Review of General Psychology
2009, Vol. 13, No. 3, 194–201

1089-2680/09/$12.00 DOI: 10.1037/a0016301

Psychology and Epigenetics

Frank Masterpasqua
Widener University

The Human Genome Project mapped the complete DNA sequence that exists in each human cell, but questions remain about how genes are expressed. Epigenetics is defined as mechanisms of gene expression that can be maintained across cell divisions, and thus the life of the organism, without changing the DNA sequence. Recent research has identified important epigenetic mechanisms that play essential roles in normal and abnormal development. Of special significance for psychology are the findings that environmental and psychosocial factors can change the epigenome. Research also suggests that some experiences and epigenetic changes of an individual can be passed down to more than one generation of descendants. Linkages between epigenetics and psychopathology are emerging that point to new possibilities for conceptualizing, preventing, and treating disorders.

Keywords: genetics, heredity, development, psychopathology

The completion of the Human Genome Project in 2003 augured a new era in the understanding of the genetic bases of physiology and behavior. The project mapped the sequence of the approximately three billion pairs of molecules that form the rungs of the DNA double-helix, and identified the approximately 25,000 genes present in each human cell. The sequences that make up the genes constitute the blueprints for virtually all human biological functions (The Human Genome Project, 2008).

The Human Genome Project resulted in one of the greatest scientific accomplishments in history: complete description of the human genome. At the same time, and as is often the case with scientific breakthroughs, it raised at least as many questions as it answered. The most significant question is not a new one, and concerns the relationship between genotype and phenotype. How do genes express themselves to become anatomy, physiology, and behavior? The regulation of gene expression is multifaceted and complex; regulation can occur before DNA is transcribed to RNA, before RNA is translated into proteins, or after proteins have been formed. Some expression mechanisms stem directly from the DNA sequence itself, the most common of which is control of whether or not DNA is transcribed to RNA. In this process, regulatory sequences in the DNA interact with proteins called transcription factors that help to increase or decrease transfer of (transcribe) genetic information from DNA to RNA (Slack, 2001; Waggoner, 2007).

Recent biological research has also focused on another mechanism by which genes are expressed; one that does not depend on the sequence of molecules in the DNA code, and that can be maintained throughout the life of the organism. This mechanism of gene expression is called epigenetics, and it refers to changes in gene expression that remain relatively stable during cell division, and sometimes across generations, that are not dependent on the genetic code itself (Allis, Jenuwein, Reinberg, & Caparros, 2007).

Frank Masterpasqua, Widener University, Institute for Graduate Clinical Psychology.

Correspondence concerning this article should be addressed to Frank Masterpasqua, Institute for Graduate Clinical Psychology, One University Place, Widener University, Chester, PA 19013. E-mail: fmasterpasqua@widener.edu

Recent years have witnessed an explosion of interest in epigenetics across a wide range of disciplines; a PubMed search for "epigenetics" resulted in over 23,000 entries most of which were published in last 10 years. In addition, there is now a multisite "Human Epigenome Project" designed to map the epigenetic chemical markers that regulate gene expression during normal and abnormal development (Bradbury, 2003).

The implications of epigenetics for understanding biological as well as psychological development and disease are far-reaching. As we'll see, epigenetic researchers have discovered that the environment, both physical and social, can cause changes in molecular structures that mediate gene expression, and that, in some cases, these changes may be passed on to future generations. This "epigenetic inheritance" is a mechanism of heredity that may complement the process of random mutations that is central to traditional notions of evolutionary change. Epigenetic inheritance implies that experiences can be passed on to future generations via an epigenetic code (Harper, 2005). The purpose of this article is to review themes in recent epigenetic research that have relevance for psychological theory, research, and practice.

Defining Epigenetics

C. H. Waddington (1942) was the first to describe epigenetics. His definition was a general one, and included all of the processes that led from the genotype to its final product. This was the "epigenetic landscape" that represented the different trajectories that a genotype might take during its development.

More recently, developmental psychobiologists have offered a broad developmental systems approach to epigenetics and to the understanding of the complex role played by the environment in gene expression. This research has gone a long way toward acceptance of the idea that how genes are expressed is invariably influenced by the milieu in which they function (Gottlieb, Wahlsten, & Lickliter, 1998; Lickliter & Honeycutt, 2003). As discussed in this article "epigenetics" is consistent with the developmental systems perspective, but is restricted to cellular changes in DNA. Epigenetics here means changes in DNA, other than variations in DNA sequence, that are replicated during cell division

(Feinberg, 2008; Goldberg, Allis, & Bernstein, 2007; Gottesman & Hanson, 2005). It is the relative stability of epigenetic changes across cell divisions that best distinguishes epigenetics from other mechanisms of gene expression.

How Epigenetics Changes Gene Function

One way to begin to understand the mechanisms underlying epigenetics is to appreciate the "architecture" of the DNA double-helix situated inside the nucleus of a cell. If the DNA inside one cell of the human body was stretched out it would reach a length of about 6 feet; this means condensing 6 feet into a space observable only under a microscope (a 10,000-fold reduction in length). Chemically mediated changes in the structure and function of this highly compacted DNA play a major role in determining whether genes are switched on or off.

Figure 1 is a schematic of DNA structure and the two major epigenetic mechanisms. The 3 billion rungs that make up the ladder-like structure of the DNA double-helix are derived from four chemical bases: a (adenine), t (thymine), g (guanine), and c (cytosine). These 6-foot long strands of DNA are compacted into a cell by multiple wrappings around globular proteins called histones. A small strand of the DNA ladder, made up of 146 base-pairs, is spooled around a group of tightly packed histones. Each DNA-histone wrapping constitutes a nucleosome, and these nucleosomes are organized into chromatin, the building block of a chromosome. "Epigenetic changes in gene expression may occur via changes in the folding of the DNA to form chromatin and the

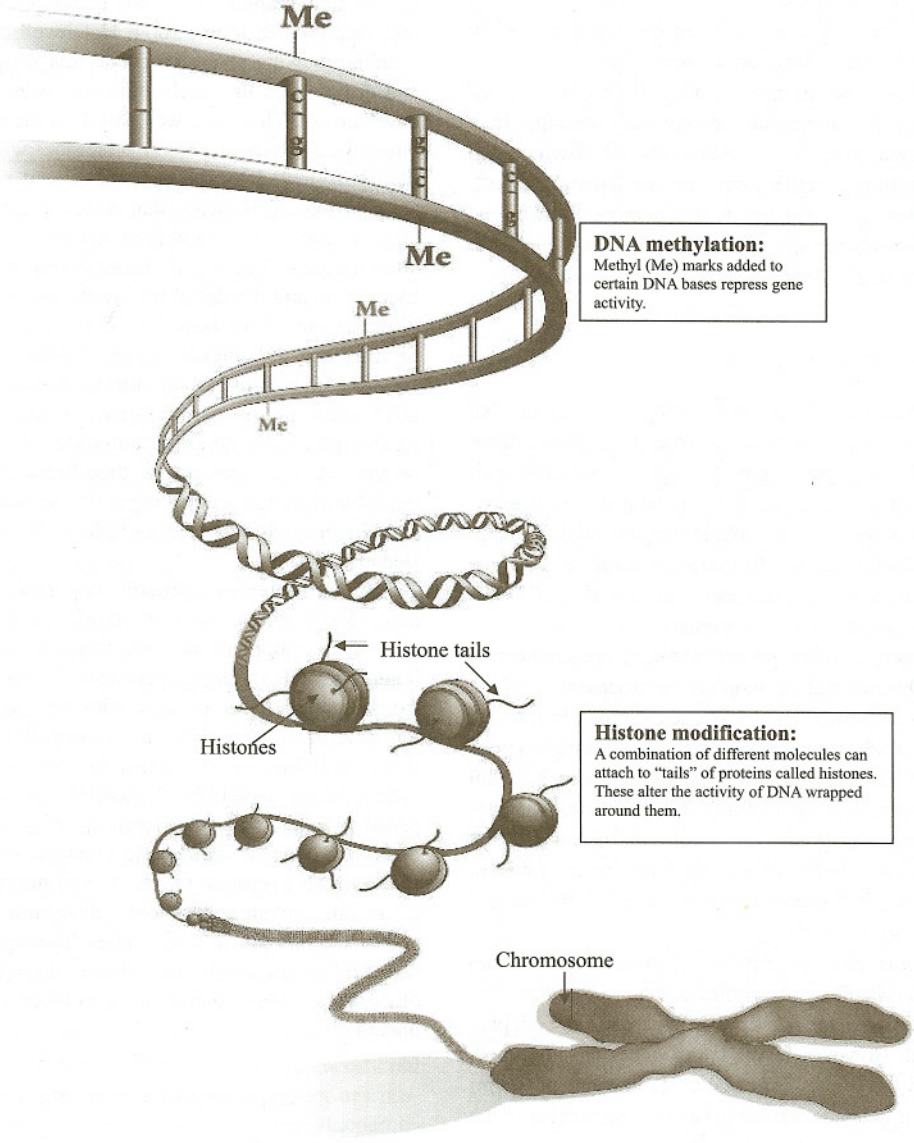

Figure 1. The two main components of the epigenetic code: DNA methylation and histone modification. Note: From "Unfinished Symphony" by J. Qiu, 2006, *Nature*, 441, p. 144. Copyright, 2006 by Macmillan Publishers Ltd. Adapted with permission.

architecture of that chromatin within the nucleus" (van Vliet, Oates, & Whitelaw, 2007, p. 1531). Depending on these epigenetic changes, parts of the highly compacted DNA will be either accessible or inaccessible to the machinery that transcribes genes into the messenger RNA that leads to protein synthesis. Accessible genes will be transcribed and active; inaccessible genes will be silenced (Szyf, McGowan, & Meaney, 2008).

Figure 1 depicts the two main mechanisms by which genes are made accessible or inaccessible for transcription: DNA methylation and histone modifications (although other mechanisms are being discovered). These mechanisms tend to interact and stabilize each other and thus maintain a relatively steady, yet modifiable, epigenome throughout the life of the organism (van Vliet et al., 2007). In mammals DNA methylation occurs when a methyl molecule attaches to cytosines within cytosine-guanine (abbreviated as CpG) base pairs. Genes are silenced (switched off) when cytosines are methylated, and are expressed (switched on) when cytosines are not methylated (Jirtle & Skinner, 2007).

The globular histone proteins around which DNA is wrapped have "tails" extending from them that are especially susceptible to more than 100 different chemical modifications, all of which can play a role in determining whether genes are switched on or off. These histone modifications form a code that is recognized by the regulatory proteins that change chromatin structure, and thus gene expression (van Vliet et al., 2007).

Epigenetics in Normal Development

All the cells of an individual human contain the same genome, but nevertheless differentiate into particular cell types (e.g., liver cells or neurons). A liver cell, for example, goes through thousands of divisions over the course of a lifetime and yet maintains its cell identity. Epigenetic changes play an important role in normal cell differentiation by determining which genes will be turned on or off for each type of tissue. These epigenetic blueprints, specific to each kind of tissue, are laid down during development of the embryo.

In addition to helping to maintain cell identity, epigenetic factors play a role in other normal developmental processes. X-chromosome inactivation in human females is one example. In females one of the 23 pairs of chromosomes is designated XX, whereas male humans have XY. X-chromosome inactivation occurs when one of the X chromosomes of the female's XX pair is "downregulated" to match the levels of gene expression seen in males. DNA methylation and histone modifications play significant roles in ensuring that genes on this X chromosome are silenced (Brockdorf & Turner, 2007; Richards, 2006).

Genomic imprinting is another normal developmental process mediated by epigenetic mechanisms. According to classic genetics, children inherit two copies of a gene, one from each parent, and both play a role in development. However, about 1% of genes are imprinted, meaning that one of the copies is silenced during egg or sperm formation by epigenetic changes derived from either the mother or the father. This silencing of one allele makes genomic imprinting especially susceptible to abnormal genetic expression. Again, DNA methylation and histone modifications play essential roles in silencing the imprinted gene (Barlow & Bartolomei, 2007).

Epigenetics and Disease

"Just as epigenetic change is at the heart of normal development, so also do disruptions in epigenetic modification disturb normal developmental programs" (Feinberg, 2008, p. 1348). The first disease to be linked to epigenetic changes was cancer, and the epigenetic-cancer connection is now widely accepted (Feinberg, 2007). Rodenheiser and Mann (2006) identified 26 different forms of cancer associated with either hypermethylation or hypomethylation of DNA. In general, hypermethylation results in the condensation of chromatin and the silencing of tumor suppressor and other genes. Hypomethylation results in instability of the chromosome, and activates oncogenes and transposons (transposons are sequences of DNA that can move to different positions within the genome). A large number of other diseases, including psychological disorders, have been linked to epigenetic abnormalities, and epigenetic therapies are already being investigated (Egger, Gangning, Aparicio, & Jones, 2004; Hatchwell & Greally, 2007).

Initial thinking about the connection between epigenetic changes and disease was that such influences were restricted to embryonic development. This view was based on the fact that before implantation the embryonic genome undergoes widespread DNA demethylation followed by the reestablishment of the genomic methylation pattern. This means that embryogenesis is especially vulnerable to epigenetic modifications that can lead to congenital abnormalities (Dolinoy & Jirtle, 2008). As examples, Angelman Syndrome and Prader-Willi Syndrome are neurodevelopmental disorders that have been linked to disturbances in genomic imprinting and the epigenetic modifications that cause them. Interestingly, both disorders are attributable to the same silencing of a DNA sequence on chromosome 15 but result in quite different phenotypes. If the abnormal imprinting (via DNA methylation) is on the paternal chromosome then Prader-Willi syndrome occurs, but if the abnormal imprinting is on the maternal chromosome then Angelman syndrome emerges (Isles & Wilkinson, 2008; Zoghbi & Beaudet, 2007).

Although epigenetic patterns seem especially susceptible during early development, there is growing evidence that they change later in development as well. Fraga et al. (2005) reported on a landmark study of the epigenome of 80 monozygotic twins ranging from 3 to 74 years of age. Although monozygotic twins have identical genotypes, they are discordant for a number of phenotypes, including the emergence of some major psychological disorders. While a number of possible explanations have been proposed to explain these differences, Fraga et al. (2005) sought to determine whether epigenetic changes might play a role. They found that 50-year-old twins showed major differences on assays of overall content and genomic distribution of DNA methylation and histone modifications, whereas the assays of 3-year-old twins were indistinguishable. In addition, the epigenetic differences of older twins were related to a number of differences in their phenotypes.

Experience Changes the Epigenome

Fraga et al. (2005) found that epigenetic changes accumulate across the life span and play an important part in programming the genome. Recent research is beginning to identify environmental factors that lead to these changes; nutritional supplements, low

dose radiation, foreign chemicals, and early parenting have been shown to change epigenetic patterns, and thereby genetic expression (Jirtle & Skinner, 2007; Szyf et al., 2008).

Waterland and Jirtle (2003) and Wolff, Kodell, Moore, and Cooney (1998) showed how changes in mice mothers' diets during pregnancy can change the epigenome and phenotype of their offspring. Agouti mice are given their name because of the activity of the agouti gene that causes them to be overweight, to have yellow coats, and to be susceptible to diabetes and cancer. Waterland and Jirtle gave pregnant agouti mothers a diet rich in methyl donors (folic acid, vitamin B12, choline. and betaine); food supplements often given to pregnant human mothers. Offspring of diet-enriched mothers had brown coats, were not overweight, and were no longer as susceptible to diseases of their parents. Moreover, the mechanism was epigenetic: these offspring showed increased methylation, and thus decreased expression, of the agouti gene.

The Caregiving Environment Affects the Epigenome in Rodents

Waterland & Jirtle's (2003) work demonstrated that chemical changes (via diet) during the formative gestational period can change the epigenome and phenotypic characteristics. However, can the epigenome and phenotype be changed after the epigenetic patterns have been laid down, and by psychosocial factors such as the caregiving environment? Recent research suggests that the answer is yes.

The early caregiving environment has long held a central place in our understanding of normal and abnormal psychological development (Bowlby, 1965; Schore, 2003). Early abuse or neglect can lead to a wide range of cognitive and emotional impairments, and there is considerable evidence that early maltreatment affects the same neural structures that mediate attachment (Roth, Levenson, Sullivan, & Sweatt, 2006). Animal models now suggest that the influence of early caregiving penetrates to DNA.

Szyf et al. (2008) reported on a series of studies comparing the differences in behavior, physiology, and epigenetics in rat pups reared by either high licking/grooming (high LG) or low lick/grooming (low LG) mothers. High LG in early development had a positive and enduring impact on the reactivity of the hypothalamic-pituitary-adrenal axis (HPA). HPA reactivity has been implicated in a number of psychological disorders (Roth et al., 2006). Adult offspring who received high amounts of licking and grooming during the first week of life showed lowered plasma adrenocorticotropin hormone (ACTH) and corticosterone responses to stress when compared with offspring who received low amounts of licking and grooming. Moreover, cross-fostering offspring of high LG mothers to low LG mothers, and vice versa, revealed that early maternal caregiving, not the genotype of the mother, determined reactivity to stress.

The decrease in HPA reactivity to stress in high LG offspring is traceable to increases in the number and density of glucocorticoid receptors in the hippocampus. Glucocorticoid receptors are proteins present in cells that are sensitive to circulating glucocorticoids. An increase in glucocorticoid receptor expression in the hippocampus reduces the amount of ACTH-releasing hormone in the hypothalamus that in turn results in less ACTH from the pituitary and thus less cortisol from the adrenal glands. The increase in glucocorticoid receptor expression in the hippocampus of high LG offspring is directly linked to changes in DNA methylation patterns in the hippocampus. It is now known that high licking/grooming leads to decreased methylation that allows greater access and transcription at glucocorticoid receptor genes in the hippocampus (Meaney & Szyf, 2006; Weaver, 2007).

Champagne et al. (2006) found that the variations observed in the maternal care of mice can be passed on to the next generation of mothers. Female offspring who received high LG became high LG mothers themselves, whereas those who received low LG became low LG mothers. The mechanism for this consistency of caregiving across a generation appears to be epigenetic. Offspring raised by high LG mothers showed higher expression of an estrogen receptor gene in the medial preoptic area of the hypothalamus, a gene and region of the brain known to be associated with maternal care. Expression of this gene was associated with changes in DNA methylation on this estrogen receptor gene.

The epigenetic and HPA changes attributable to early maternal behavior are relatively stable, yet reversible. For example, Weaver et al. (2004) injected the brains of adult offspring of low HG mothers with an agent known to reduce methylation. The injections not only decreased DNA methylation to levels indistinguishable from high LG offspring, but also reduced responsivity to stress to match that of high LG offspring. Conversely, Weaver et al. (2005) injected adult offspring of high LG mothers with an agent known to increase methylation and found changes in methylation and responsivity that matched adult offspring of low HG mothers.

Early Caregiving and Epigenetics in Humans

Recent research suggests that early caregiving may result in epigenetically induced changes in physiology and behavior in humans, as well as rodents. The effects of early psychosocial, albeit prenatal, factors on epigenetics and HPA reactivity were recently observed in human infants. Oberlander et al. (2008) followed infants born to mothers who, during the third trimester of pregnancy, were: (a) being treated for depression using serotonin reuptake inhibitors, (b) not being treated for their depression, or (c) not showing symptoms of depression. Controlling for postnatal age and postnatal mood, the authors concluded that the effects of depression during pregnancy appear to have been epigenetically transmitted to infants. Prenatal exposure to depressed/anxious mood resulted in increased DNA methylation at the glucocorticoid receptor gene. Moreover, prenatal exposure to negative mood, and increased methylation were associated with increased HPA reactivity as assessed by salivary cortisol stress responses at 3 months of age.

McGowan et al. (2009) recently reported on a study that clarifies how epigenetics may mediate the long-term effects of child maltreatment. Postmortem examinations were performed on the hippocampuses of three groups: suicide victims who had a history of child abuse, suicide victims who did not have history of child abuse, and controls who died suddenly from causes other than suicide and who had no history of child abuse. Compared to the suicide-only and control groups, victims of suicide who had experienced child abuse had decreased levels of glucocorticoid receptor expression, as well as increased levels of methylation specific to the gene known to regulate glucocorticoid expression.

McGowan et al. concluded: "These findings translate previous results from rats to humans and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression" (p. 342). As described earlier, glucocorticoid receptor expression in the hippocampus is known to influence HPA reactivity that, in turn, has been implicated in a number of psychological disorders (Roth et al., 2006).

Epigenetic Inheritance Across Multiple Generations

Thus far, we have seen evidence that prenatal and postnatal environments can change epigenetic patterns and consequently the health and behavior of the first generation of offspring. However, perhaps the most intriguing finding to come from recent epigenetic research is the discovery that some environmentally induced epigenetic changes can be maintained beyond the first generation, even when original environmental conditions have changed (Harper, 2005). This means that epigenetic patterns not only play a role in cell division and differentiation in one generation (through mitosis), but can also affect the germ cells (through meiosis) that produce gametes.

For instance, Anway, Cupp, Uzumcu, and Skinner (2005) exposed pregnant rats to endocrine disruptors (chemicals that were either antiandrogenic or estrogenic) during the period of gestation in which gonadal sex determination occurs. As might be predicted from the previous discussion, the male offspring of these mothers (the first generation) showed decreased spermatogenic capacity and increased male infertility. However, in addition these changes were seen in nearly all males down to the fourth generation, and were associated with altered patterns of DNA methylation in the germ cells.

Epigenetic changes also seem to be involved in mating preferences that extend across generations. Crews et al. (2007) found that when pregnant rats were injected with an antiandrogenic chemical "females three generations removed from the exposure discriminate and prefer males who do not have a history of exposure" and conclude: "our observations provide direct experimental evidence for a role of epigenetics as a determinant factor in evolution" (p. 1542).

The effects of early caregiving can also extend across more than one generation, although these transgenerational effects have yet to be shown to be epigenetic. Working with mice, Curley, Champagne, Bateson, and Keverne (2008) found that impaired maternal care during early development led to increased fear of new situations and decreased exploratory behavior in both the first and second generations of female progeny. Because of the breeding design of the study the authors were able to conclude that these transgenerational influences were not a result of genetic mutations. As with the Anway et al. (2005) study showing the consistency of epigenetic changes across generations, the transgenerational effects of early caregiving may also be mediated by epigenetic markers passed through the germline. However, without evidence for these markers, and without controlling for the possible intergenerational similarities in the early caregiving environment, it is not possible to conclude that epigenetic mechanisms were at work.

The epigenetic effects of early caregiving appear to be reversible. Champagne and Meaney (2007) found that the postweaning environment of female rat offspring reversed the effects of their immediate postnatal environment on exploratory behavior, and licking and grooming behavior. When the postweaning environment was enriched, the negative effects of poor postnatal treatment were mitigated. Conversely, when positive postnatal rearing was followed by deprived postweaning conditions, the salutary effects of early positive rearing were reversed. As with postnatal effects, these changes resulting from postweaning environments were passed on to the second generation of female progeny. Results such as these indicate that early social experiences are both transferable across generations, and remediable. Once again, although the phenotypic similarities across generations appear to be mediated by common caregiving experiences, as of yet there is no evidence for associated epigenetic markers passed down the germline.

Experience and Multigenerational Effects in Humans

The evidence from animal studies indicates that epigenetic effects because of diet and chemical exposure can be transmitted across more than one generation. Because of obvious ethical restrictions, conclusions about the role of epigenetic inheritance on human descendants are of necessity based on the results of longitudinal and correlational research rather than on controlled designs. Nevertheless, in some cases the data are compelling.

In a series of classic epidemiological studies, Susser, Hoek, and Brown (1998) reported on the effects of famine in the Netherlands during World War II on subsequent generations. Because of a Nazi-imposed food embargo toward the end of the war over 20,000 Dutch citizens died of starvation. Detailed records collected during and after the "Dutch Hunger Winter" have enabled researchers to identify the long-term effects of prenatal exposure to famine. Compared to offspring who were not exposed to prenatal famine, the exposed cohort showed higher rates of a wide range of childhood and adult disorders including low birth weight, infant mortality, obesity, diabetes, coronary heart disease, and cancer. Results also showed increased rates of schizophrenia and diagnoses of schizoid personality disorder in the exposed group. Moreover, the grandchildren of the women who experienced famine also showed below normal birth weights (Lumey & Stein, 1997).

Using harvest and food price records, Kaati, Bygren, and Edvinsson (2002) and Pembrey et al. (2006) analyzed the amount of food available to cohorts born in 1890, 1905, and 1920 in a small town in northernmost Sweden. Results indicated that changes in food supply for one generation may have effects on mortality spanning two generations. More specifically, they found significant associations between grandparents' food supply and grandchildren's longevity, and death because of cardiovascular disease or diabetes. These results were sex-specific: paternal grandfathers' food supplies were linked only to the mortality rates of their grandsons, whereas mortality rates of granddaughters were linked only to the food supplies of their paternal grandmothers. The authors concluded: "Our findings add a new, multigenerational dimension to the interplay between inheritance and environment in health and development; they provide proof of principle that sex-specific, male-line transgenerational effects exist in humans" (Pembrey et al., 2006, p. 164).

Lamarckism and Epigenetic Inheritance

To summarize, controlled animal studies provide persuasive evidence for the impact of some environmental effects on epigenetic markers across more than one generation (Anway et al.,

2005; Crews et al., 2007). Historical human studies, although far from definitive, offer the suggestion that humans too may be influenced by the experiences of their ancestors. The idea that organisms are genetically affected by the experiences of their ancestors runs counter to a major tenet of the "modern synthesis" of evolutionary genetics: that is, genetic variation is due solely to random mutations in the DNA sequence (Richards, 2006). The modern synthesis was contrasted with the ideas of Jean-Baptiste Lamarck, a pre-Darwinian theorist who proposed that individuals could pass on acquired characteristics to their descendants. Lamarck suggested that use or disuse of an organ or appendage would lead to its strengthening or atrophy in an individual. In turn, the descendants of that individual would acquire that strengthened or weakened characteristic. Lamarckism was discredited largely because of the absence of a mechanism to explain it, but epigenetics offers a molecular mechanism for a less extreme variation of Lamarckism called "soft inheritance" (Richards, 2006). Reports of epigenetic inheritance described earlier provide evidence for a soft inheritance that complements inheritance because of random mutation, and allows for more rapid adaptations to environmental circumstances.

Are there particular kinds of environments that are more likely to lead to epigenetic inheritance? Jablonka and Lamb (1995) suggested that epigenetic inheritance is especially advantageous in environments in which traumatic events occur regularly but unpredictably across generations. Such events that are beyond the individual's control would be especially conducive to epigenetic inheritance. Harper (2005) identified famine and conquest (repression) as common phenomena in human history for which epigenetic inheritance may provide an especially effective, yet reversible, form of adaptation. Indeed, both animal (e.g., Zamenhof, van Marthens, & Grauel, 1971) and human (e.g., Lumey & Stein, 1997) studies implicate famine as an epigenetic factor in transgenerational birth weight and behavior. Similarly, animal studies have shown that the effects of restrictive social environments can be passed down across at least one generation, and can lead to inhibited response style (Szyf et al., 2008).

Epigenetics and Psychological Disorders: Depression and Schizophrenia

A number of recent reviews have emerged describing the linkage of psychological disorders to epigenetic changes (e.g., Isles & Wilkinson, 2008; Mill & Petronis, 2007; Stuffrein-Roberts, Joyce, & Kennedy, 2008; Tsankova, Renthal, Kumar, & Nestler, 2007). Each review points to the considerable potential of epigenetics in helping us to better understand, prevent, and treat psychological disorders. On the other hand, they note that the field is clearly in its infancy, with most of the data coming from animal models or correlational studies with humans.

With regard to complex disorders such as major depression and schizophrenia, Mill and Petronis (2007) point out that the results of epigenetic studies lead inevitably to a novel perspective concerning the relative etiological contributions of genes and environment. Given that the epigenetic patterns that control gene expression can be influenced by wide range of random as well as hormonal and psychosocial factors, the epigenetic perspective requires that we attend to salient environmental factors that can change the epigenome. One example described earlier is the influence that early caregiving can have on DNA methylation patterns, glucocorticoid receptors, and reactivity of the HPA axis (Szyf et al., 2008). HPA reactivity has been implicated in the etiology of both mood and anxiety disorders (Roth et al., 2006).

Berton et al. (2006) described an animal model of depression mediated by brain-derived neurotrophic factor (BDNF). (BDNF is a protein that sustains and nourishes neurons, and has been found to be at abnormally low levels in humans with depression.) Berton et al. exposed adult mice to chronic social defeat stress which led to submissive and anxious behaviors as well as social avoidance; behaviors that mimicked anxiety and depression in humans. It was subsequently found that these mice had abnormally low levels of BDNF in the hippocampus, and that these low levels were attributable to histone changes on the BDNF gene that blocked BDNF production. Just as importantly, treating the mice with the antidepressant imipramine increased BDNF production, and reversed epigenetic patterns at the BDNF gene.

After reviewing the BDNF stress studies and those linking early caregiving to the HPA axis, Tsankova et al. (2007) concluded:

> Together, these studies indicate that several epigenetic modifications . . . . . are important in animal models of stress, depression and antidepressant treatment. However, this work has so far focused only on BDNF and GR genes, and only on the hippocampus. Work is now needed to investigate other brain regions that have been implicated in depression and its treatment, and to investigate the involvement of additional genes in mediating long-term effects of stress and antidepressant treatments on gene transcription (pp. 362).

Poulter et al. (2008) recently reported on depression research that focused on other areas of the brain. Comparing the brains of persons who had suffered from major depressive disorder and committed suicide with those who had died suddenly from causes other than suicide, their results implicated hypermethylation in the frontopolar cortex as a mediator of major depression followed by suicide. "These data are consistent with the hypothesis that DNA methylation aberrations may be an underlying cause of major depressive disorder and suicide and may open new strategies for its therapeutic management" (p. 651).

Most of the epigenetic research on schizophrenia has focused on the protein reelin. Reelin is expressed during development, is important in the formulation and modulation of neuronal connections, and is found in adult neurons containing GABA (Tsankova et al., 2007). GABA is the major inhibitory neurotransmitter in the central nervous system. Postmortem studies have found significantly reduced concentrations of reelin in the brains of persons who suffered from schizophrenia (Torrey et al., 2005). The reduced concentrations of reelin in the brains of schizophrenic patients appear to be attributable to DNA hypermethylation on the reelin gene. One hypothesis is that the reduction of reelin in GABA-containing neurons causes disruption in neuronal circuits that are mediated by GABA that in turn disturbs higher brain functions (Tsankova et al., 2007).

Mill et al. (2008) recently reported on a comprehensive epigenomic study of major psychosis using DNA obtained from the frontal cortices of schizophrenic and bipolar patients, and a matched control group. The authors were able to conclude: "Our data are consistent with the epigenetic theory of major psychosis and suggest that DNA-methylation changes are important to the etiology of schizophrenia and bipolar disorder" (p. 696).

These results connecting epigenetic changes to psychopathology beg the question: What kinds of environmental factors might induce the epigenetic changes that lead to psychopathology? Noting the association between schizophrenia and child abuse, Roth et al. (2006) speculate that severe trauma in early development might lead to epigenetic changes that increase predisposition to schizophrenia. There is an irony about these findings with special relevance for psychologists; that is, recent advances in the understanding of genetic/molecular mechanisms underlying psychological disorders require an enhanced appreciation for the role of environmental and psychosocial experiences.

Summary and Implications

There is now substantial research demonstrating that alterations in the epigenetic patterns surrounding DNA play an essential role in normal development, as well as in the etiology of a number of diseases. These patterns are dynamic within the life span of the individual, may be influenced by experience, and, in some instances, may be transferred to subsequent generations. In addition to prenatal chemical and dietary influences, early caregiving can have long-term effects on epigenetic markers, neurophysiology, and behavior in offspring. While epigenetic inheritance across more than one generation has been observed in mice exposed to prenatal chemical and nutritional changes, the evidence for transgenerational effects in humans, although suggestive, has yet to be corroborated by controlled studies. Nevertheless, these results suggest that the consequences of an individual's lifestyle may extend beyond their own mortality to include their descendants.

The research on epigenetic factors in psychopathology is promising but preliminary. It suggests that we may need to reconceptualize the etiology of some disorders, even those, such as schizophrenia, believed to have strong genetic components. An important goal for future research is to identify those experiences that can change epigenetic patterns that underlie psychopathology. As more is learned about how the environment affects epigenetic patterns related to psychopathology, prevention efforts will focus on identifying and avoiding pathogenic experiences.

Research has already shown that the epigenetic consequences of inadequate early caregiving in mice can be erased using pharmacological interventions (Weaver et al., 2004). Future pharmacological therapies may focus on erasing epigenetic patterns. For instance, Higgins (2008) recently predicted that a methylation antagonist blocker might serve to reduce the impact of posttraumatic stress disorder.

Finally, research with animals demonstrating that epigenetic patterns established early in life can be changed by subsequent psychosocial experiences (Champagne & Meaney, 2007) implies that meaningful psychotherapy may have an impact beyond behavior and personality to include how genes are expressed. Future psychotherapy research may focus not only psychological outcomes, but also on the epigenetic changes that mediate them.

References

Allis, C. D., Jenuwein, T., Reinberg, D., & Caparros, M. (Eds.). (2007). *Epigenetics.* Cold Spring Harbor, NY: Cold Spring Harbor Laboratory.

Anway, M. D., Cupp, A. S., Uzumcu, M., & Skinner, M. K. (2005). Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science, 308,* 1466–1469.

Barlow, D. P., & Bartolomei, M. S. (2007). Genomic imprinting in mammals. In C. D. Allis, T. Jenuwein, D. Reinberg, & M. Caparros (Eds.), *Epigenetics* (pp. 357–375). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory.

Berton, O., McClung, C. A., DiLeone, R. J., Krishnan, V., Rentahl, W., & Russo, S. J. (2006). Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science, 311,* 864–868.

Bowlby, J. (1965). *Attachment.* New York: Basic Books.

Bradbury, J. (2003). Human epigenome project-Up and running. *PLoS Biology, 1,* e82.

Brockdorf, N., & Turner, B. M. (2007). Dosage compensation in mammals. In C. D. Allis, T. Jenuwein, D. Reinberg, & M. Caparros (Eds.), *Epigenetics* (pp. 322–340). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory.

Champagne, F. A., & Meaney, M. J. (2007). Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. *Behavioral Neuroscience, 121,* 1353–1363.

Champagne, F. A., Weaver, I. C., Diorio, J., Dymov, S., Szyf, M., & Meaney, M. J. (2006). Maternal care associated with methylation of the estrogen receptor-alpha 1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. *Endocrinology, 147,* 2909–2915.

Crews, D., Gore, A. C., Hsu, T. S., Dangleben, N. L., Spinetta, M., Schallert, T., et al. (2007). Transgenerational epigenetic imprints on mate preference. *Proceedings of the National Academy of Sciences, USA, 104,* 5942–5946.

Curley, J. P., Champagne, F. A., Bateson, P., & Keverne, E. B. (2008). Transgenerational effects of impaired maternal care on behaviour of offspring and grandoffspring. *Animal Behaviour, 75,* 1551–1561.

Dolinoy, D. C., & Jirtle, R. L. (2008). Environmental epigenomics in human health and disease. *Environmental and Molecular Mutagenesis, 49,* 4–8.

Egger, G., Gangning, L., Aparicio, A., & Jones, P. A. (2004). Epigenetics in human disease and prospects for epigenetic therapy. *Nature, 429,* 457–463.

Feinberg, A. P. (2007). Phenotypic plasticity and the epigenetics of human disease. *Nature, 447,* 433–440.

Feinberg, A. P. (2008). Epigenetics at the center of modern medicine. *The Journal of the American Medical Association, 299,* 1345–1350.

Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., et al. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences, USA, 102,* 10604–10609.

Goldberg, A. D., Allis, C. D., & Bernstein, E. (2007). Epigenetics: A landscape takes shape. *Cell, 128,* 635–638.

Gottesman, I. I., & Hanson, D. R. (2005). Human development: Biological and genetic processes. *Annual Review of Psychology, 56,* 271–286.

Gottlieb, G., Wahlsten, D., & Lickliter, R. (1998). The significance of biology for human development: A developmental psychobiological systems view. In W. Damon (Series Ed.) & R. M. Lerner (Vol. Ed.), *Handbook of child psychology: Vol. 1. Theoretical models of human development* (5th ed., pp. 233–273). New York: Wiley.

Harper, L. V. (2005). Epigenetic inheritance and the intergenerational transfer of experience. *Psychological Bulletin, 131,* 340–360.

Hatchwell, E., & Greally, J. M. (2007). The potential role of epigenomic dysregulation in complex human disease. *Trends in Genetics, 23,* 588–595.

Higgins, E. S. (2008). The new genetics of mental illness. *Scientific American Mind,* 41–47.

Isles, A. R., & Wilkinson, L. S. (2008). Epigenetics: What is it and why is it important to mental disease? *British Medical Bulletin, 85,* 35–45.

Jablonka, E., & Lamb, M. J. (1995). *Epigenetic inheritance and evolution.* Oxford, England: Oxford University Press.

Jirtle, R. L., & Skinner, M. L. (2007). Environmental epigenomics and disease susceptibility. *Nature Reviews Genetics, 8,* 253–262.

Kaati, G., Bygren, L. O., & Edvinsson, S. (2002). Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. *European Journal of Human Genetics, 10,* 682–688.

Lickliter, R., & Honeycutt, H. (2003). Developmental dynamics: Toward a biologically plausible evolutionary psychology. *Psychological Bulletin, 129,* 819–835.

Lumey, L. H., & Stein, A. D. (1997). Offspring birth weights after maternal intrauterine undernutrition: A comparison within sibships. *American Journal of Epidemiology, 146,* 810–819.

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., et al. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with child abuse. *Nature Neuroscience, 12,* 342–348.

Meaney, M. J., & Szyf, M. (2006). Maternal care as a model for experience-dependent chromatin plasticity? *Trends in Neuroscience, 28,* 456–463.

Mill, J., & Petronis, A. (2007). Molecular studies of major depressive disorder: The epigenetic perspective. *Molecular Psychiatry, 12,* 799–814.

Mill, J., Tang, T., Kaminsky, Z., Khare, T., Yazdanpanah, S., Bouchard, L., et al. (2008). Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. *The American Journal of Human Genetics, 82,* 696–711.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics, 3,* 97–106.

Pembrey, M. E., Bygren, L. O., Kaati, G., Edvinsson, S., Northstone, K., Sjostrom, M., et al. (2006). Sex-specific, male-line transgenerational responses in humans. *European Journal of Human Genetics, 14,* 159–166.

Poulter, M. O., Du, L., Weaver, I. C. G., Palkovits, M., Faludi, G., Merali, Z., et al. (2008). GABAA receptor promoter hypermethylation in suicide brain: Implications for the involvement of epigenetic processes. *Biological Psychiatry, 64,* 645–652.

Richards, E. J. (2006). Inherited epigenetic variation: Revisiting soft inheritance. *Nature Reviews Genetics, 7,* 395–401.

Rodenheiser, D., & Mann, M. (2006). Epigenetics and human disease: Translating basic biology into clinical applications. *Canadian Medical Association Journal, 174,* 341–348.

Roth, T. L., Levenson, J. M., Sullivan, R. M., & Sweatt, J. D. (2006). Epigenetic marking of the genome by early experiences: Implications for long-lasting effects of early maltreatment on adult cognitive and emotional health. In S. M. Sturt (Ed.), *Child abuse: New research* (pp. 79–114). New York: Nova Science Publishers.

Schore, A. N. (2003). *Affect dysregulation and disorders of the self.* New York: Norton.

Slack, J. (2001). *Essential developmental biology.* London: Blackwell Science.

Stuffrein-Roberts, S., Joyce, P. R., & Kennedy, M. A. (2008). Role of epigenetics in mental disorders. *Australian and New Zealand Journal of Psychiatry, 42,* 97–107.

Susser, E., Hoek, H. W., & Brown, A. (1998). Neurodevelopmental disorders after prenatal famine: The story of the Dutch famine study. *American Journal of Epidemiology, 147,* 213–216.

Szyf, M., McGowan, P., & Meaney, M. J. (2008). The social environment and the epigenome. *Environmental and Molecular Mutagenesis, 49,* 46–60.

The Human Genome Project. (2008). Retrieved June 5, 2008, from The Human Genome Project: http://www.genome.gov

Torrey, E., Barci, B., Webster, M., Bartko, J., Meador-Woodruff, J., & Knable, M. (2005). Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biological Psychiatry, 57,* 252–260.

Tsankova, N., Renthal, W., Kumar, A., & Nestler, E. J. (2007). Epigenetic regulation in psychiatric disorders. *Nature Reviews Neuroscience, 8,* 355–367.

van Vliet, N. A., Oates, N. A., & Whitelaw, E. (2007). Epigenetic mechanisms in the context of complex diseases. *Cellular and Molecular Life Sciences, 64,* 1531–1538.

Waddington, C. H. (1942). The epigenotype. *Endeavor, 1,* 18–20.

Waggoner, D. (2007). Mechanisms of disease: Epigenesis. *Seminars in Pediatric Neurology, 14,* 7–14.

Waterland, R., & Jirtle, R. (2003). Transposable elements: Targets for early nutritional effects on epigenetic regulation. *Mollecular and Cell Biology, 23,* 5293–5300.

Weaver, I. C., Cervoni, N., Champagne, F. A., D'Allesio, A. C., Sharma, S., Seckl, J. R., et al. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7,* 847–854.

Weaver, I. C., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., et al. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. *Journal of Neuroscience, 25,* 11045–11054.

Weaver, I. C. G. (2007). Epigenetic programming by maternal behavior and pharmacological intervention, nature versus nurture: Let's call the whole thing off. *Epigenetics, 2,* 22–28.

Wolff, G. L., Kodell, R. L., Moore, S. R., & Cooney, C. A. (1998). Maternal epigenetics and methyl supplements affect agouti mice expression in Avy/mice. *Federation of American Societies for Experimental Biology Journal, 12,* 949–957.

Zamenhof, S., van Marthens, E., & Grauel, L. (1971). DNA (cell number) in neonatal brain: Second generation (F2) alteration by maternal (F0) dietary protein restriction. *Science, 172,* 850–851.

Zoghbi, H. Y., & Beaudet, A. L. (2007). Epigenetics and human disease. In C. D. Allis, T. Jenuwein, D. Reinberg, & M. Caparros (Eds.), *Epigenetics* (pp. 435–456). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory.

Received November 20, 2008
Revision received January 29, 2009
Accepted February 8, 2009 ■