Epigenetics, Gender, and Sex in the Diagnosis of Depression

Lewis Mehl-Madrona1-6,*, Patrick McFarlane1 and Barbara Mainguy4-6

1Eastern Maine Medical Center Family Medicine Residency, Bangor, ME 04401, USA; 2Department of Family Medicine, University of New England College of Osteopathic Medicine, Biddeford, ME 04005, USA; 3Department of Psychiatry, University of Vermont College of Medicine, Burlington, VT 05405, USA; 4Coyote Institute, Orono, ME 04469, USA; 5Graduate School, University of Maine, Orono, ME 04469, USA; 6Wabanaki Health and Wellness, Bangor, ME 04401, USA

Abstract: Background: A marked sexual dimorphism exists in psychiatric diagnoses. Culture derived gender bias in diagnostic criteria is one explanation. Adverse childhood events, including sexual and physical abuse, are more reliable and consistent predictors of later psychiatric diagnoses, including depression and post-traumatic stress disorder. Some interesting interactions between genes and experience have been uncovered, but the primary effect appears to be epigenetic with life experience altering gene expression and being transmitted to subsequent generations.

Objectives: To determine if reconceptualizing depression as encompassing both internalizing and externalizing strategies would eliminate gender differences in the diagnosis of depression

Methods: We reviewed 74 life stories of patients, collected during a study of the effect of physicians’ knowing patients’ life stories on the quality of the doctor-patient relationship. Looking at diagnoses, the prevalence of women to men was 2.9 to 1. We redefined depression as a response to being in a seemingly hopeless situation accompanied by despair, either externalizing ((more often diagnosed as substance use disorders, impulse control disorders, antisocial personality disorder, or bipolar disorder) or internalizing (the more standard diagnosis of depression). Then we reviewed these life stories from that perspective to determine how many would be diagnosed as depressed.

Results: With this reconceptualization of depression, the sex ratio changed to 1.2 to 1.

Conclusions: From this perspective, men and women are equally likely to respond to hopelessness, though men are more socialized to externalize and women to internalize. Considering depression in this way may help to better identify men at risk for suicide.

Keywords: Epigenetics, sexual dimorphism, depression, gender, genetics, hormones, culture, adverse, childhood experience, child abuse.

1. INTRODUCTION

In medicine, we do not often reflect upon how our diagnoses are stories that we construct to make sense of our clinical world. These stories are often quite plausible and backed by evidence, but they, like all theories, are stories that tie facts together and render a meaningful whole. Our current story about depression, as codified in the Diagnostic and Statistical Manual of the American Psychiatric Association, 5th edition (DSM-5) and the coding schema of the International Classification of Diseases, 10th edition (ICD-10) is still such a story. In this paper, we present another way to conceptualize depression that may actually explain the observed facts better. As such, this is a contribution toward narrative medicine, as we understand that all our theories are stories, told to help us make sense of our world and operate better within it. This story begins with gender differences in depression and moves toward another conceptualization that may eliminate these differences.

Gender differences exist in susceptibility to many diseases, and not just psychiatric diagnoses. Multiple sclerosis, rheumatoid arthritis, Crohn’s disease, panic disorder, structural heart disease and hyperthyroidism are more common in females, while males are more often affected with autism, Hirschsprung’s disease, ulcerative colitis, Parkinson’s disease, alcoholism, allergies and asthma (especially at young age) [1]. These differences have been assumed to be due to sex hormones, but the specific molecular mechanisms of such hormonal effects have not been explained. Strong cases have been made that gender differences can also be the result
of the very different life experiences of men and women in contemporary and historical times. Life experience modifies gene expression through epigenetic mechanisms and can be transmitted to the offspring for at least seven generations. Epigenetics permits resolution of the nature vs. nurture debate in showing how, for example, a person’s experience of abuse, poverty, and adverse circumstances modifies genes and is transmitted to the offspring.

1.1. Epigenetics

The term “epigenetics” was introduced by Waddington based upon the observation that the effects of genes (phenotypic expression) did not always match the gene itself (genotype). [2]. The term was used to describe different outcomes of gene expression that resulted from the interaction of genes with environment, as well as from random processes [3]. This definition has expanded to include any potentially inheritable process that can temporarily or permanently alter gene expression without altering the gene sequence [4]. Epigenetic processes include the addition of a methyl group to DNA itself, usually cytosines; or modifications of chromatin proteins, including acetylation, methylation, and phosphorylation of the histone molecule [5]; and the deployment of microRNAs, all of which changes the shape of the DNA, which alters transcription, or specifically blocks transcription. In mammals, DNA methylation occurs most commonly at locations in which cytosine is directly followed by guanine, forming a CpG dinucleotide, also called CpG islands [6]. When methyl groups are added to cytosine, the function of that gene is usually suppressed. Increased DNA methylation is usually associated with gene silencing, and decreased DNA methylation with gene activation. Maintenance of existing DNA methylation and de novo DNA methylation is catalyzed by several types of enzymes known as DNA-methyltransferases [7]. Methylation of CpG islands prevents the binding of enzymes to the promoter region of the genome to activate the creation of mRNA [8-10]. A complete loss of maintenance DNA-methyltransferase function results in death of mice in early embryogenesis [11].

MicroRNAs are small, non-coding RNA sequences, usually around 22 nucleotides, that inactivate or silence genes. They were first discovered in the 1990s, but only after 2000 was their function actually understood. They are vital for regulating gene expression and do so epigenetically.

Epigenetic mechanisms can affect gene expression and regulation in gametes, which can cause phenotypic variation to be transferred from generation to generation during meiosis [12], occurring before reproduction. More commonly, modifications in genes expression are transferred to daughter cells through the usual process of mitosis [4, 13].

The term “gene expression” refers to the synthesis of a gene product, often a protein, from the DNA sequence of a particular gene [14]. During protein synthesis, a copy of the genomic sequence is made within the cell nucleus (messenger RNA or mRNA) as the first step in gene expression [15]. The binding of enzymes known as mRNA transcription initiating factors to the promoter region of the gene sequence, also known as a regulatory region, activates the production of mRNA. At this transcriptional level, chromatin remodeling and DNA methylation exert their epigenetic effect [14]. Genomic DNA is packaged as chromatin within the cell nucleus. It can be open or closed in functionality, which regulates how accessible it is to mRNA transcription initiating factors. Chromatin remodeling can change the region from open to closed and vice versa, however, a closed region is not copied, thereby blocking gene expression.

DNA methylation can also block the binding of enzymes at the promoter region by rendering them physically inaccessible [8, 10, 16]. When the promoter region is open, the genome is unwound, and RNA polymerase makes a mRNA copy of the DNA sequence. Splicing removes non-protein coding regions (introns) from the mRNA. The spliced DNA is transported from the cell nucleus to the ribosomes which translate the mRNA sequence into protein, which can be hindered at this level by the microRNAs. Left unhindered, the ribosomes assemble proteins from component amino acids directed by the mRNA sequence by the mRNA sequence. Once translated, the amino acid chain makes structural changes and folds in specific manners to create functional proteins.

Genomic protein is organized as chromatin to permit efficient storage within the cell nucleus. The basic unit of chromatin is the nucleosome, containing about 147 nucleotide base pairs of DNA wrapped around a core of histone proteins [17, 18] which make up the major protein constituents of the nucleus. The nucleosome histone core contains two copies of four histone proteins: H2A, H2B, H3, and H4. Each core histone protein contains an outward facing tail consisting of amino acids. A fifth histone protein called H1, links the nucleosome units. Acetylation or methylation of lysine on the histone tails modifies the interaction between the genomic DNA and the histone core and alters gene expression [17, 19]. Enzymes called histone acetyltransferases activate the chromatin by adding acetyl groups to the histone tail, causing it to unfold in order to permit access transcription enzymes to the promoter regions, thus initiating the process of gene expression [20-24]. Removal of acetyl groups by histone deacetylases causes chromatin condensation and decreases gene expression (protein production) [22, 25].

Epigenetics can explain how adverse life events, especially adverse early childhood experiences, can lead to stable, enduring changes in gene function [26, 27]. The evidence for epigenetic effects in human mental disorders has only recently appeared [28], though animal studies have supported this idea since 1990s.

Epigenetic effects can continue across multiple generations if the changes which led to them persist. These include changes in diet, behavior, or in the environment. Simple measures can reverse these effects, including the provision of methyl donors in the diet (eating foods containing methionine or other amino acids), through direct administration of methyl donors to the young, or through changing environmental conditions [29-31]. Hence, environmentally induced epigenetic states can be reversed by entering into a different environment. This has been called context-dependent epigenetic change [32]. Meaney and colleagues [33] have demonstrated this type of change in their studies of how the effects of the care a rat pup receives from its mother in the first week of life can change its later life reactions to stress. These arise predominantly through epigenetic effects.
on the glucocorticoid receptor (GR) in the hippocampus. The effect of maternal care crosses generations. This research group also showed that infusing methionine, a histone deacetylase inhibitor, into the hippocampus can reverse these events. They showed that rats selectively bred to be poor mothers became good mothers when housed together with other rat mothers and that their offspring were good mothers after they gave birth even when housed alone with their pups due to the epigenetic modifications resulting from having been well-mothered when they were young. Could this also happen among at-risk human mothers? Caspi and colleagues showed that nurturing childhood environments could overcome the influence of genotypes associated with violent behavior [34].

1.2. What are Complex Diseases?

Depression is considered a complex disease in that it lacks a simple, Mendelian inheritance pattern. Virtually all psychiatric conditions are complex diseases except for some early onset dementias (Huntington’s and some early-onset Alzheimers). Complex diseases tend to be common, are more often sporadic than familial, and are more likely to be discordant rather than concordant among identical twins [35]. Simple genetic diseases are rare and occur less than 0.1% of the time. They clearly run in families and are concordant among identical twins. Complex diseases have a later onset while the majority of simple genetic diseases occur before puberty (90%). Less than one percent occur after the age of 40 [36]. Complex diseases exhibit major variations in their level of severity, sometimes show improvement in symptoms as the patient ages, and sometimes are associated with a complete recovery. The risk of developing a complex disease often depends on the sex of the affected parent. Asthma, bipolar disorder, and epilepsy are more often transmitted from an affected mother, whereas type I diabetes more often comes from an affected father. Differential susceptibility to disease by sex exists, which is termed sexual dimorphism [36]. Currently, unfolding opinion holds that the reason for the variability in complex diseases is that they are largely epigenetically mediated.

In the epigenetic model of complex disease, pathology results from a sequence of unfavorable epigenetic events that begin with a primary epigenetic defect, or pre-epimutation, occurring in the germline during the error-prone epigenetic-reprogramming process [37, 38]. Pre-epimutation increases the risk of developing a disease without rendering the disease inevitable. These pre-epimutations may not cause immediate clinical problems with the age of onset of the disease being delayed for a relatively long time. It may take decades until the epigenetic dysregulation reaches a critical threshold beyond which the cell is no longer able to function normally. The phenotypic outcome depends on the overall effect of a series of epigenetic events.

1.3. Sexual Dimorphism and Disease

Statistical surveys show that multiple sclerosis, rheumatoid arthritis, Crohn’s disease, panic disorder, structural heart disease and hyperthyroidism are more common in females, while males are more often affected with autism, Hirschsprung’s disease, ulcerative colitis, Parkinson’s disease, alcoholism, allergies and asthma (especially at young age) [39]. Sexual dimorphism has also been found in a number of psychiatric conditions through epidemiological studies and includes such conditions as Alzheimer’s disease, schizophrenia, alcoholism, and mood and anxiety disorders [1]. The risk for women for being diagnosed with eating disorder, major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder, anxiety and panic disorders, seasonal affective disorder, Alzheimer’s disease, and other dementias is two-fold higher than for men [32], yet men have a suicide rate four times greater than women [40]. Feminist theorists have proposed gender-bias in the categories created by DSM for diagnosing psychiatric conditions among women. Scholars of men’s studies have supported these conclusions [41], arguing for change in diagnosis so that internalizing behaviors (most of the categories of behavior needed for diagnosing depression) that are socially sanctioned responses of women for dealing with adversity and externalizing behaviors (most of the categories of behavior needed for diagnosing antisocial personality or mania) that are the socially sanctioned behaviors for men for dealing with adversity, can be subsumed under the same label. One could imagine a label for depression that included the modifiers, -internalizing type, -externalizing type, or -mixed type. One could also imagine abandoning categorical type diagnoses of the DSMs and looking at how people respond to adverse childhood experience, sexual abuse, and the like, generating more narrative descriptors for coping strategies that arise, however maladaptive they may be later in life.

This sex difference in behavioral response to adverse circumstances is likely epigenetically mediated, and also socially reinforced. A gender-associated response set tendency to adverse circumstances may arise from social conditions and gender stereotyping and then be epigenetically transmitted to subsequent generations, only to further maintained by continued adverse circumstances and gender stereotyping. Any linkage to sex hormones could be illusory related to our tendency to ascribe behavior differences to sex hormones, when these behavioral differences may be transmitted quite differently. The biological, the sociological, and the psychological are frequently confused for men and women. Epigenetic analyses could help untangle this confusion.

1.4. Hormone Studies

Androgens and estrogens have different effects on neural development, affecting programmed cell death, cellular migration, synaptogenesis, axonal migration, and the formation of sexually distinct neuronal circuits [42, 43]. Androgens are related to neurite arborization, while estrogens stimulate synapse formation and the initiation of cellular communication [44]. The different ratio between sex hormones in males leads to masculinization and defeminization processes mediated by estrogen receptors a and b [45]. Females have a higher recovery rate from brain trauma or ischemic injury due to the neuroprotective effects of estrogen and progesterone [46]. Estrogen and progesterone replacement therapy in older women and men reduces obesity [47] and the symptoms of Alzheimer’s disease [48]. While sex hormones are important and do have certain effects, their effects are also mediated by epigenetic processes. Moreover, the factors
leading to conditions, such as depression may be very different from ordinary daily functions of the sex hormones.

Diseases, such as congenital adrenal hyperplasia with higher levels of androgens during the prenatal period that greatly affect gender identity and role, teach us the potential importance of sex hormones [49, 50]. Even modestly higher in utero exposure to increased levels of androgens before birth can have later impact. Studies on dizygotic twins in which one of the pairs is female and the other is male as compared to two female twins, showed that the female twin exposed to male hormones was, on average, more prone to aggression, more likely to engage in risk-taking behavior, and showed a more male pattern of cerebral lateralization [51-54]. Both men and women exposed to diethylstilbestrol (DES) in utero are more likely to be later diagnosed with depression compared to their unexposed siblings [55-57].

Oxytocin has been a candidate for a hormone related to depression. This neuropeptide dampens hypothalamic-pituitary-adrenal (HPA) axis over-activity by reducing excess cortisol [58]. Oxytocin reduces anxiety by reducing the experience of stress by promoting trust, bonding, social support seeking, empathy, attachment, and social cognition [59, 60]. Oxytocin stimulates lactation, increases the strength of uterine contractions during labor, and promotes mothering behaviors [60].

However, despite all these exciting hormones and their effects, none have been shown to consistently and substantially contribute to depression or other psychiatric diagnoses or to explain why depression is diagnosed twice as often among women.

1.5. Genetic Studies

Even though the heritability of depression ranges from 31 to 42%, no reproducible gene loci have been identified that contribute to its occurrence [61]. The 50% discordance rate between monozygotic twins suggests other mechanisms of transmission [62].

Sex-specific effects have been found in major depression studies. For example, a genome-wide linkage study in a sample of 100 Utah people with a history of major depression identified significant LOD scores demonstrating a linkage at gene 12q22-q23.2 markers, specific only to males [63]. Another genome scan showed possible locations of linkage to major depressive disorders specific to females, with the most prominent linkage on 2q33-q35 displaying LOD scores of 6.2 and 6.9 at D2S2321 and D2S2208, respectively [64]. A case-control association study identified a significant association of the DISC1 region with bipolar disorder among women (p = 0.00026) [65]. A study of 458 individuals in Finland showed that the HEP3 haplotype can protect women against depression (p = 0.00024) [66]. The results of these and other studies point to multiple possibilities, but do not necessarily explain the sexual dimorphisms observed.

In an intriguing study, Guinotivano, et al. [67] recruited 1517 women at six weeks postpartum from obstetrical clinics in North Carolina. Post-partum depression (PPD) was diagnosed among 549 women using the Mini International Neuropsychiatric Interview-plus. Psychiatric history was extracted from the medical record. Depression was assessed using the Edinburgh Postnatal Depression Scale and self-report instruments were used to identify adverse life events. Levels of estradiol, progesterone, brain-derived neurotrophic factor, oxytocin, and allopregnanalone were measured. Principal components from genotype data were used to assess genetic ancestry. Sixty-eight percent of the women were black; 13%, Latina; and 18%, European-derived. Logistic regression was used to identify predictors of PPD. Genetic ancestry did not predict PPD, nor did any of the hormones or neurosteroids. A history of previous major depression (p = 4.01E-14), a past diagnosis of an anxiety disorder (p = 1.25E-34), and adverse life events (p = 6.06E-06) predicted current PPD. Early-life adversity, and especially childhood abuse, is highly associated with later suicide and suicidal behavior, regardless of gender [68].

Gene-experience interaction is becoming increasingly more often studied in relation to mental illness. Uddin, et al. [69]studied the interaction of childhood maltreatment of 495 women (from the Detroit Neighborhood Health Study) with the ADCYAP1R1 genotype in relation to later diagnoses of PTSD and depression. They found that childhood maltreatment had a significant main effect on both PTSD and depression. They found no significant main effects of ADCYAP1R1 genotype on the occurrence of PTSD or on its severity. However, they did find a significant interaction of genotype with childhood maltreatment on both incidence of PTSD and its severity with carriers of the “C” allele showing enhanced risk for these outcomes among women exposed to childhood maltreatment. Those with the “CC” allele were at the highest risk. Ressler, et al. [70] performed a similar study and found an association of ADCYAP1R1 with depression, but their population was more impoverished. When Uddin, et al. re-analyzed their data with the highest quartile of child maltreatment, they also found this same association. PACAP and its receptor ADCYAP1R1 are implicating in regulating the stress response.

1.6. Psychosocial Studies

The quality of mental health varies over the course of a lifetime as a function of socioeconomic status (SES) [71]. People at lower SES levels have a higher risk for childhood behavioral disorders, depression and other related disorders, and drug abuse [72-74]. The contribution of SES to mental health is such that even those individuals in the middle of the middle classes have more mental problems than those in the upper middle classes, a finding that also exists for heart disease and overall mortality [75-77]. Indeed, the effects of SES are graded and linear and exist even when controlling for health status at birth and in countries with universal health care, in which access to medical services is less prohibited by SES. These effects are more closely correlated with education than with income and relate to factors, such as locus of control and self-esteem.

Low SES is correlated with increased exposure to chronic stressors [78-81] and with increased levels of adrenal glucocorticoids and sympathetic catecholamines [79, 82, 83]. Low SES in early childhood is a sustained and independent risk factor for mental health, and for some conditions, it is a bet-
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ter predictor for adverse mental health than the person’s SES status as an adult. These contributions of low childhood SES to mental health risk are mediated in part by variations in the quality of parental care [84-86]. Childhood SES predicts later alcohol dependence in adulthood and remains unchanged as a predictor even when SES increases in adult life [87]. An extensive, prospective study showed a significant predictive role of childhood SES on subsequent adult depression [88]. Other studies have shown a predictive relationship for adult hostility and hopelessness [89]. Adverse childhood SES predicts a lower locus of control, greater neuroticism, and poorer coping styles, also independent of subsequent adult SES [90]. Meaney has proposed that low childhood SES creates vulnerability for depression with its actual emergence being related to both developmental factors and current stressors [91].

Bouvette-Turcot, et al. [92] performed a prospective, longitudinal cohort study of 243 mothers. They constructed a maternal childhood adversity score using an integrated measure taken from the Childhood Trauma Questionnaire and the Parental Bonding Index. Maternal depression was measured in the prenatal period using the Center for Epidemiological Studies Depression scale. They measured socio-economic status using maternal level of education and family income obtained prenatally. They found a significant interaction between maternal childhood adversity and maternal depression during pregnancy that predicted prenatal family income. Women who reported higher levels of childhood adversity combined with higher levels of depressive symptoms were more likely to live in poor neighborhoods. Higher levels of childhood adversity were associated with lower levels of maternal education independent of other factors. We can begin to appreciate how trauma and adversity beget depression across generation [93].

Depressed mothers show reduced maternal sensitivity, responsiveness, and attachment. As a result, they have difficulty bonding with their child, soothing them, or responding to their needs [93-95]. Perinatal depression has been identified as a risk factor for behavioral problems in children, including conduct disorders, learning difficulties, and impaired emotional regulation [96, 97]. Post-partum depression may also lead to poorer immune function, increased sensitivity to stress in later life, and higher risk for psychopathology in the child [98-100].

Culture affects depression. For example, the risk for depression increases as Hispanic youth acculturates to U.S. society [101]. In Lorenzo-Blanco, et al.’s study, females suffered more from the disruption of family cohesion and from greater family conflict than boys in reference to diagnosed depression.

All these studies lead us back to the conclusion that early life experience, sexual abuse, other forms of social humiliation and life in low status categories may be more important than any intrinsic biological factor for the genesis of depression among males and females. These experiences have biological effects on the genome through epigenetics and change the underlying biology of the person. Our attention, however, should be on the cause and not the effect. Reducing poverty could have far more effect on the incidence of depression than pharmacological compounds. Preventing abuse and raising the social status of women and giving men alternate socially-sanctionable roles for managing adversity could also have a profound impact on the incidence and prevalence of depression and other disorders.

1.7. Sex Differences and Psychiatric Diagnoses

Feminist scholars have critiqued the finding that the incidence and prevalence of some psychiatric conditions are higher for women than for men. Marcie Kaplan [102], argued that gender bias is inherent to the diagnostic categories of the various DSMs, because we cannot step out of our culture far enough to see that our definitions of “abnormal” behaviors are weighed against the stereotypical sex role behaviors assigned to that of women. She also admits the possibility that women may have suffered more adversity and are more socially disadvantaged, and therefore are more readily diagnosed than men for a number of conditions. Crews notes the general agreement that sex hormones and stress hormones play a role in the development and display of many disorders, but it has been difficult to demonstrate except for stress hormones and anxiety [103]. He notes that sex differences in diagnoses do seem to appear at puberty, though Kaplan and similar theorists would counter that this is when stereotypical sex-role behavior demands become enforced. Crews also notes that schizophrenia symptoms tend to worsen for women during pregnancy, postpartum, and around the menopause [35, 104, 105].

In comparisons of men and women diagnosed with chronic major depressive disorder, women’s symptoms were more severe on a variety of depression scales [106]. Women reported greater psychomotor retardation than men, along with greater functional impairment in their relationships [3]. Echoing early proposals of some feminist theorists, Martin, et al. [107] proposed that the experience and symptomatology of depression differ between men and women. They concluded that depressive symptoms in men include anger, aggression, risk taking, and substance abuse, whereas, women present with more traditional internalizing symptoms. When more male associated symptoms are included in how depression is diagnosed, sex differences disappear.

A number of authors [108-111] have proposed that men’s symptoms are different from women in the following ways: more substance abuse, more compulsive behavior, fewer gastrointestinal symptoms, unusual drop in tolerance of stress, decrease in effort at tasks, decrease in emotional control, increased impulsivity, unusual aggressiveness, hyperactivity (in sex, sports, work, or other activities), increased risk-taking and breaking of rules, increased irritability and dysphoria, increased attacks of rage and/or anger with a sense of having over-reacted, an awareness of loss of control, all accompanied by autonomic manifestations (tachycardia, hyperventilation, increased temperature).

Zierau, et al. [112] developed the Gotland Male Depression Scale (Fig. 1). They showed that the use of this scale in a population of men diagnosed with alcohol use disorder increased the percentage of those diagnosed with major depression from 17% to 39%, thereby eliminating the gender difference in the diagnosis of depression. The scale is public domain and is reproduced below:
The scoring goes this way: Less than 13 points = no signs of depression; 13 to 26 points = depression possible; greater than 26 points = depression, see physician.

Interesting but unexplained differences have been found in the responsiveness of men and women to specific antidepressants. Men younger than age 50 respond less well to SSRIs than women. The difference disappears after age 50. Men respond less well to MAO inhibitors. Men and women respond equally to dual inhibitors of serotonin and norepinephrine (venlafaxine, duloxetine, mirtazapine). Men respond better to tricyclic antidepressants than women, but with a slower time course of response. Men respond better to selective inhibitors of norepinephrine such as reboxetine [113-115].

1.8. Epigenetics and Psychiatric Diagnoses

Affective disorders arise amidst interactions of environmental, genetic, and epigenetic factors during brain development and later in life, but how this all works is relatively unknown [116, 117]. We are now becoming aware that the origins of such effects can be in previous generations. The experiences of our ancestors modify regulatory factors and affect gene expression so as to substantially change our own physiology and behavior. This is critically important for feminist critiques of gender-bias in the diagnosis of affective disorders, for it provides an explanatory mechanism for how the unsatisfying and often abusive lives of our mothers and many generations of women before them, still affect behavior and physiology in the present. The effects of disenfranchisement of women and suppression of growth and creativity do not just have a psychological effect on the offspring, but also have biological effects on multiple generations.

Kaminsky, et al. [35] suggest that sex hormone action may be mediated via gene-specific epigenetic modifications of DNA and histones, which can explain sex effects at DNA sequence polymorphisms and haplotypes identified in gender-stratified genetic linkage and association studies. Hormone-induced DNA methylation and histone modification changes at specific gene regulatory regions may increase or reduce the risk of a disease. The epigenetic interpretation of sexual dimorphism fits well into the epigenetic theory of complex disease, which argues for the primary pathogenic role of inherited and/or acquired epigenetic mis-regulation rather than DNA sequence variation.

Studies are in process to examine epigenetic correlates of major depressive disorder in women. For example, Montalvo-Ortiz, et al. [118] studied 100 European-American women of whom 55 had been diagnosed with major depressive disorder and 54 aged-matched controls, not diagnosed. The median age was 43 with a standard deviation of 14.5 years. They found a significantly differentially methylated CpG site at cg03450102 which mapped to the exonuclease 1 (EXO1) gene. EXO1 is implicated in DNA repair and related to age at menopause.

A number of studies have shown that the degree of methylation of genes BDNF and NR3C1 is correlated with depression among either gender [119]. Recent human studies have also shown that DNA methylation of the glucocorticoid re-
1.9. Epigenetics and Early Experience

Early experience can significantly affect physiology and behavior through epigenetic modification of regulatory factors that influence gene expression [32]. These epigenetic effects can act immediately upon initial exposure or can be transmitted across generations. For example, differences in experiences with siblings result in genetically identical rats and knockout mice behaving differently as adults. Similarly, exposure to the fungicide vinclozolin early in pregnancy results in distinct behavioral profiles and unique patterns of gene expression in specific brain regions. Thus, both present and past environments modify social and affiliation behaviors through their effects on genes which affect the related brain areas.

Childhood physical abuse (CPA) and sexual abuse (CSA) interact with monoamine oxidase A (MAOA) gene polymorphism to modify risk for mental disorders [122]. These authors studied 114 Swedish women, who completed standardized diagnostic interviews, questionnaires to report CSA and CPA, and provided saliva samples for DNA extraction. DNA was genotyped for MAOA-uVNTR polymorphisms, and methylation of a MAOA region of interest (chrX: 43,515,544-43,515,991) was measured. CSA but not CPA was associated with increased methylation (hypermethylation) of the MAOA first exon relative to no-abuse. The association strongly remained after adjustment for psychoactive medication, alcohol and drug dependence, and current substance abuse. CSA and MAOA-uVNTR genotype, but not their interaction (the study may easily have been underpowered to detect interactions with only 114 subjects), were both associated with increased MAOA methylation. CSA was also associated with drug abuse, alcohol abuse, anxiety disorders, and conduct disorder. Hypermethylation of the MAOA first exon mediated the association of CSA with current depression. Both the level of methylation and CSA independently predicted lifetime depression.

Champagne [123] has demonstrated the epigenetic transmission of postpartum maternal care from mothers to offspring in rats, involving estrogen-oxytocin interactions and the differential methylation of hypothalamic estrogen receptors. Environmental influences offset genetic deficits or enhance them, depending upon the circumstances through epigenetic mechanisms. Their research group [124] reported that increased pup licking and grooming (LG) and arched-back nursing (ABN) by rat mothers altered the offspring epigenome at a glucocorticoid receptor (GR) gene promoter in the hippocampus. Offspring of mothers that showed high levels of LG and ABN were found to have differences in DNA methylation, as compared to offspring of ‘low-LG-ABN’ mothers. These differences emerged over the first week of life, were reversed with cross-fostering, persisted into adulthood and were associated with altered histone acetylation and transcription factor (NGFI-A) binding to the GR promoter. Higher levels of maternal care were associated with more robust stress responses in the offspring as adults. Central infusion of a histone deacetylase inhibitor removed the group differences in histone acetylation, DNA methylation, NGFI-A binding, GR expression and hypothalamic-pituitary-adrenal (HPA) responses to stress, suggesting a causal relation among epigenetic state, GR expression and the maternal effect on stress responses in the offspring. Thus, the epigenomic state of a gene can be established through behavioral programming and is potentially reversible.

Weaver, et al. [30] observed that naturally occurring variations in maternal behavior of rats are associated with the development of individual differences in behavioral and HPA responses to stress in the offspring. As adults, the offspring of ‘high-LG-ABN’ mothers are less fearful and showed more modest HPA responses to stress than the offspring of ‘low-LG-ABN’ mothers. Cross-fostering studies showed that the biological offspring of low-LG-ABN mothers reared by high-LG-ABN dams resembled the normal offspring of high-LG-ABN mothers (and vice versa). These findings suggested an epigenetic transmission of individual differences in stress reactivity across generations.

Weaver, et al. [30] showed that stress responses in the adult rat are set early in life by the quality of maternal care and are correlated with epigenetic effects on the hippocampal exon I of glucocorticoid receptor promoter. They found that the epigenetic effects were reversible in adult life if they infused the adult rats with l-methionine, a precursor of S-adenosyl methionine, which donates methyl groups for DNA methylation. The infusion reversed the effects of nerve growth factor-inducible protein-A binding to the exon I of glucocorticoid receptor promoter, glucocorticoid expression, and hypothalamic-pituitary-adrenal and behavioral responses to stress, showing that the effects of adverse childhood experiences are potentially reversible in adult life. Their conclusions, however, are important. They say, “Ultimately, we will need to contend with the reality that neural development, function and health are defined by social and eco-
nomic influences [71].” This is contrary to psychiatry’s implicit function of biological influences being primary, though in keeping with the data considered in this review.

2. METHODS

2.1. Patient Selection

Patients with diagnoses of chronic pain were invited to have a life story interview, conducted by a medical student, a resident physician, and sometimes, a faculty physician or nurse-practitioner. Each interview was approximately 1.5 to 2 hours long. Our Institutional Review Board approved the research project. Informed consent to participate was obtained from all subjects and the Declaration of Helsinki principles were followed. We complied with the guidelines of the International Committee of Medical Journal Editors (www.icmje.org) with regard to the patient’s consent for research and participation in a study.

2.2. Data Collection

A semi-structured interview guideline was developed as an adaptation of the Northwestern University Life Story Interview. That interview was developed in Evanston, Illinois, in the 1980s by Dan McAdams and has been widely used. We used a modification of the Northwestern University Life Story Interview, which we are calling the Maine Life Story Interview (available upon request). Our modification lowered the language level of the Northwestern instrument to a sixth-grade level and provided content more specific to Maine.

2.3. Data Analysis

We first calculated the ratio of females to males with the diagnosis of depression. We tabulated the frequency of diagnoses present in the sample by gender. Then we reviewed the life story to look at the context of the person’s life at the time their initial psychiatric diagnosis was made. We asked if the context was perceived as unresolvable by the person at that time, meaning they had no hope of finding a solution to their difficulties. We asked how people responded to these situations. What were their behavioral strategies for managing their hopeless situations? We asked if the concepts of internalizing and externalizing strategies could be used to classify people’s behavioral strategies and if there were gender differences in internalization and externalization.

We used a constructivist grounded theory approach [125-130] similar to what we have done in previous research [131]. Constructivist grounded theory methods involve iterative interaction of the research team with the data. Our process involved a continuing exploration of the transcript with team discussions of the concepts until we reached agreement on conclusions reached. Stage I, “coding,” involved (a) immersion into the data and multiple close “readings” (listening to audio recordings, reading the interview transcripts, and examining the field notes) and then (b) integrating this knowledge back into our preliminary broad coding scheme. During this stage of analysis, chunks of data, quotes, and keywords that were deemed important and relevant to the research question were highlighted and assigned a code. The list of codes was then continuously refined.

Stage II “coding to interpretation” began once the data had been coded (organized into various categories). At this point, the coded data were systematically explored to generate meaning by looking for patterns, themes, contrasts, contradictions, paradoxes, similarities, and differences.

3. RESULTS

We obtained life story interviews from 76 patients. Forty were women and thirty-six were men. All of the women had a diagnosis of depression in at least one or more of its various iterations. Twelve of the men had been diagnosed with depression. Nine of the men were diagnosed with bipolar disorder. Twelve of the men were diagnosed with ADHD. Four were diagnosed with impulse control disorder. Four were diagnosed with borderline personality disorder. Nine were diagnosed with antisocial personality disorder.

Twenty-six of the men were diagnosed with an anxiety disorder, and forty of the women. Twenty of the men had a variety of other diagnoses.

The male:female ratio for depression was 1:2.9.

We reviewed the transcripts, asking if people had experienced life circumstances about which they reported feeling hopeless. We identified those life circumstances and worked toward consensus in agreeing about the description of hopelessness. Then we asked how the people responded to these hopeless situations and classified their responses as internalizing or externalizing as discussed above.

When we conceptualized depression as a response to hopeless or unchangeable life circumstances with internalizing and externalizing types, our female to male ratio dropped to 1.16 to 1, which was not statistically significantly different. With this conceptualization, the number of men with depression rose from 12 to 31.

Some examples of hopeless situations include

1. Domestic violence with no perceived possibility for exit.
2. Addictions without hope for recovery.
3. Homelessness without perceived possibility for housing.
4. Poverty without hope for improvement.
5. Humiliating relationship with no easy exit.

Examples of externalizing strategies:

1. A 43-year-old man loses his job and can’t find another. He loses his house. His wife leaves him and moves back to her mother’s home with their children. His car is repossessed. He becomes homeless. He starts drinking heavily and gets into fights and gets arrested. He spends time in jail and gets discharged to the homeless shelter. He’s diagnosed with antisocial personality disorder. However, prior

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1Sadly our data is not available for independent analysis for it consists of participants’ life stories which contain identifying data from which they could be recognized.
to his extensive losses, he hadn’t engaged in any of these behaviors.

2. A 30-year-old male had a serious motor vehicle accident and lost his left lower leg amidst other injuries. After extensive rehabilitation, he was discharged. At home he became isolated, when winter came and he started driving his snowmobile recklessly. He comes to clinical attention again when he was re-admitted after an accident in which he ran into a tree. He was with diagnosed impulse control disorder.

3. A 22-year-old is admitted for septicemia from intravenous drug use. During hospitalization, it becomes apparent how hopeless he feels. He has been homeless since age 15, sometimes trading sex for housing, sometimes couch surfing, sometimes staying in a homeless shelter for adolescents, sometimes staying briefly with girlfriends, though his relationships rarely last long. His thoughts are disorganized, and occasionally he hears voices. He tells us about his indescribable pain. He has been diagnosed with an anxiety disorder, though he appears to have psychotic features. He has also been diagnosed with antisocial personality disorder, though this seems questionable, since he hasn’t actually engaged in any criminal activity besides buying heroin.

4. A 30-year-old male shoots himself in the face and survives. He has been previously diagnosed with attention deficit hyperactivity disorder, but not depression. His symptoms began after his wife and 2 children died in a house fire. Since then, he began drinking excessively, getting into fights in bars, driving his snowmobile recklessly, driving his car at excessive speeds. Feeling completely hopeless with the idea that he has nothing for which to live, he shoots himself.

4. DISCUSSION

Epigenetics presents exciting opportunities for ending the nature vs. nurture debate. Life experience changes the expression of our genes (the phenotype). While ample evidence exists that the categories by which DSM diagnoses of depression are made are gender-biased, importantly also, women may be more often diagnosed with depression due to having been socialized to an internalizing strategy when faced with insurmountable life experiences. This tendency may be passed from generation to generation via epigenetic mechanisms. The social roles for men promote more externalizing strategies which match the DSM categories for other disorders, including antisocial personality disorder, intermittent explosive disorder, impulse control disorder, and bipolar disorder, type I, manic. While men may have experienced different socialization and lower status than men, all have suffered from impossible life circumstances. We suffer from the effects of the life experiences of our ancestors. Intergenerational trauma is real and supported by the evidence. When we help people live better lives today, we influence potentially future generations. Thus, recognizing that the genders have been socially directed to different strategies for managing impossible life circumstances and that these patterns are transmitted epigenetically can help us to better understand gender differences in mental health and reach toward the social circumstances and forces that create them. Thinking differently about male depression could help us to recognize and assist the men who are currently committing suicide but understanding that their externalizing behavior is a sex-role sanctioned way to express hopelessness and despair. Changing our culture to one that rejects poverty, sexual abuse, and either internalizing or externalizing strategies could do more for curing depression than pharmacological research.

Contemporary history-taking in medicine and psychiatry could also stand to be revised. Typical histories gloss over adverse childhood experiences, do not often inquire about physical and sexual abuse, and operate from classical genetic assumptions for conditions that are complex and epigenetic. An implicit assumption exists that genetic factors cannot be altered, whereas the reality is that epigenetic factors can be changed – even by diet, supplements, or corrective emotional experiences. An appreciation of epigenetics and a revision of our habits of thoughts about causes and treatment could eliminate sexual dimorphisms in depression, and potentially other mental health diagnoses.

CONCLUSIONS

Depression may be less gendered than we have previously believed. People respond to seemingly hopeless situations in socially sanctioned and taught ways. Women have been socialized to respond by internalizing strategies, which conventionally we identify as depression. Men have been socialized to externalize, which we have interpreted as conduct disorders, antisocial personality disorders, impulse control disorders, and even bipolar disorder. However, when we reconceptualize depression as a response to apparently hopeless situations with either internalizing or externalizing strategies, the gender difference disappears. We propose that this conceptualization is more respectful of the role of social factors in how people respond to the events of their lives and could also allow us to appreciate and recognize male depression early and to intervene sooner to reduce male suicide, which is currently much higher than female suicide, despite the greater incidence of depression among women in conventional conceptualizations.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Ethics Committee of Northern Light Eastern Maine Medical Center/ Clinical Research Center, (IRB: 15-1-M-295), Bangor, ME, USA.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The reported experiments were performed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Not applicable.
AVAILABILITY OF DATA AND MATERIALS

Sadly our data is not available for independent analysis for it consists of participants’ life stories which contain identifying data from which they could be recognized.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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