated with many different proteins. Histones are proteins that are the foundation for the structure of chromosomes (fig. 3, panel 2 gray balls), and organize the DNA in progressively more compact arrangements within the nucleus (fig. 3, panels 3–5).[26] The way that the DNA interacts with histones has great influence on expression of genes in localized regions of the genome. In brief, winding DNA more tightly around histone proteins prevents transcription-related proteins from binding DNA and producing RNA at a given site.[27] Thus, changes that promote histone-DNA association decrease gene expression, and changes that inhibit histone-DNA association increase gene expression.

Histone proteins undergo many different types of chemical modifications, including phosphorylation, acetylation, ubiquitination, and methylation. Each of these changes is catalyzed by an enzyme, and those enzymes bind preferentially to methylated regions of DNA.[28] The overall pattern of histone modifications in a region has been termed the "histone code," and the resulting chromatin remodeling will influence how much transcription occurs from promoters in that area.

Finally, expression of small noncoding RNA molecules named "microRNAs" can alter expression of genes by acting within the cytoplasm to alter the stability or translation efficiency of specific messenger RNAs (mRNAs).[29] Transcription of these regulatory RNAs is often regulated by the DNA methylation and histone modifications described previously, thus allowing those two mechanisms to both directly control expression of genes and to indirectly control gene expression through transcription of the microRNA regulators.

Epigenetic Changes in Alcohol Abuse: Human and Animal Studies

All three of the following epigenetic mechanisms have been observed to be involved in gene expression changes during abuse of different substances.

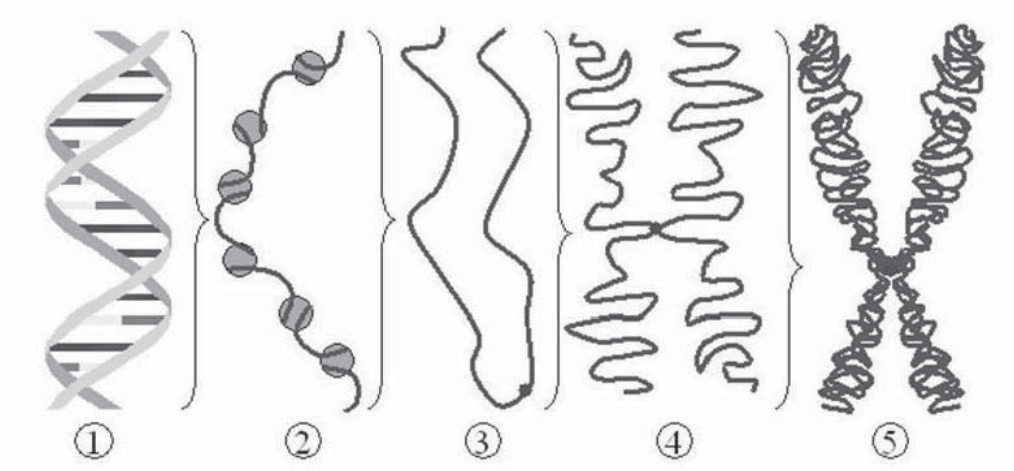

Figure 3. Overview of Eukaryotic Chromosome Structure. Panel 1: Schematic of the DNA double helix. Panel 2: DNA in eukaryotic cells is wound around core particles made of histone proteins (gray balls). Each DNA-histone unit is called a "nucleosome." Panel 3: Nucleosomes self-associate to further condense DNA during times when a cell is not directly dividing. Histone modifications control this condensation in localized regions of the chromosome. Greater condensation is associated with less transcription activity. Panel 4: DNA is replicated during S phase of the cell cycle. Panel 5: During mitosis, the duplicated chromosomes condense further to the X-shaped structures visible during this stage in the cell cycle. Diagram from https://commons.wikimedia.org/wiki/File:Chromatin_chromosome.png.

Alcohol consumption in humans is associated with changes in gene expression in many parts of the brain. The interplay between methylation and histone modifications in controlling transcription is exemplified by a 2012 study in which Igor Ponomarev and colleagues used a microarray experiment to identify many genes with altered expression. Notably, the GC-rich regions of the genome were transcribed more in alcohol abusers than in nonabusing control individuals, while GC-poor regions showed less transcription activity. This observation clearly points to a role for DNA methylation in gene expression.[30] This study also observed decreased expression of *DNMT1*, which encodes DNA methyltransferase; reduction of methylation in GC-rich regions would correspond to increased transcriptional activity.

Changes in histone modifications have also been indirectly observed in both rats and humans after alcohol consumption, with measurement of reduced histone deacetylase (HDAC) expression, an enzyme that removes acetyl groups from histones.[31] Interestingly, using drugs to directly inhibit HDAC activity reversed or blocked the formation of behaviors associated with ethanol abuse in rodents,[32] an observation earlier observed in a clinical study of human alcoholics; here, the HDAC inhibitor valproate reduced withdrawal symptoms and relapse.[33]

Finally, changes in microRNA (miRNA) expression are observed in brain samples from human alcoholics. Changes appear in several miRNA species that coordinate many other biological processes, including expression of genes involved in neuronal excitability and neurodegeneration disorders.[34]

There is no clear smoking gun here. Many genes are subject to epigenetic control during chronic alcohol consumption, and it is likely that some of the genetic risk for alcoholism stems from differences in responses to this epigenetic regulation, and from differences in the extent of epigenetic regulation in individuals, including expression levels of enzymes involved in DNA methylation and histone modifications.[35]

Epigenetic Changes in Other Addictions

Cocaine exposure studies also demonstrate many epigenetic changes in the brain of both animals and humans. In a manner similar to the mechanism of changes observed in alcohol studies, methylation patterns generally change in rodent brains, and the activity of enzymes responsible for DNA methylation is increased.[36] Acetylation and methylation of histones has been demonstrated in rats and mice,[37] and mice deficient in enzymes responsible for histone acetylation have been shown to be less sensitive to cocaine.[38] MiRNA populations also change in response to chronic cocaine exposure, with hundreds of downstream-regulated transcripts changing in abundance as a result, in a coordinated response that changes behavior in the test animals.[39]

While nicotine addiction may not have the negative behavioral issues associated with abuse of alcohol or illegal drugs, the public health costs of nicotine addiction are immense, amounting to as much as $170 billion in healthcare costs in the US alone.[40] A recent study using cultured neuronal cells demonstrated that nicotine causes repositioning of histones throughout the genome, with predicted expression changes in genes associated with histone modifications, neurotransmitter production, and neuronal signaling.[41] Studies in mice recently identified a specific miRNA, *mmu-miR-15b*, that is methylated in response to nicotine, resulting in its reduced expression in both the nicotine-exposed mouse and its first generation of offspring. Interestingly, behavior hyperactivity changes seen as a result were reversible by delivering either the miRNA or a protein that is regulated by the miRNA directly into the mouse brain—a key experiment that demonstrates a cause-effect relationship rather than just a correlation.[42]

Passing on Epigenetic Changes to Future Generations in Animal Studies of Addiction

This last example of changes in nicotine-driven miRNA expression is the first thus far in this article to mention epigenetic effects appearing in offspring. The mechanisms for transmitting epigenetic modifications to future generations of offspring are a rich area of current research. In short, any change to DNA methylation, histone modifications/chromatin remodeling, or miRNA expression, must occur in egg or sperm production, and be maintained after fertilization through development of the offspring. Extensive demethylation of nearly all of the genome occurs immediately following fertilization of vertebrate embryos,[43] although a small number of genes are protected from this resetting event.

New methylation patterns are established during development and are then carried through the many rounds of mitosis that occur as the organism grows to adulthood. One of the earliest examples of a gene maintaining a methylation state from sperm or egg was observed in the mouse gene for insulin-like growth factor (*Igf2*), a gene that contributes to body size in this species. Mice that do not express normal *Igf2* are about half the size of normal mice. Oddly enough, scientists observed that inheriting a mutant copy of *Igf2* from the egg did not produce a tiny mouse, while inheriting the same mutation from sperm did.[44] This observation was termed "imprinting," and the mechanism was later explained by differential methylation of the gene. In mice, the gene for insulin-like growth factor-2 (*Igf2*) is methylated in sperm, and unmethylated in eggs. Because the different methylation states are maintained from sperm and egg through development, only the maternal copy of *Igf2* is transcribed.[45]

Similar differential methylation patterns that are maintained through early development can contribute to expression of miRNAs or to association of DNA methylases or histone-modifying proteins, regulating expression of other genes. Again, only a small subset of genes maintain this differential methylation after fertilization, so this means of sharing changes in expression patterns through generations of offspring is the exception, not the rule. To date, studies relating to addiction use animal models to measure addictive behaviors. One of the most mature sets of experiments investigates multigenerational behaviors in the offspring of cocaine-exposed male rats. Cocaine administration in rats produces a desire for more cocaine; however, after a delay of time, rats avoid further administration of the drug and exhibit anxious behaviors.[46] In a 2014 report, male but not female offspring of cocaine-exposed sires showed decreased cocaine consumption as adults.[47]

Wimmer's group at the University of Pennsylvania later reported that male offspring of cocaine-exposed male rats have increased anxiety-like behaviors, while female offspring of these sires did not show behavioral differences.[48] Earlier studies had indicated that rats with higher baseline anxiety self-administered cocaine at lower levels,[49] which might suggest a protective effect against addiction in the offspring of exposed male rats. Exposing the offspring males themselves to cocaine delayed their feeding behavior in a new environment, a measure of anxiety, when compared to offspring of unexposed sires.[50] Thus, it appears that in rats, paternal exposure to cocaine passes on at least some increase in anxious behavior in the offspring, which may predispose them to less cocaine-seeking behavior.

In a follow-up study, this group measured very specific changes in memory functions, neuronal activity in the hippocampus, levels of the N-methyl-D-aspartate (NMDA) co-agonists D-serine and glutamate, and increased brain expression of D-amino acid oxidase (DAO1), an enzyme that degrades D-serine—all specific to male offspring.[51] Memory deficits are a common occurrence in individuals exposed to cocaine, and in the offspring of rats, memory performances for short-term and long-term tasks were also deficient. Changes in histone modifications, particularly acetylation, were observed near the *Dao1* gene; this explains the observation of reduced D-serine levels and potentially poorer memory formation in that NMDA receptors are key players in this process. Whether this epigenetic change in brain gene expression and memory formation is maintained across a third generation—with or without exposure of the second generation to cocaine—is an interesting question to address in the future.

Animal studies have also shown a pattern of epigenetic inheritance passed from male rats to their male offspring following ethanol exposure. Interestingly, there were clear reductions in ethanol consumption among these male offspring, although ethanol reduced anxiety significantly more in these offspring than in control rats, indicating an increased responsiveness to the drug.[52] Reduction in overall CpG methylation was observed in the sperm of ethanol-exposed rats, and in the DNA of both their male and female offspring. The studies investigated methylation of specific promoters within the genome, and as in the cocaine studies, saw reduced expression of *Bdnf* in specific brain regions.[53] However, clear cause-effect relationships between reduced *Bdnf* expression and either cocaine or alcohol consumption in male offspring of drug-exposed sires are not yet evident.

Other examples of intergenerational transmission of changes in gene expression in brain tissues have been reported following exposure of parent animals to stress[54] and nicotine.[55] It seems likely that in upcoming years more animal studies will use developing genomic technologies to more closely identify a set of genes with differential methylation patterns in the offspring of exposed animals, leading to a richer set

of testable hypotheses for gene expression changes that cooperate to predispose future generations to addictive behaviors. Eventually, these studies may help in developing more effective drug therapies for addiction recovery programs. Most of the current slate of pharmaceuticals either alleviate withdrawal symptoms by activating the same biochemical pathways without producing the same "high" as the addictive drug (for example, methadone treatment for heroin addiction), alleviate withdrawal symptoms by other pathways (for example, gabapentin's use as an anti-convulsant and anti-anxiety drug for alcohol addiction), or cause aversive responses to the addictive substance (for example, Antabuse for alcoholic recovery). Development of more-specific molecules that could target specific changes in gene expression associated with addiction, whether generally or to a specific substance, could be very useful in aiding the recovery of addicts, hopefully increasing the safety and long-term efficacy of the recovery process.

How Does the Church Show Grace and Love to Addicted Individuals and Their Families?

To return to the 1982 car ride with my friend, do these studies provide hope or hopelessness? The choice to take the first cigarette, the first drink, the first hit was still the choice for my friend to make. While her environment and her genetics, as well as her propensity to choose one way or another, exerted pressure on her responses to chemicals, a Christian perspective on this topic cannot fail to note the individual's responsibility to act faithfully to the God who created her. It is interesting that the Temperance movement that was so active in Protestant circles a century ago is almost absent from our churches today. To be sure, some churches and denominations still hold abstinence in high regard, but it is no longer a hallmark of Protestant Christianity. The question of abstaining from legal intoxicants will only expand as more US states and Canada move to legalizing recreational marijuana. In light of the strong evidence of genetic changes, and changes in brain function presented in other papers in this issue, revisiting church support for complete abstinence may be a good idea in many congregations.

However, the implication of the science is clear: regardless of the moral agency involved in developing an addiction, addicts who want to change to sobriety face a tremendously difficult journey. The epigenetic changes that are being more fully described each day by research scientists provide a biological explanation for both short-term and long-term consequences of choices, as well as why recovering from an addiction is so incredibly difficult for most people, more difficult than never starting at all. The Alcoholics Anonymous claim "once an alcoholic, always an alcoholic"[56] is consistent with these biological findings—the epigenetic changes in a person's brain are long term. The ability to change back to the unaddicted state has not been investigated, but there is a clear implication from the psychological and behavioral data that taking another drink/hit/puff, at least for many years, is a dangerous step for an addict who wishes to stay clean. Avoiding the addictive substance altogether for a lifetime is the surest way to maintain sobriety.

Acknowledging that recovery from addiction is more than a decision that involves sheer willpower or moral strength is important—it is physically difficult to overcome the state of gene expression and downstream effects in their brain. Graciousness from the church, encouragement without judgment, and love when the stumbles occur along the journey are essential. Teaching in Christian circles must acknowledge the real biological changes in the brains of addicts. Too often the church writes off individuals who could benefit from the love and support of believers because they are seen as too morally weak to be part of the community. Every church must stand alongside a recovering addict in acknowledgment of the physical challenges he or she faces in getting and staying sober.

Addiction Prevention Work within the Church Community

The work of the Christian community to support moral choices through loving care and healthy relationships for people at greater risk of addiction is an important consideration for every congregation. The idea of the actions of an addict causing epigenetic changes to their children is likely new to many readers, but important to consider. The children from these families have more than just environmental challenges to overcome, but the great hope is that by overcoming them, the chain of epigenetic inheritance may be broken for the next generation. Unfortunately, church families may withdraw from the hurting families that may be broken as a result of

the addiction, rather than enfolding the children in healthy community relationships. It is imperative for leaders in the church, both formal leaders and influential church members, to set the lead in accepting and enfolding families in these situations. Are these families, and particularly their children, included in invitations to after-church lunches, weekend barbeques, playdates at the park, sleepovers? If not, a great opportunity is being ignored. Pastoral leadership should deliberately challenge families to do this work of love and gracious acceptance in ways that honor and respect the families who are struggling with an active or recovering addict.

In many ways, youth pastors are at the forefront of preventative medicine for teenage children of parents who have abused drugs or alcohol. We now know that adolescent brains are particularly susceptible to epigenetic changes induced by alcohol and nicotine.[57] Fostering healthy relationships and developing useful ways to help students avoid substance abuse altogether is the best way to address substance abuse. There is no literature that describes human brain epigenetic changes in response to occasional intake of these substances, but the absence of data does not indicate an absence of an effect. Church-based programs that offer supportive social environments to children and that are deliberately welcoming to all children, not just those of upstanding families, can play a huge role in keeping children healthy. Proactively addressing substance abuse with vigor and in a multidisciplinary approach at the very first sign of a young person's abuse is important. Understanding the underlying motivations that led the youth to abuse in the first place will be essential to preventing further abuse, and understanding the child's motivations in a way that is humble and welcoming rather than fault finding and condemning is critical. The National Institute on Drug Abuse, one of the United States National Institutes of Health, has an excellent online resource for characteristics of effective drug prevention programs for those interested in exploring this topic further.[58]

In conclusion, it is evident that the genetic basis for addictions is complex. Much remains to be learned about how individual genetic code changes, as well as changes in gene expression acquired throughout the lifespan, contribute to the overall development of these very difficult outcomes. The gap between model animal studies and human measurements is significant, and will be important to address as genetic and genomic studies become more powerful and affordable in coming years. Thirty years on, the questions that surfaced in the car ride to the music festival are only beginning to be answered, and children of parents who struggle with addiction face challenges, both biological and environmental. While we await the development of drugs that can assist with weaning individuals off their addictions, it is essential to provide all the supports possible to address the nongenetic aspects of the disease, both for the addict and for their family.

Notes

[1]American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5* (Washington, DC: American Psychiatric Association, 2013).
[2]D. W. Goodwin, "The Cause of Alcoholism and Why It Runs in Families," *British Journal of Addiction* 74, no. 2 (1979): 161–64.
[3]Ibid.
[4]M. T. Reilly et al., "Genetic Studies of Alcohol Dependence in the Context of the Addiction Cycle," *Neuropharmacology* 122 (2017): 3–21.
[5]J. Berg, J. Tymoczko, and L. Stryer, *Biochemistry,* 5th ed. (New York: W. H. Freeman, 2002).
[6]Reilly et al., "Genetic Studies of Alcohol Dependence."
[7]J. D. Jones and S. D. Comer, "A Review of Pharmacogenetic Studies of Substance-Related Disorders," *Drug and Alcohol Dependence* 152 (2015): 1–14.
[8]T. Strachan and A. P. Read, *Human Molecular Genetics 3* (New York: Garland Science, 2004).
[9]Ibid.
[10]D. M. Dick and T. Foroud, "Candidate Genes for Alcohol Dependence: A Review of Genetic Evidence from Human Studies," *Alcoholism: Clinical Experimental Research* 27, no. 5 (2003): 868–79
[11]M. L. Samuels, J. A. Witmer, and A. Schaffner, *Statistics for the Life Sciences,* 4th ed. (Boston, MA: Prentice Hall, 2012).
[12]Strachan and Read, *Human Molecular Genetics 3.*
[13]L. J. Bierut et al., "A Genome-Wide Association Study of Alcohol Dependence," *Proceedings of the National Academy of Sciences USA* 107, no. 11 (2010): 5082–87.
[14]N. D. Volkow and R. D. Baler, "Addiction Science: Uncovering Neurobiological Complexity," *Neuropharmacology* 76, Pt. B (2014): 235–49.
[15]Q. F. Hou and S. B. Li, "Potential Association of DRD2 and DAT1 Genetic Variation with Heroin Dependence," *Neuroscience Letters* 464, no. 2 (2009): 127–30.
[16]Jones and Comer, "A Review of Pharmacogenetic Studies of Substance-Related Disorders."
[17]T. K. Clarke et al., "The Dopamine Receptor D2 (DRD2) SNP rs1076560 Is Associated with Opioid Addiction," *Annals of Human Genetics* 78, no. 1 (2014): 33–39; and R. A. Moyer et al., "Intronic Polymorphisms Affecting Alternative Splicing of Human Dopamine D2 Receptor Are Associated with Cocaine Abuse," *Neuropsychopharmacology* 36, no. 4 (2011): 753–62.
[18]W. S. Bush and J. H. Moore, "Chapter 11: Genome-Wide Association Studies," *PLoS Computional Biology* 8, no. 12 (2012): e1002822.

[19]A. B. Hart and H. R. Kranzler, "Alcohol Dependence Genetics: Lessons Learned from Genome-Wide Association Studies (GWAS) and Post-GWAS Analyses," *Alcoholism: Clinical and Experimental Research* 39, no. 8 (2015): 1312–27.
[20]E. A. Tawa, S. D. Hall, and F. W. Lohoff, "Overview of the Genetics of Alcohol Use Disorder," *Alcohol and Alcoholism* 51, no. 5 (2016): 507–14.
[21]Hart and Kranzler, "Alcohol Dependence Genetics."
[22]Tawa, Hall, and Lohoff, "Overview of the Genetics of Alcohol Use Disorder."
[23]I. R. Gizer et al., "Whole Genome Sequence Study of Cannabis Dependence in Two Independent Cohorts," *Addiction Biology* 23, no. 1 (2018): 461–73.
[24]A. Bird, "Putting the DNA Back into DNA Methylation," *Nature Genetics* 43, no. 11 (2011): 1050–51.
[25]B. Alberts et al., *Molecular Biology of the Cell,* 6th ed. (New York: Garland Science, 2015), 404–5.
[26]Ibid., 187–93.
[27]Ibid., 194–96, 211–12.
[28]Ibid., 196–201.
[29]Ibid., 429–31.
[30]I. Ponomarev et al., "Gene Coexpression Networks in Human Brain Identify Epigenetic Modifications in Alcohol Dependence," *Journal of Neuroscience* 32, no. 5 (2012): 1884–97.
[31]J. A. López-Moreno et al., "Histone Deacetylase Gene Expression Following Binge Alcohol Consumption in Rats and Humans," *Alcoholism: Clinical and Experimental Research* 39, no. 10 (2015): 1939–50.
[32]A. J. Sakharkar et al., "Effects of Acute Ethanol Exposure on Anxiety Measures and Epigenetic Modifiers in the Extended Amygdala of Adolescent Rats," *International Journal of Neuropsychopharmacology* 17, no. 12 (2014): 2057–67; and V. Warnault et al., "Chromatin Remodeling—A Novel Strategy to Control Excessive Alcohol Drinking," *Translational Psychiatry* 3, no. 2 (2013): e231.
[33]L. P. Longo, T. Campbell, and S. Hubatch, "Divalproex Sodium (Depakote) for Alcohol Withdrawal and Relapse Prevention," *Journal of Addictive Diseases* 21, no. 2 (2002): 55–64; and H. Myrick, K. T. Brady, and R. Malcolm, "Divalproex in the Treatment of Alcohol Withdrawal," *The American Journal of Drug and Alcohol Abuse,"* 26, no. 1 (2000): 155–60.
[34]A. S. Warden and R. D. Mayfield, "Gene Expression Profiling in the Human Alcoholic Brain," *Neuropharmacology* 122 (2017): 161–74.
[35]S. C. Pandey, E. J. Kyzar, and H. Zhang, "Epigenetic Basis of the Dark Side of Alcohol Addiction," *Neuropharmacology* 122 (2017): 74–84.
[36]G. Sadri-Vakili, "Cocaine Triggers Epigenetic Alterations in the Corticostriatal Circuit," *Brain Research* 1628, Pt. A (2015): 50–59.
[37]A. Kumar et al., "Chromatin Remodeling Is a Key Mechanism Underlying Cocaine-Induced Plasticity in Striatum," *Neuron* 48, no. 2 (2005): 303–14.
[38]A. A. Levine et al., "CREB-Binding Protein Controls Response to Cocaine by Acetylating Histones at the fosB Promoter in the Mouse Striatum," *Proceedings of the National Academy of Sciences USA* 102, no. 52 (2005): 19186–91.
[39]Sadri-Vakili, "Cocaine Triggers Epigenetic Alterations in the Corticostriatal Circuit."
[40]X. Xu et al., "Annual Healthcare Spending Attributable to Cigarette Smoking: An Update," *American Journal of Preventive Medicine* 48, no. 3 (2015): 326–33.
[41]A. N. Brown et al., "Nucleosome Repositioning: A Novel Mechanism for Nicotine- and Cocaine-Induced Epigenetic Changes," *PLoS One* 10, no. 9 (2015): e0139103.
[42]J. Dai et al., "Paternal Nicotine Exposure Defines Different Behavior in Subsequent Generation via Hyper-methylation of *mmu-miR-15b*," *Scientific Reports* 7, no. 1 (2017): 7286.
[43]Alberts et al., *Molecular Biology of the Cell,* 6th ed.
[44]T. M. DeChiara, E. J. Robertson, and A. Efstratiadis, "Parental Imprinting of the Mouse Insulin-Like Growth Factor II Gene," *Cell* 64, no. 4 (1991): 849–59.
[45]R. Stöger et al., "Maternal-Specific Methylation of the Imprinted Mouse *lgf2r* Locus Identifies the Expressed Locus as Carrying the Imprinting Signal," *Cell* 73, no. 1 (1993): 61–71.
[46]A. Ettenberg et al., "Evidence for Opponent-Process Actions of Intravenous Cocaine," *Pharmacology Biochemistry and Behavior* 64, no. 3 (1999): 507–12.
[47]F. M. Vassoler and G. Sadri-Vakili, "Mechanisms of Transgenerational Inheritance of Addictive-Like Behaviors," *Neuroscience* 264 (2014): 198–206.
[48]S. L. White et al., "Enhanced Anxiety in the Male Offspring of Sires That Self-administered Cocaine," *Addiction Biology* 21, no. 4 (2016): 802–10.
[49]D. E. Bush and F. J. Vaccarino, "Individual Differences in Elevated Plus-Maze Exploration Predicted Progressive-Ratio Cocaine Self-administration Break Points in Wistar Rats," *Psychopharmacology* 194, no. 2 (2007): 211–19.
[50]White et al., "Enhanced Anxiety in the Male Offspring of Sires That Self-administered Cocaine."
[51]M. E. Wimmer et al., "Paternal Cocaine Taking Elicits Epigenetic Remodeling and Memory Deficits in Male Progeny," *Molecular Psychiatry* 22, no. 11 (2017): 1653.
[52]A. Finegersh and G. E. Homanics, "Paternal Alcohol Exposure Reduces Alcohol Drinking and Increases Behavioral Sensitivity to Alcohol Selectively in Male Offspring," *PLoS One* 9, no. 6 (2014): e99078.
[53]Ibid.; and F. M. Vassoler, E. M. Byrnes, and R. C. Pierce, "The Impact of Exposure to Addictive Drugs on Future Generations: Physiological and Behavioral Effects," *Neuropharmacology* 76, Pt. B (2014): 269–75.
[54]A. B. Rodgers et al., "Transgenerational Epigenetic Programming via Sperm MicroRNA Recapitulates Effects of Paternal Stress," *Proceedings of the National Academy of Sciences USA,* 112, no. 44 (2015): 13699–704.
[55]Dai et al., "Paternal Nicotine Exposure Defines Different Behavior."
[56]Alcoholics Anonymous World Services, *Alcoholics Anonymous: The Big Book*, 4th edition (New York: Alcoholics Anonymous World Services, 2001).
[57]Pandey, Kyzar, and Zhang, "Epigenetic Basis of the Dark Side of Alcohol Addiction"; and M. Yuan et al., "Nicotine and the Adolescent Brain," *Journal of Physiology* 593, no. 16 (2015): 3397–412.
[58]E. B. Robertson, S. L. David, and S. A. Rao, "Preventing Drug Use among Children and Adolescents (In Brief)," National Institute on Drug Abuse, National Institutes of Health, and the US Department of Health and Human Services (October 2003), accessed April 30, 2018, https://www.drugabuse.gov/publications/preventing-drug-use-among-children-adolescents-in-brief.