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Behavioral Genetics, Genetics, and Epigenetics

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Abstract and Keywords

When considering how "nature" and "nurture" contribute to development, psychologists often take the former to mean "influenced by genes." Traditionally, behavioral geneticists have used twin and adoption studies to assess the extent of genetic influence on various behaviors. Recently, the heritability statistics these studies generate have been criticized as meaningless, partly because biologists have established that genes cannot influence development independently of environmental factors; genetic and nongenetic factors always cooperate to build traits. This chapter considers genetic contributions to some psychological characteristics, thereby demonstrating what genes can and cannot do. New discoveries regarding the control of genes via epigenetic mechanisms are of interest to developmental psychologists because they have the potential to reveal how environments and genes interact, help us understand certain behavioral disorders, and illuminate normal psychological processes like learning and memory; in addition, they cast doubt on the neo-Darwinian dogma that ancestors' experiences cannot influence descendants' development. Advances in genetics have clarified how molecular factors contribute to psychological characteristics and indicated that all of our characteristics are influenced by developmental circumstances.

Keywords: development, nature–nurture, developmental systems, heredity, heritability, genes and behavior, epigenetics and behavior, epigenetic inheritance, gene-by-environment interactions

Key Points

1. In building traits during development, genes operate collaboratively with nongenetic biological factors (many of which are influenced by environmental factors). Therefore, neither biological, psychological, nor pathological characteristics can be accurately labeled "genetic" (i.e., genetically determined); genetic abnormalities do not even straightforwardly cause the symptoms of monogenic disorders like cystic fibrosis, Huntington's disease, or phenylketonuria. Nonetheless, the development of *all* of our characteristics is influenced by genes.
2. Understanding that phenotypes are built during development as genetic factors interact with nongenetic factors draws attention to the developmental processes that are actually responsible for the phenotypes and thereby highlights multiple points in the developmental system where interventions could be effective.
3. Genes do not exist in a coherent state in our bodies. Rather, unedited and ambiguous segments of DNA are cut, mixed, and recombined in a context-dependent way to produce temporary edited molecules that represent how genetic information is actually used.
4. Twin studies—and the heritability statistics they generate—cannot illuminate the extent to which genetic versus environmental factors contribute to the development of traits in individuals. Furthermore, in normal developmental circumstances, heritability estimates are not measures of how inheritable phenotypes are. Finally, because traits that are perfectly heritable in one context can be profoundly influenced by environmental factors in other contexts, heritability estimates do not reflect how easily a phenotype can be influenced by an environmental manipulation.
5. The heritability of a characteristic tells us about a population that has been studied, not about the characteristic itself. In part, this is because heritability estimates always reflect the amount of variation present in the environments of the population being studied.
6. Heritability estimates do not enable meaningful comparisons of (a) individuals to groups, (b) groups to other groups, or (c) traits to other traits. Furthermore, they do not enable functional interventions in development.
7. Environmental factors affect what genes do, either directly (as happens with immediate-early genes) or indirectly (as when, for example, environmental events influence hormone concentrations that in turn influence gene expression). Thus, genes are better thought of as reactive than as agentic.
8. Genetic and epigenetic research is illuminating the operation of normal psychological functions such as learning and memory, as well as the origins of some behavioral disorders. Pharmacological interventions that target epigenetic marks have already been found able to improve memory in mice.
9. Studies that have found statistical interactions between genes and developmental experiences (e.g., Caspi et al., 2002, 2003) have not typically studied the actual causal–mechanical interplay known to characterize gene–environment interaction. Therefore, any future failures to find statistical interactions in these sorts of studies would not mean that genetic factors and environmental factors do not interact to produce the phenotypes in question.
10. A lifetime of experiences leaves epigenetic marks on our genomes, altering how—and even if—our genes are expressed. Because genes can be epigenetically upregulated or downregulated, what matters is not simply whether an individual has particular genes, but rather what that individual's genes are or are not being induced to do.
11. In rats, specific maternal behaviors directed toward newborn offspring have been found to epigenetically influence the offspring's stress

reactivity into adulthood; seemingly analogous phenomena have been reported in human populations. Certain drugs appear able to alter epigenetic states in rats in ways that eliminate the increased stress reactivity caused by exposure to these maternal behaviors; thus, epigenetic modifications produced by life experiences have proven to be experimentally reversible.

12. Epigenetic modifications acquired by at least some mammals during development can be transmitted to descendant generations. This discovery will force a rethinking of the neo-Darwinian concept of inheritance, as theorists work to construct a unified theory of phenotypes that encompasses both evolutionary and developmental phenomena.

Questions regarding the origins of our characteristics are the proper domain of developmentalists, and developmental psychologists have been motivated by these questions from the outset. As early as 1582, a teacher named Richard Mulcaster used the words “nature” and “nurture” when describing the factors that influence the development of children (West & King, 1987), but it was not until 1869 that Francis Galton conducted what many consider to be the first studies that attempted to address these questions scientifically (Plomin, 1994). Although the notion of “genes” had not yet appeared on the scientific stage, Galton’s conceptualization of the relationship between nature and nurture formed the theoretical foundations of the branch of psychology that ultimately came to be known as quantitative behavioral genetics, and as the twentieth century brought advances in molecular biology, the idea that some of our characteristics could be explained with reference to genes became dominant.

The modern field of behavioral genetics takes two decidedly different approaches to the study of how genes contribute to behavior. For most of the twentieth century, “behavioral genetics” was understood to be the branch of population genetics (one of biology’s subdisciplines) that was devoted to using population-genetics methods to explore how genes contribute to behaviors; this approach still characterizes a subdiscipline of psychology now known as *quantitative* behavioral genetics. In contrast, a newer approach to the study of how genes contribute to behavior, known as *molecular* behavioral genetics, has grown out of molecular biology, a branch of biology devoted to exploring the structure and function of biological molecules such as DNA. Because this chapter is focused on psychological/behavioral phenomena, the word “genetics” in the title can be taken to refer to molecular behavioral genetics, whereas the words “behavioral genetics” in the title—in keeping with the historical use of these words—can be taken to refer to quantitative behavioral genetics.

By the end of the twentieth century, a map of the genome of a human being had been published for the first time (see International Human Genome Sequencing Consortium, 2001; Venter et al., 2001). This remarkable achievement was accompanied by excited predictions about its ability to answer, at long last, questions about how genes contribute to the origins of our behavioral and other characteristics. Clearly, questions about the contributions of genes and experiences to trait origins continue to stimulate research across the biological and psychological sciences.

In retrospect, those who thought genetic factors might be uninvolved in the development of some of our characteristics were somewhat naïve, because all of the characteristics of complex animals—including both biological and behavioral characteristics—have to be built in development, and we now know that genes play essential roles in that process. However, even as the importance of genes has become clear, so has the fact that they never deterministically dictate the final forms of our characteristics (i.e., phenotypes). Phenotypes, including physical traits like the colors of our irises, or behavioral traits like introversion or the tendency to overindulge in alcohol, result from complex interactions between genetic and environmental factors, as well as between these types of factors and other biological (but nongenetic) factors (Gottlieb, 2007; Johnston & Edwards, 2002). Furthermore, these nongenetic biological factors are influenced by the actions of the genetic and environmental factors present in their local environments (Gottlieb, Wahlsten, & Lickliter, 1998; Lickliter & Honeycutt, 2010). Although we now understand that genetic factors must play important roles in the development of all of our characteristics (Ramus, 2006), we also know that they do not determine the development of any of them (Eisenberg, 2004; Gottlieb et al., 1998; Johnston, 2010; Lewkowicz, 2011; Lewontin, 2000; Lickliter, 2009; Michel & Moore, 1995; Moore, 2001; Noble, 2006).

The belief that interactions are always at the heart of the processes that build biological and behavioral characteristics is not new. In 1909, even as an inextricable link was being forged between the hypothetical “factors” that Gregor Mendel posited to explain the results of his famous pea plant studies and the “genes” we now think of as constituting DNA (Johannsen, 1911), Woltereck’s experiments established the fact that a given genotype can yield a variety of different phenotypes when development is allowed to proceed in varying environmental conditions (this is why predicting outcomes is impossible when a developing organism is facing novel environmental circumstances; see Gottlieb, 1995, Platt & Sanislow, 1988, or Sarkar, 1999, for additional information on Woltereck’s work and its implications). Likewise, in part as a reaction to the nativism inherent in the work of Konrad Lorenz in the first half of the twentieth century and in the provocative writings of quantitative behavioral geneticists and evolutionary psychologists in the latter half of that century, scientists such as Daniel Lehrman (1953) and Gilbert Gottlieb (1991a, 1997, 1998) wrote powerful defenses of the interactionist approach to understanding the developmental origins of phenotypes. In the past 25 years, a body of work has begun to define a perspective known as developmental systems theory, which has argued for the importance of understanding how traits emerge during development from the complex interactions of genetic and nongenetic factors on a variety of levels of analysis, from the molecular to the interpersonal (see Lickliter, this volume 1, for additional information).

As early as 1970, Gilbert Gottlieb was drawing attention to the fact that development is an epigenetic process (Gottlieb, 1970). That is, the final forms of our characteristics cannot be determined by factors that are present prior to development, or that operate independently of developmental processes. Rather, development is probabilistic, because it is influenced by physical events that take place in real time as development occurs and that are themselves probabilistic. As Gottlieb came to see it, behavioral (and other) characteristics *emerge* during development as a result of interactions that occur among factors operating at diverse levels of analysis, each of which is nested within the others. These levels include the level of the genes, the level of the chromatin, the level of the organelles within cells, and so on, up through the levels of the organs, bodies, and larger environmental contexts including homes, communities, and cultures. In models like this, functional interactions are understood to occur at the interfaces of these various levels. Because Gottlieb was particularly concerned with behavior, he thought of genetic activity as influencing neural activity, neural activity as influencing behavior, and behavior as influencing the physical, social, and cultural environments in which it occurs. Importantly, his conceptualization also explicitly represented the facts that the physical,social, and cultural environments influence behavior, that behavior influences neural activity, and that neural activity influences genetic activity (Gottlieb, 2007). Thus, although this conceptualization is at odds with the received view that genes influence development in a unidirectional manner—a portrait of genes in vogue since Francis Crick presented the world with the

"central dogma of molecular biology" in 1958—Gottlieb was confident that development entails the *coaction* of genetic and nongenetic factors that mutually influence one another (Gottlieb et al., 1998).

Gottlieb (2007) used the word "epigenetic" to describe developmental processes that involve genetic factors and myriad other, nongenetic factors that together constitute a single, complex developmental system. Thus, he believed that all biological and psychological development could be described as epigenetic, because all developmental processes entail the interactions of such factors. However, the prefix "epi-" literally means "on," "upon," or "over," so the word "epigenetic" evokes for many biologists and physicians images of factors that physically lie on top of the genes. For this reason, most working biologists today understand "epigenetic" to refer to the ways in which molecular factors such as DNA methylation patterns and histone modification patterns regulate gene expression across the lifespan (Brena, Huang, & Plass, 2006). The review below will explain in detail what these molecular factors are, how they work, and what roles they are now understood to play in development. For the moment, it is enough to note that it has become clear that some epigenetic factors literally perform their functions *on* the genes. Even so, because developmental systems theorists trained in fields as diverse as philosophy of science (Robert, 2008), genetics (Jablonka & Lamb, 2002, 2005), and developmental psychobiology (Gottlieb, 2007; Lickliter, 2008) have adopted a broader usage of the word "epigenetic," a thorough consideration of epigenetics would include discussion of how both molecular and nonmolecular factors influence psychological development (even if we currently do not understand how some of these factors have the influences they do). But given that the focus of this chapter is on current understandings of *molecular* contributions to behavior, epigenetic development construed more broadly will not be considered further here; interested readers can consult Jablonka and Lamb (2005, 2007) and other chapters in this volume (e.g., Lickliter) for additional information on this topic.

Because ideas develop over time as earlier conceptions are altered to fit new empirical observations, modern conceptualizations bear a family resemblance to older ideas; new ideas do not spring forth fully formed from a theorist's head like Athena from Zeus' but instead reflect earlier ways of thinking. Consequently, a consideration of what we currently know about genetic contributions to our characteristics will benefit from a consideration of how earlier generations of theorists conceived of genes and their effects. Given that the field of quantitative behavioral genetics has its intellectual roots in the pre-Mendelian era of Francis Galton, it will be helpful to briefly consider some of the history of ideas surrounding the emergence of twentieth-century conceptions of how "nature" (initially) and "genes" (subsequently) were thought to influence development. This history will be followed by a critical analysis of the sort of data that studies of quantitative behavioral genetics provide (i.e., heritability statistics). Likewise, because we came to understand aspects of genetics long before we understood anything about epigenetics, this chapter will continue with a primer on what we now know about genes' structures and functions. This will be followed by a consideration of how genetic factors contribute to the development of specific psychological/behavioral characteristics, and a consideration of what exactly genes are, how they actually work, and what they can and cannot do. The chapter will conclude with an introduction to emerging knowledge about epigenetics and a review of studies that have demonstrated both how behavior can influence gene expression via epigenetic processes and how the resultant epigenetic effects can be detected in descendant generations.

Behavioral Genetics

The Roots of Behavioral Genetics

Sir Francis Galton was interested in the extent to which characteristics run in families, a question not surprising given his familiarity with the work of his cousin, Charles Darwin. An inveterate measurer (and the man ultimately responsible for giving the world the regression analysis), Galton studied everything from people's weights, breathing powers, and arm spans to their "eminence" in British society. After reporting in 1869 his discovery that most of nineteenth-century Britain's political, artistic, and intellectual leaders were related by birth, Galton set out to determine why personal attributes such as these might run in families. And like others who speculated on this question before him, Galton saw nature and nurture as the only two possible contributors to such characteristics. Moreover, he saw these two factors as distinct; he defined nurture vaguely, as "food, clothing, education, or tradition…all these and similar influences whether known or unknown" (Galton, 1874, p. 12), and he left the rest to nature.

As the first theorist to attempt to take a scientific approach to the question of the inheritability of behavioral characteristics, Galton's belief that "nature" and "nurture" could be clearly distinguished is noteworthy. To Galton, it would have seemed obvious that some characteristics, like skin color, could be "inherited" in a way that would ensure that a child born to African immigrants in England would have dark skin even if she spent her entire life in England. In contrast, other characteristics, like speaking English as a primary language, could be influenced by the contexts in which development occurs. Consequently, Galton wrote in 1883 that he felt "perfectly justified in attempting to appraise [the] relative importance" of nature and nurture to the appearance of various traits (p. 131, cited in Gottlieb, 1992, p. 50), and that same year, he proposed the use of a research design that involved the study of identical and fraternal twins at various points in their lifetimes.

The approach Galton suggested—the twin design—grew into one of the most important tools available to quantitative behavioral geneticists, one still in use today. This design entails comparing the observed similarity of members of identical-twin pairs to the observed similarity of members of fraternal-twin pairs; greater similarity among the identical twins is taken as support for the hypothesis that genetic factors contribute to the observed similarity. An additional approach used by modern quantitative behavioral geneticists is the adoption design, in which an adopted child's resemblance to her biological parents is compared to her resemblance to her adoptive parents; here, too, if the child is observed to be more similar to her biological parents than to her adoptive parents—despite the fact that her biological parents have not been present in (or contributed to the construction of) her developmental environment—the observed similarity is taken to be a result of genetic influences.

Perhaps the most powerful of the designs used by modern quantitative behavioral geneticists is the adoption–twin combination design, which takes advantage of both the genetic "experimental" manipulation that nature provides us with when twinning occurs and the environmental "experimental" manipulation that adoption brings about. The logic underlying the adoption–twin combination design holds that if a group of monozygotic (MZ, or "identical") twins can be found who were separated at birth, and if a group of dizygotic (DZ, or "fraternal") twins can be found who were separated at birth, studying their characteristics later in life can reveal things about the influences of life experiences on trait development. Because the MZ twins

and the DZ twins were separated at birth—and therefore grew up in environments that were no more similar to each other than are any random pair of environments—if the MZ twins are more similar to each other than the DZ twins are, it must be because the MZ twins share identical genes, whereas the fraternal twins do not. Coupling this logic with statistical techniques that originated in the work of Galton himself yields the ability to compute a statistic known as "heritability," which is defined as the proportion of variance in a trait across a population that can be accounted for by genetic variance in that population.

Heritability

Regardless of which of these research designs are used, the goal of quantitative behavioral genetics studies has always been to measure the extent to which variation in a characteristic in a population can be accounted for by genetic variations—that is, to compute heritability statistics. This goal can be traced directly back to Galton's belief that the relative contributions of "nature" and "nurture" to our traits can be measured. Unfortunately, although we now know that "nature" and "nurture" are not the separable influences on development that Galton believed they were (Lickliter, 2009; Oyama, 2000)—and that therefore his entire project was suspect—the results of an enormous number of quantitative behavioral genetics studies continue to be published each year. In the latest edition of their textbook *Behavioral Genetics,* Plomin, DeFries, McClearn, and McGuffin (2008) note that "more than 5000 papers on twins were published during the five years from 2001 to 2006" (p. 80). Each of these studies produced heritability estimates that would ordinarily be the primary subject of attention in a review of the quantitative behavioral genetics literature.

However, heritability statistics have been severely criticized over the past four decades (e.g., by Block, 1995; Lewontin, 1974; Moore, 2006; and Oftedal, 2005). In a recent book by one of the rare philosophers of science still attempting to defend heritability analyses, Sesardic (2005) provided an impressive catalogue of evaluations of heritability that have been offered by biologists, psychologists, philosophers, and other theorists. He wrote

> that it has been said that the term 'heritability' is 'no longer suitable for use in *human genetics* and its use should be discontinued' (Guo, 2000, p. 299); that to apply the heritability formula to humans is 'virtually impossible' (Park, 2002, p. 407); that heritability estimates are 'both deceptive and trivial' (Hirsch, 1976, p. 168); that they are 'nearly equivalent to no information at all for any serious problem of human genetics' (Feldman & Lewontin, 1975, p. 1168); that they are 'unscientific and, indeed, meaningless' (Layzer, 1976, p. 199);…that inferences about genetic determination of traits should be 'disavowed once and for all' (Kitcher, 1990, p. 97); that 'mathematical estimates of heritability tell us almost nothing about anything important' (Jencks et al., 1972, p. 76); that the attempt quantitatively to determine the part of the phenotypic variance due to genetic causes is 'biological nonsense' (Lewontin, 1982, p. 14–15);…that 'the next century will treat heritability analysis with the same regard that this one treats phrenology' (Sarkar, 1999, p. 230); that heritability analysis 'ought to be relegated to the history of science along with phlogiston, penis envy and cold fusion' (Wahlsten, 1994, p. 265);…that the talk about substantial heritability of IQ is '*scientifically meaningless garbage'* (Lewontin, 1973–italics in the original), and so forth. (p. 23–24)

In light of the fact that so many theorists question the meaning, the utility, and ultimately the value of the heritability estimates generated in traditional quantitative behavioral genetics studies, a review of the literature that reports these statistics might not be in the best interests of the scientific community at this point in history (in contrast, studies in the quantitative behavioral genetics *tradition* that rely on the consideration of genotype-by-environment interactions will be considered both in a later section of this chapter and in the chapter by Deater-Deckard, volume 2). Therefore, the remainder of this section will examine the limitations of the traditional quantitative behavioral genetics approach that relies on the consideration of heritability estimates.

The Limited Utility of Heritability Estimates

As Plomin and colleagues (2008) note, "Quantitative genetics estimates the extent to which observed differences among individuals are due to genetic differences of any sort and to environmental differences of any sort without specifying what the specific genes or environmental factors are" (p. 59). Thus, the goal of traditional quantitative behavioral genetics is to study *differences* in behavioral characteristics among those in a population; the goal is not to identify genes that cause traits in individuals. This is because the methods used by such researchers are correlational; they are suitable for detecting the co-occurrence of genomes and behaviors, but not for establishing causation of behaviors (or of any other characteristics). Of course, it may initially seem strange that discovering a genetic difference associated with a behavioral difference is not tantamount to discovering a gene that causes a behavior; this seems strange because if a particular gene is found in people who perform well on, for instance, IQ tests, and if that gene, furthermore, is absent in people who perform poorly on such tests, it certainly seems like the gene in question is responsible for how well people perform on IQ tests. But on closer examination, this is not the case (Block, 1995; Lewontin, 1974).

Consider the following analogy. When we think about what causes a given baseball game to end up with the score that is ultimately recorded in history books, we can think of many different factors that might contribute to the final outcome: the weather in the home team's city that day, the actions taken by the various coaches prior to and during the game, the state of health of the various players on game day, the players' abilities to communicate with one another both verbally and nonverbally, the referees assigned to the game, and the presence or absence of committed fans in the bleachers, to name just a few of the variables that could influence the game's outcome. Now, imagine an identical game being played simultaneously in an alternate, nearly identical universe, except that the starting pitcher is different than in the original game. Clearly, because the two games were identical except for this one factor, the difference between the final scores in the two games can be accounted for by referring only to the effect of the starting pitcher. But in neither game can the final score be said to have been caused by the starting pitcher, because we have already established that the final score in any given baseball game is a function of many different factors. By the same token, discovering that particular genetic differences in a group of people are associated with particular IQ-score differences in those people does *not* mean that their IQ scores were caused by the varying genes in question; while those genes certainly could influence IQ scores—just as the starting pitcher can have some influence over the final score of a game—they do not cause the measured outcome. Importantly, if the score of the original game was 24–1 and the score of the "alternative universe" game was 26–1, it is apparent that although the starting pitchers had some effect on the final scores, other factors must be considered if we are to understand what caused the final scores themselves (i.e., what was responsible for such lopsided outcomes).

Quantitative behavioral geneticists understand the distinction between discovering the "cause" of a difference and discovering the cause of a behavioral characteristic, and they sometimes state that they know heritability statistics do not reflect the latter (e.g., Plomin, 1990). Nonetheless, there seems to be a tendency to misinterpret such numbers (Keller, 2010). It is not uncommon to encounter behavioral geneticists interpreting heritability statistics in a way that leads them to draw unwarranted conclusions; for example, Deater-Deckard, Petrill, Thompson, and DeThorne's (2006) interpretation of their heritability statistics led them to conclude that "the causes of…stability shift with development—from shared environmental influences in early childhood to genetic influences in middle childhood" (p. 503), even though the traditional methods of quantitative behavioral geneticists are unable to reveal such things as the causes of developmental stability.

What the methods of quantitative behavioral geneticists *can* do is reveal the fact that genetic factors contribute to behaviors. In an earlier era in which serious scholars might have argued in ignorance that some behaviors are completely uninfluenced by genes, a tool to help determine which behaviors are and which behaviors are not influenced by genes might have been of value. However, the consensus among many neuroscientists (Edelman, 1992), philosophers of science (Griffiths & Gray, 1994; Robert, 2004), and developmentalists working in biology (Gilbert & Epel, 2009), in psychology (Rutter, 2007), and at the interface of those two disciplines (Blumberg, 2005, 2009; Lickliter & Honeycutt, 2010) is that all human characteristics—behavioral and otherwise—are influenced by genes. After all, behaviors reflect the brain's structures and functions, both of which are demonstrably influenced by genetic activity. Consequently, the claim that a particular characteristic is influenced by genetic factors is empty, because there are no biological or psychological characteristics that are unaffected by genetic activity. When Plomin and colleagues (2008) report that "genetic factors contribute substantially to schizophrenia and cognitive ability" (p. 82), we can be forgiven for wondering how it is that that adds anything of value to what we already knew.

Of course, most quantitative behavioral geneticists believe that heritability statistics do more than just allow claims about genetic influence; they write as if these numbers allow them to evaluate the extent to which genetic factors contribute to traits. For example, Plomin and colleagues' (2008) claim that genetic factors are substantial contributors to schizophrenia implies that there are other behavioral conditions to which genetic contributions are less substantial. However, because heritability statistics do not reveal anything about the causes of characteristics (since such statistics merely assess correlations), it is not the case that the development of a highly heritable trait is more influenced by genetic factors than is the development of a less heritable trait. This point is related to the fact that heritability is a measurement of the extent to which genetic variation accounts for variation in a trait, not of the extent to which genetic factors contribute to the development of the trait in the first place—and it is such an easily misunderstood point that additional consideration here might be helpful.

Highly heritable traits are not traits whose development is powerfully influenced by genetic factors. Instead, if a trait is highly heritable, that just means that much of the variation in the trait can be accounted for by variation in genetic factors. Consider for example the weight of human bodies; this case will be illuminating, because although Plomin and colleagues (2008, p. 2) have written that heritability analyses show that "differences among us in weight are much more a matter of nature (genetics) than nurture (environment)," environmental factors like diet are nevertheless known to influence body mass. There is variation in the weights of adults living in Boston, and if most of the measured variation in weights among Bostonians can be accounted for by variation in their genes, then the heritability of weight for this population would be high. The problems for heritability statistics begin when we then assess the heritability of weight in a different group of people, for instance a population consisting of those world citizens whose income is near the median for their country. For this more diverse population, although genetic factors might still account for some of the variation in people's weights, they will account for less of it (because some of the variation in weights will be accounted for by other factors, like variations across countries in available food supplies). Consequently, the heritability of weight for these citizens of the world can be expected to be lower than the heritability of weight for the citizens of Boston, even though genetic factors do *not* more powerfully influence the weights of Bostonians than they do the weights of those in more diverse populations.

One way to think about this is to conduct a thought experiment like one proposed by Lewontin in the 1970s. First, imagine a situation in which an experimenter finds a way to hold constant all of the nongenetic factors that contribute to body weights, so that every individual in her study population experiences the identical environment. In such a case, the heritability of weight would be 1.00 (100%), because all of the variation in people's body weights would be accounted for by genetic variation (since in this imaginary situation, genes are the only factors relevant to body-weight that are free to vary). However, if the experimenter were able to clone a person so as to produce a population of genetically identical zygotes, and then proceeded to let each clone develop in one of the many different environments people around the world normally develop in, the heritability of weight in this population would be 0.00, because in this case, all of the variation in people's body weights would be accounted for by environmental variation (since there is no genetic variation in a population of clones at all). In general, when two different factors (e.g., genetic factors and environmental factors) both play necessary roles in causing a particular outcome—and this is *always* the case in phenotype development—the amount of variation in the outcome that can be accounted for by one factor always depends on the amount of variation in the other factor (Moore, 2006). Thus, heritability estimates are always a function of the population we have studied, and they are importantly affected by variation present in those people's *environments*.

For this reason, heritability estimates cannot be generalized from one population to another, including to the population of people-in-general (Eisenberg, 2004). Clearly, this situation renders heritability statistics of less value than they might otherwise be. Now, one strategy for dealing with this problem would be to measure all of the environmental factors that influence the development of a particular trait to see whether the variability of those factors experienced by a study population actually does *not* differ from the variability experienced by other populations (because in that case, we could be more confident that the heritability estimates computed for the two populations are comparable). But unfortunately, before we have done the real work of exhaustively cataloguing the specific factors that contribute to the development of a particular trait, we can have no idea if we are aware of all of the environmental factors that are important (Gottlieb, 1991a; Moore, 2001; for some specific examples that support this claim, see Masataka, 1993, or Moore, 1992). In most cases, we simply do not know enough about the developmental origins of our traits to ascertain with confidence whether the important environmental factors vary in similar ways for two different populations. Therefore, there is no effective way to implement the measure-the-environment strategy, and we are left with heritability estimates that cannot be appropriately generalized beyond the populations that generated them.

There is an additional lesson we can take from the insight that heritability estimates vary across populations: the heritability of a trait is not a characteristic of the trait at all but is instead a characteristic of the studied population. Just as we can ask about the *average* weight of Bostonians, we

can ask about the *heritability* of weight among Bostonians. The number we compute says something about Boston and its people, not about weight *per se*, even though the heritability of a characteristic seems like it should reflect something about the characteristic itself, namely how "inheritable" it is.

Once we understand heritability statistics in this way, it is useful to ask what purpose such numbers serve. Continuing with the analogy between averages and heritabilities, averages allow us to compare numbers generated for individuals (e.g., a person's weight) to numbers generated for populations (e.g., the average weight in a particular society); this is one way to evaluate whether or not a specific person is statistically normal. However, heritability measurements cannot be generated for individuals—given how heritability is defined, the heritability of a trait in an individual makes no sense—so one of the ways in which population statistics can be useful is not applicable to heritability.

Some population statistics can also be used to compare two populations. But if the heritability of weight in population *A* is greater than the heritability of weight in population *B*, what have we learned? Such a situation can arise if the variability of unknown (but influential) environmental factors is greater for population *B*, if the variability of unknown (but influential) genetic factors is greater for population *A*, or if the range of weights found in population *A* is less restricted than is the range of weights found in population *B*. (This is not meant to be an exhaustive list of possible explanations for why studies might yield differing heritability estimates for the same trait in two different study populations; the point is merely that multiple explanations are always possible.) Therefore, without knowing beforehand which environmental factors contribute importantly to the development of a characteristic, it is impossible to know what differing heritability estimates mean about the populations being compared.

Finally, to return to the question of whether or not highly heritable traits are more influenced by genetic factors than are less heritable traits, it might seem as if knowing how heritable two different traits are in a given population would allow us to draw some conclusions about the relative extents to which genetic factors influence the development of those two traits. For example, the heritability of IQ has been found in several studies to hover around 0.70 (e.g., Bouchard, Lykken, McGue, Segal, & Tellegen, 1990), whereas religiosity has been reported not to be heritable at all (Plomin, 1990). But this does not allow us to conclude that IQ is "more genetic" or "more inheritable" than religiosity, because we do not have a comprehensive understanding of how various environmental factors contribute to IQ or to religiosity, and so we therefore know nothing about the variability of these factors for the population being studied. Thus, heritability estimates for IQ and religiosity cannot be considered reliable indicators of the strength of "genetic influence" on the development of the traits in question. Because traits that are *perfectly* heritable can nonetheless be profoundly influenced by environmental factors (Lewontin, 1974), and because traits that are *not* particularly heritable—for example, the number of fingers on a human hand (see Block, 1995, for an explanation of this truly counterintuitive finding)—are nonetheless profoundly influenced by genetic factors, it is not the case that we should think of highly heritable traits as "more genetic," "more inheritable," or even "more influenced by genetic factors" than are less heritable traits.

Consequently, it is not clear what purpose heritability statistics can serve for us. They do not allow us to compare individuals to groups, they do not allow two groups to be compared in a way that gives reliable answers to important questions, and they do not give us information that allows us to compare two traits to each other in a meaningful way. Furthermore, they do not leave us with practical tools that enable functional interventions of any sort. To affect the development of a trait—for instance, if we want to reduce the likelihood that the offspring of people with substance abuse disorders will develop such disorders—we need to know how it is that various influential genetic and nongenetic factors interact to produce the trait. Knowing that the trait is highly heritable (1) does not tell us what to do to affect its development, (2) does not tell us whether its development would be difficult to influence with an environmental manipulation (because once you understand what causes a trait to develop, influencing its development need not be difficult, even if it is highly heritable), and (3) does not even allow for accurate predictions about the likelihood that offspring of affected parents will develop the trait themselves (because a heritable trait "breeds true" only if the environmental factors that contributed to its development in the parents also characterize the environments in which the offspring develop). The only contexts in which heritability estimates have proven useful are those in which people are trying to breed plants and animals with particular traits; in those contexts, the environments in which the offspring develop can be controlled with some degree of precision. However, because the environments in which people develop often differ in important ways from the environments in which their parents developed, heritability estimates lose their predictive utility in these contexts.

For all of these reasons, it is ultimately of little to no value to know how heritable a characteristic is without understanding how genetic and nongenetic factors contribute to its development. Even when twin studies take on the patina of scientific sophistication through the use of advanced brain mapping technologies (e.g., Thompson et al., 2001), it remains the case that twin studies are typically unable to provide information that can actually be useful. Similarly, although quantitative behavioral geneticists are optimistic about more advanced methods now on the technological horizon—for example, genome-wide association studies, which, through the use of DNA microarrays (Plomin & Schalkwyk, 2007), promise to reveal correlations between particular phenotypic characteristics and particular genetic characteristics known as single-nucleotide polymorphisms (Hirschhorn & Daly, 2005)—these approaches, too, have been subject to criticism (Weiss & Terwilliger, 2000). Until we understand what role a gene plays in the development of a characteristic, knowing that it co-occurs with that characteristic is no more valuable than knowing there is a correlation between any two variables that are not necessarily causally connected. In trying to assess the real value of such information, it might be worthwhile keeping in mind the well-worn textbook example about the high correlation between daily sales of ice cream cones and drownings in public swimming pools; variables like the presence of particular genes and the presence of particular traits can, like any other variables, be correlated for a variety of reasons besides the genes being causally responsible for the traits.

Genetics

Historical and Modern Meanings of the Word "Gene"

The story of Gregor Mendel's experiments with pea plants in his eastern European monastery in 1866 is well known. Although the discovery of the role DNA plays in intergenerational transmission of traits was not to occur for another 40 to 50 years, Mendel's results led him to hypothesize the existence of inheritable particles he considered to be "form-building elements," irreducible factors that he thought were present in gametes and were responsible

for an organism's characteristics. These hypothetical factors ultimately came to be called "genes," the entities we typically first encounter in secondary-school biology classes when we are taught that a "big B" represents a gene that determines brown eyes and that a "little b" represents a gene that—when paired with another "little b" gene—determines blue eyes. Such entities are commonly used to explain the patterns of transmission of characteristics from generation to generation. Moss (2003) has called these sorts of genes "Genes-P," because they are spoken of as if they determine phenotypes *p*reformationistically ("preformationism" was an eighteenth-century theory that held that an organism's features are present at conception—even if they are so small at that point as to be invisible—and that development entails merely growth of those features). In distinguishing this use of the word "gene" from the use that actually refers to elements of molecules in our bodies, Moss wrote

> When scientists and clinicians speak of genes for breast cancer, genes for cystic fibrosis, or genes for blue eyes, they are referring to a sense of the gene defined by its relationship to a phenotype…and not to a molecular sequence. The condition for having a gene for blue eyes…does not entail having a specific nucleic acid (DNA) sequence but rather an ability to predict…the likelihood of some phenotypic trait. What molecular studies have revealed is that…there is no specific structure for the gene for…blue eyes or the gene for many diseases…Blue eyes are not made according to the directions of the Gene-P for blue eyes…Reference to the gene for blue eyes serves as a kind of instrumental short hand with some predictive utility. (pp. 44–45)

This sense of the word "gene" refers to Mendel's nearly 150-year-old construct, an idea that provided the conceptual bedrock upon which quantitative behavioral genetics was built.

Early in the twentieth century, biologists began searching for the actual, material gene-elements in cells, and several believed they would be found on the chromosomes, relatively large molecules residing in the nuclei of most cells. In 1910, Morgan was trying to show that genes are *not* on chromosomes when he discovered that this was incorrect. He then embarked on a program of research that led him to conclude that Mendelian genes *are* related to chromosomes, because factors influencing sexual characteristics, eye and body color, and wing shape "segregated together with the X chromosome" (Moss, 2003, p. 37). Morgan's work lifted the curtain on the modern age of genetics and led to his receiving the Nobel Prize in 1933, a mere 20 years before James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin discovered the dual-stranded, twisted structure of DNA. Watson and colleagues' discovery demonstrated that segments of DNA could potentially carry the information they would have to carry in order to be the genetic material, and this demonstration led eventually to the conclusion that these segments were the inheritable particles that Mendel had posited 87 years earlier.

Moss (2003) has called these chromosomal segments "Genes-D," because when used in this way the word "gene" refers to segments of DNA as *d*evelopmental resources. Thus, whereas the "Gene-P" sense of the word "gene" refers to a nineteenth-century construct posited by Mendel, the "Gene-D" sense of the word "gene" refers to a mid-twentieth-century construct first conceived after elucidation of the structure of DNA in 1953. And whereas quantitative behavioral genetics was conceived as a way to explore the effects of genes in the "Genes-P" sense, genes in the "Genes-D" sense have provided the conceptual bedrock upon which *molecular* behavioral genetics has been built. In distinguishing Genes-P and Genes-D, Moss wrote

> …where a Gene-P is defined strictly on the basis of its instrumental utility in predicting a phenotypic outcome…, a Gene-D is a specific developmental resource defined by its specific molecular sequence…yet, it is indeterminate with respect to ultimate phenotypic outcomes…Gene-P and Gene-D are distinctly different concepts…They play distinctly different explanatory roles. There is nothing that is simultaneously both a Gene-D and a Gene-P…[A Gene-D]…is not a gene for an organismic phenotype…[and it cannot serve as a] tool for predicting phenotypes. (pp. 47–48)

This means that the Mendelian "genes" we often think of as causing blue eyes, for example, are not actual physical entities that can be located on chromosomes. It also means that the actual physical DNA segments that *are*, in some cases, associated with particular phenotypes do not cause the development of those phenotypes in any sort of a deterministic way. Moss has been joined in his effort to distinguish different meanings of the word "gene" by Griffiths and Stotz (2006) and Rolston (2006), among others.

As argued above, skepticism about the central goal of quantitative behavioral genetics seems warranted, but having said that, there can be little doubt that molecular genes—Genes-D—play important roles in the development of all biological and psychological traits. Nonetheless, the idea that there are genes that single-handedly *determine* those characteristics is no longer tenable. Of course, there are still molecular biologists who occasionally draw deterministic conclusions from their work (e.g., Demir & Dickson, 2005; Gehring, 1998), but this is because such scientists operate within paradigms that purposely hold important nongenetic variables constant while their experimental subjects develop. In fact, there are no such things as "genes for" traits, if by that phrase we mean genes that inevitably produce those traits independently of the contexts in which development takes place (Jablonka & Lamb, 2005; Lewontin, 2000; Moore, 2001; Sturtevant, 1915). Furthermore, there is little reason to believe that *complexes* of genes produce traits in a way that is any more independent of developmental context (Eisenberg, 2004; Noble, 2006). Because of the nature of DNA, genetic factors are inherently interactive, and the development of even our simplest traits can theoretically be influenced with environmental manipulations. An understanding of that nature requires some knowledge of what DNA is and how it works with other molecules in cells to produce proteins, other functional polypeptides, and micro-RNAs capable of regulating other genes. A brief primer on the structure and function of DNA follows, because only an understanding of what DNA actually is and does can permit well-informed evaluations of particular sorts of claims, for instance assertions that particular behavioral or psychological characteristics are "genetically determined" (Silberg & Eaves, 2004, p. 349), are "primarily accounted for by genetic factors" (Jaffee et al., 2004, p. 1048), are "under substantial genetic influence" (Ramus, 2006, p. 248), "show significant genetic influences" (Neiderhiser et al., 2004, p. 343), or "are somewhat genetically influenced" (Thompson, 2001, p. 1253); such claims are still readily found in the behavioral genetics literature despite the fact that they are misleading and are sometimes simply false. After this primer, the roles of genes that have been implicated in the development of specific psychological or behavioral characteristics will be discussed. This discussion will reveal that although genetic factors play essential roles in the development of our characteristics, they do not single-handedly cause phenotypes, even disease states that we often think of as "genetic." Therefore, if our goal is to understand the causes of characteristics in a way that will allow us to prevent psychopathology or otherwise influence development, the best strategy is to seek an understanding of how such characteristics develop—and development is always a process that entails many steps involving both genetic and nongenetic factors.

The Structure and Function of DNA: Basics

Inside most of the cells that make up our bodies are nuclei that contain our chromosomes, each of which consists of material known as chromatin. Chromatin contains both DNA and specific proteins known as histones, around which long strands of DNA can be tightly wrapped (Bernstein & Allis, 2005; Luger, Mader, Richmond, Sargent, & Richmond, 1997). Different sections of the chromatin from a single chromosome can be in different states at different times. When DNA is tightly wrapped around histone proteins, other molecules cannot access the information present in the DNA[1]; consequently, chromatin in this compact state is known as "silent" chromatin. In contrast, when the DNA in a section of chromatin is not tightly wound around histones, that portion of DNA is available for interaction with other biological molecules; chromatin in this state is known as "active" chromatin (Gibbs, 2003). Because the building blocks that make up chromatin are responsible for "packaging" DNA in the cells' nuclei in this way, they are "the primary determinant of DNA accessibility" (Luger et al., 1997, p. 251).

When chromatin is in its active state, a variety of molecules can gain access to its DNA. As is well known, DNA itself is a double-stranded molecule containing four basic components, known as "nucleotide bases," each of which is normally represented by the first letter of its name; A, C, G, and T refer to the bases adenine, cytosine, guanine, and thymine, respectively. A single strand of a double-stranded DNA molecule can be thought of as a very long sequence of these bases strung one after another, so that a particular portion might read, for example, ACCCGCGGTATTTCGATC. In the right context, each triplet of bases strung along a DNA strand (for instance, in the example above, "ACC" followed by "CGC," etc.) can effectively be interpreted by "cellular machinery" (Oyama, 1992, p. 57) as corresponding to a particular amino acid (e.g., tryptophan followed by alanine, etc.). Because amino acids are the building blocks of proteins—each of which is a chain of amino acids strung together in a particular sequence—the major function of some portions of DNA is to hold a code specifying the sequence of amino acids that make up a given protein. Among the many sorts of proteins that are of particular importance for behavioral scientists are those that serve as receptors for neurotransmitters on the postsynaptic membranes of neurons; some examples of proteins that play roles in psychological phenomena include the serotonin transporter protein (involved in the reuptake of the neurotransmitter serotonin from synapses, and implicated as playing a role in depression), the glucocorticoid receptor protein (involved in modulating fearful responses in stressful situations), and the monoamine oxidase A enzyme (involved in metabolizing a variety of neurotransmitters, including norepinephrine, serotonin, and dopamine, and implicated as playing a role in aggressive behavior).

The fact that proteins can be associated with behavioral phenomena has led to optimism in some quarters that "it is only a matter of time before we obtain complete lists of genes involved in most cognitive traits and disorders of interest" (Ramus, 2006, p. 248). To date, genetic contributions to a wide variety of psychological phenomena have been studied, including attention (Posner, Rothbart, & Sheese, 2007), language/speech (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001; Marcus & Fisher, 2003), psychopathic emotional dysfunction (Blair, 2006), suicide (De Luca et al., 2010), and aggression (Velez, Sokoloff, Miczek, Palmer, & Dulawa, 2010), among many others (for a critical review of some of the work on the genetic basis of cognition, see Flint, 1999; to see samples of more recent work in this area, see the following special journal issues: *Cognition*, *101*(2); *Behavior Genetics*, *40*(2); and portions of *Developmental Science*, *10*(1)). Studies of such phenomena invariably report associations between particular genes and behaviors, but a more general lesson has emerged from this work: as Fisher (2006) has noted, there are never "straightforward linear relationships between specific genes and particular behavioural and/or cognitive outputs. [Rather than specifying behaviors or cognitive processes, genes]…make regulatory factors, signaling molecules, receptors, enzymes, and so on, that interact in highly complex networks, modulated by environmental influences, in order to build and maintain the brain" (p. 270). Thus, although particular biological and behavioral traits might sometimes be described as "genetic," the DNA segments we call "genes" can never do more than contribute sequence information used in the construction of proteins; genes cannot even single-handedly determine protein structures (Johnston, 1987; Lewontin, 2000), let alone cause the development of full-blown traits (Moore, 2001). For this reason, the balance of this review will focus not on discovered associations between particular genes and particular psychological phenomena, but on the essentially interactive nature of genes. By illustrating several ways in which genetic factors can contribute to the development of our psychological characteristics, the inherent complexity of developing biological systems can be highlighted in a way that shows genes *not* to be independently acting agents that can cause the appearance of behavioral phenotypes.

Interactions Between DNA Segments and the External Environment

One class of genes that are of particular interest to behavioral scientists are the immediate early genes (IEGs), so called because they are the first genes to be recruited into the protein production process following particular forms of environmental stimulation (in contrast, genes not in this class are normally expressed only when other genes induce them to contribute to protein production). The two best-studied IEGs are called *c-fos* (Morgan & Curran, 1989) and *zif-268* (Davis, Bozon, & Laroche, 2003), but as early as the late 1990s, the number of different IEGs present in neurons was already estimated to be between 30 and 40 (Lanahan & Worley, 1998). Although a popular misconception holds that our genes contribute to our characteristics early in development and then remain largely silent, the discovery of IEGs has made it clear that chromatin is dynamic (Clayton, 2000; see also Levenson & Sweatt, 2005) and that our genomes are responsive to stimulation originating in the environment. Thus, these genes contribute to neural plasticity as well as to the initial construction of the normal human nervous system (Michel & Moore, 1995). Another common misconception holds that genes contribute to the structure and function of cells, organs, and organisms in a bottom-up manner; thus, genes are mistakenly thought to influence phenotypes unidirectionally. IEGs, however, illustrate one way in which genes and environments interact throughout our lives. Their discovery drives home the bidirectional nature of various influences on phenotypes; environmental factors affect what genes do (Gottlieb, 1998; Johnston, 2010; Johnston & Edwards, 2002; Noble, 2006).

Much of the research done on IEGs to date has examined animal models. For example, IEGs that respond to light cycles—and thereby are able to adjust circadian rhythms—have been studied in hamsters (Rusak, Robertson, Wisden, & Hunt, 1990) and cats (Rosen, McCormack, Villa Komaroff, & Mower, 1992), and IEGs that respond to species-specific birdsongs have been studied in zebra finches and canaries (Mello, Vicario, & Clayton, 1992). However, the human genome contains IEGs as well; in considering IEGs, Clayton (2000) wrote that "the brain's genomic response to stimulation appears to be a discrete and ancient process that is engaged commonly during normal brain physiology" (p. 186) and that it "is a basic part of the biology of all cells" (p. 187). In fact, because these genetic responses have functions in common with the action potentials that characterize neural

responses, Clayton calls them “genomic action potentials.” Of course, action potentials operate on a timescale of milliseconds whereas IEGs operate on a much slower timescale of minutes or hours, but their responsiveness to environmental stimuli—and the fact that they integrate signals from multiple discrete sources (Levenson & Sweatt, 2005)—suggests that they should nonetheless be considered part of organisms’ information-processing systems (Clayton, 2000).

One of the important features of IEG responses is that the cellular changes to which they contribute can be long-lasting, even if the stimuli that produced them were transient. Thus, activation of *c-fos* (Tischmeyer & Grimm, 1999) and activation of *zif-268* (Davis et al., 2003) have been associated with various forms of learning. For example, *c-fos* has been found to be activated in several different brain areas in rats by tasks as diverse as brightness discrimination, motor skill learning, avoidance learning, and performance in the Morris water maze (Tischmeyer & Grimm, 1999), and *zif-268*—also known as *egr-1* and *Zenk*—has been found to be activated in the temporal cortex in macaque monkeys by tasks requiring visual association learning (Okuno & Miyashita, 1996). In their 2003 review of studies on the role of *zif-268* in learning, Davis and colleagues noted that “there is a general consensus that *zif-268* activation may constitute a critical mechanism for the encoding of long-lasting memories…[and that] *zif-268* is necessary in the processing of several types of memory” (p. 17), even though a consensus had not yet formed regarding the particular aspects of memory and learning in which *zif-268* is involved.

Interactions Between DNA Segments and the Internal (i.e., Molecular) Environment

IEGs and other DNA segments that are used to produce proteins rely on the fact that DNA’s structure allows for the storage of coded information that can be used in protein production, but it has become clear that most of the bases constituting normal human DNA are not actually used to produce proteins (Mattick & Makunin, 2006) and should therefore be considered to be “noncoding DNA.” In 1999, Francis Collins—the director of the Human Genome Project and the National Human Genome Research Institute—suggested that most of our DNA does not appear to code for anything at all; he wrote that the coded segments of the DNA in our bodies are “scattered throughout the genome like stars in the galaxy, with genomic light-years of noncoding DNA in between” (Collins, 1999, p. 28). Eight years later, it had become clear that DNA that does not code for protein likely still carries information for *something* important; a 2007 analysis using data from 35 research teams led to the conclusion that “protein-coding DNA makes up barely 2% of the overall genome, yet 80% of the bases studied [i.e., a selected sample of 30 million nucleotide bases] showed signs of being expressed” (Pennisi, 2007, p. 1556). In fact, most of the DNA in complex organisms is used to produce products other than proteins, and although some of these other products are known to be involved in regulating activity in other portions of the genome, many of them have unknown functions (Mattick & Makunin, 2006). So, it remains true that some of our DNA really might be meaningless “junk” that has accumulated through millions of years of evolution and that is dutifully replicated in descendant generations simply because it does not adversely affect survival or reproduction. But we now understand that noncoding DNA segments can play several sorts of functional roles, and because some of the products of this noncoding DNA influence other segments of DNA, these lengths of noncoding DNA can properly be considered to be part of the molecular environment in which these other DNA segments function.

Such lengths of DNA can be involved in the regulation of activity in other regions of the genome. The first example of a portion of DNA serving this function was discovered in the bacterium *Escherichia coli* by Jacob, Perrin, Sanchez, and Monod in 1960. Jacob and colleagues’ so-called *lac operon* consisted of several sections of noncoding DNA, including portions called the promoter, operator, and terminator regions, as well as three coding portions bearing information for the sequencing of proteins. As long as lactose is not present in the (external) environment of the bacterium, a molecule called the lactose repressor remains tightly bound to the operator segment of the DNA strand, preventing the use of the sequencing information trapped in the other sections of the strand. However, when environmental circumstances change—that is, when lactose is present—the shape of the repressor molecule is altered so that it can no longer bind with the operator. When the operator is no longer bound by the repressor, a particular enzyme can bind with the promoter, beginning a process that leads to the production of proteins that allow the bacterium to digest the lactose. This process is facilitated significantly when lactose is present but glucose is absent in the environment (because if glucose is present, the bacterium will metabolize the glucose instead of the lactose). In this way, external environmental conditions are given regulatory control over the functioning of a gene, via alterations to the status of noncoding sections of DNA that themselves are in the molecular environment of the sections that contain protein-sequencing information. Fifty years of additional research have revealed that gene activity is regulated in complex organisms as it is in bacteria, and although the mechanisms involved are not identical to that just described, genetic activity in general can be understood to be an inherently interactive phenomenon. Genetic activity can be upregulated or downregulated by environmental events.

Lengths of DNA never actually produce proteins directly but instead code for lengths of RNA (which, like DNA, is composed of nucleotide bases, but unlike DNA, is composed of just a single strand of bases). One form of RNA serves as a kind of “messenger” (mRNA) that can carry sequencing information from the DNA to structures called ribosomes, which are the sites outside of a cell’s nucleus where proteins are actually constructed. However, as just described, many of the RNA molecules that DNA codes for do not play roles in the production of proteins but are instead involved in other essential cellular processes. It now seems that these noncoding RNAs probably “constitute a critical hidden layer of gene regulation in complex organisms” (Mattick, 2005, p. 1527), although their function is, in most cases, still unknown (Dinger, Pang, Mercer, & Mattick, 2008). Among the disorders now known to be characterized by abnormal RNAs that do not code for protein are Alzheimer’s disease (Faghihi et al., 2008), Prader-Willi syndrome (Sahoo et al., 2008), and other “cancers and neurological diseases” (Mattick & Makunin, 2006, p. R21).

RNA molecules known as microRNAs (miRNAs), for example, are able, like some proteins, to bind to DNA in ways that influence the functioning of other lengths of DNA. Thus, miRNAs can regulate genetic activity. Still other RNA molecules, for example small nuclear RNAs (snRNAs), work in collaboration with specific proteins and are involved in several functions in the nucleus, including *preparing* messenger-RNA molecules to be used in protein construction at the ribosomes.

The Structure and Function of DNA: RNA Splicing and Alternative Splicing

The reason messenger-RNA molecules need to be prepared before being used at the ribosomes is related to the fact that sequences of “junk” nucleotide bases are scattered liberally among potentially meaningful sequences of nucleotide bases in the DNA of all complex organisms; that is,

most of our genes do not exist as uninterrupted sequences of DNA bases. Instead, sequences of bases that can represent sequences of amino acids are interspersed with sequences of bases that cannot; the former "meaningful" sequences are called *exons*, and the latter "meaningless" sequences are called *introns* (Gilbert, 1978). When the information in a particular length of DNA is to be used in the construction of a protein, that length—including both exons and introns—is first used to construct a complementary length of RNA in a process known as "transcription." Then, before the RNA can be used in the construction of a protein, it must undergo a nother process known as RNA splicing. In this process, the introns in the RNA must be excised and the exons must be joined together. To use a metaphor, this process is akin to an editorial process that changes a sentence like "spago catkwoje urthe walksnipesdoglkuf ran to thesprach lslspetku storehwed" to the sentence "the dog ran to the store;" in this metaphor, the words "the," "dog," "ran," etc. are akin to exons, and the other extraneous letters (e.g., spago catkwoje ur) make up nonsense "words" akin to introns.

More than three decades ago, researchers discovered that a single length of DNA can sometimes be spliced in different ways so that the complementary RNA strand produced from the DNA "can be processed in different ways to yield different end products" (Ziff, 1980, p. 491). This so-called "alternative splicing" was subsequently found to depend, at least in part, on the cellular contexts in which the splicing was taking place. For example, Amara, Jonas, Rosenfeld, Ong, and Evans reported as early as 1982 that the gene known to be involved in the production of the hormone calcitonin is sometimes spliced in a way that leads to the production of a distinctly different product, a neuropeptide; when the splicing occurs in thyroid cells, the gene produces calcitonin, but when the splicing occurs in the hypothalamus, the very same gene produces the neuropeptide.

Thus, a given sequence of information encoded in DNA can be used to create more than one end product; by analogy, the sentence above—"spago catkwoje urthe walksnipesdoglkuf ran to thesprach lslspetku storehwed"—can be spliced to yield the sentence "the dog ran to the store," but it can also be spliced to yield the sentence "a cat walks to the pet store," a sequence with an entirely different meaning. Amazingly, a segment of DNA containing a sequence of exons that we arbitrarily identify as Exon A, Exon B, Exon C, and Exon D (dispersed among introns that we will ignore for the moment) can be spliced to yield RNA of an amazing number of different forms, for example ABCD, ACD, BCD, AD, AC, or even just A, B, C, or D, or (reversing the order in which they lie on the DNA segment) DCBA, BDCA, DA, etc. (Noble, 2006). Because the process of protein production works this way, RNA splicing can be understood to effectively control the *function* of any particular length of DNA (Smith, Patton, & Nadal-Ginard, 1989). Therefore, DNA cannot be thought of as containing a code that specifies particular predetermined (or context-independent) outcomes (Noble, 2006). Instead, products coded for by "individual mammalian genes…may have related, distinct, or even opposing functions" (Wang et al., 2008, p. 470).

As recently as 15 years ago, theorists had concluded that alternative RNA splicing is more common than anyone had previously suspected; Neumann-Held (1998) estimated that alternative splicing was occurring during the processing of as much as one third of our DNA. Five years later, after studying over 10,000 human genes, Johnson and colleagues (2003) concluded "that at least 74% of human multi-exon genes are alternatively spliced" (p. 2141). More recent studies, however, have revealed that alternative RNA splicing is "actually a universal feature of human genes" (Trafton, 2008, p. 6, quoting Burge). Pan, Shai, Lee, Frey, and Blencowe (2008) estimated "that transcripts from ~95% of multiexon genes undergo alternative splicing" (p. 1413), and Wang and colleagues (2008), after studying genetic activity in 15 different human tissues, concluded "that 92–94% of human genes undergo alternative splicing" (p. 470). Even more interesting for psychologists is the fact that although most of the variation in splice products detected by Wang and colleagues occurred across varying tissue types, some of the variation occurred across individual people. Thus, a given gene in Barack Obama might do something different than that identical gene would do in George W. Bush.

The fact that a given sequence of DNA bases can give rise to multiple protein products as a function of the context in which the DNA is being expressed has raised the question of what exactly we are referring to when we use the word "gene." At present, there is no agreed-upon definition of this construct, despite the fact that it remains at the center of the field of genetics. Sometimes, alternative splicing entails simply excising a single sequence of bases from a strand of RNA in one situation but not in another. But in other cases, the exons that are ultimately decoded are sequences of DNA that *overlap* one another, so that the bases that make up the tail end of one functional sequence are the same exact bases constituting the initial length of another functional sequence. Summing up this situation in 1998, Neumann-Held commented that "there is no fundamental way by which the classical…gene concept could be applied to DNA segments. One focuses at the same bit of DNA, and different structures and functions can appear. One focuses on different levels of the expression process…and again different structures and functions appear" (p. 125). Two years later, Keller (2000) wrote that "the sheer weight of the findings…have brought the concept of the gene to the verge of collapse" (p. 69) and that working biologists now use the word to refer to many different things. As recently as 2007, upon finding that some functional RNAs are produced by splicing together exons originating in two different "genes" located thousands of bases away from each other, Reymond concluded that "we have still not truly answered the question, 'What is a gene?'" (quoted in Pennisi, 2007, p. 1557). Complicating matters further is the discovery that in some not-necessarily-rare cases, particular RNAs appear able to function both as messenger (i.e., protein-coding) RNAs and also as noncoding RNAs that perform entirely different cellular functions (Dinger et al., 2008). What is clear is that the genes most of us imagine lying in a coherent state somewhere in our bodies, waiting to deterministically dictate their instructions, do not exist (Jablonka & Lamb, 2005, 2007). Instead, unedited, ambiguous segments of DNA—which, arguably, are not themselves "genes"—are cut, mixed, and recombined in a context-dependent manner to produce temporary edited RNAs that represent how genetic information is actually used.

Applications: How a Systems Approach Influences Thinking About Psychopathology

Prader-Willi syndrome. Although we currently know little about the functional role of alternative splicing in the development of human characteristics, an example will illustrate how important this process can be. The snRNAs described above contribute to the structure of the conglomerate responsible for RNA splicing, but other snRNAs, such as small nucleolar RNAs (snoRNAs), have been found to regulate alternative splicing in some cases. Prader-Willi syndrome is a rare disorder characterized by behavioral disturbances, including poor gross motor skills, obsessive behavior, emotional lability, irritability, aggression, and global developmental delay, including mild to moderate mental retardation (Holm et al., 1993; Wadsworth, McBrien, & Harper, 2003). Since the late 1980s, Prader-Willi syndrome has been known to be associated, about 60% to 70% of the time (Nicholls, Knoll, Butler, Karam, & Lalande, 1989; Sahoo et al., 2008), with the deletion of genetic material on the fifteenth chromosome inherited from a patient's father (Schulze et al., 1996). More recent work has revealed that the absent DNA codes not for a protein but for a particular collection of snoRNAs; among the snoRNAs encoded in this region of the fifteenth chromosome are HBII-52 and HBII-85 (Sahoo et al., 2008). The exact function of HBII-85 is not yet clear,

but HBII-52 regulates alternative splicing of mRNA associated with the production of serotonin receptors 5-HT_{2C}R (Kishore & Stamm, 2006), and HBII-85 likely contributes to the alternative splicing of mRNA as well (Bazeley et al., 2008). HBII-52, which regulates the splicing of mRNA generated from a gene on a different chromosome, appears to play a less significant role in the development of Prader-Willi syndrome than does HBII-85 (Sahoo et al., 2008); nonetheless, an HBII-52 deficiency probably contributes to the development of the Prader-Willi phenotype to some extent, and to that extent, Prader-Willi patients lacking HBII-52 can be expected to produce abnormal mRNA associated with 5-HT_{2C}R serotonin receptors, presumably because the alternative splicing that normally regulates the processing of this mRNA does not occur in these individuals.

This sort of arrangement—in which complex phenotypes reflect the action of a factor that has been affected by another factor that has been affected by another factor, and so on—is characteristic of complex biological systems. The ubiquity of this kind of causal architecture in biology led Smith (1999) to write that development can be "determined, not by some prescribed outcome…but as the product of a history of cascading causes in which each subsequent change depends on prior changes and constrains future changes" (p. 140). Consequently, it is generally an unhelpful simplification to claim that a behavioral or psychological characteristic—whether normal or abnormal—is "genetic," because such a claim merely papers over the actual developmental mechanisms that give rise to the characteristic (Johnston & Edwards, 2002). If there were normal or abnormal characteristics that could manifest without the involvement of DNA, perhaps a useful distinction could be made between "genetic" and "nongenetic" characteristics; however, because genetic factors play *some* role in the emergence of all human characteristics (Ramus, 2006), a claim that a particular condition is "genetic" is effectively an empty statement.

In contrast to focusing on the association between the *presence* of particular genes and particular abnormal characteristics, focusing on gene *activities*—and on the causal cascades to which they contribute—can draw attention to multiple potential treatments for pathological conditions. As a case in point, several potentially useful interventions are suggested by the proposition that some symptoms associated with Prader-Willi syndrome are influenced by (1) abnormalities related to serotonin receptors, which (2) are caused by the abnormal alternative splicing of strands of mRNA, which (3) reflects the absence of a snoRNA that is (4) ordinarily produced during transcription of DNA on a different chromosome. For instance, because the DNA associated with the relevant serotonin receptors is normal in patients with Prader-Willi syndrome, a treatment for the symptoms in question could be sought by focusing not on genetic abnormalities known to exist on the fifteenth chromosome, but instead on the regulation of the DNA associated with the serotonin receptors. Understandings based not on associations between the presence of certain genes and the presence of certain behaviors but on the *processes* by which those behaviors emerge in development (Spencer et al., 2009) are bound to yield information that will be useful in the management of syndromes with concomitant behavioral abnormalities.

Phenylketonuria (PKU). PKU will serve as another instructive example, in part because it is a disorder often presented as being caused by a single Mendelian genetic defect (Cole, Cole, & Lightfoot, 2005). Because of this defect, patients with PKU cannot metabolize an amino acid—phenylalanine—that people normally consume in their diets; consequently, phenylalanine builds up in the bodies of those with the defective gene and produces the symptom of PKU: severe mental retardation, tremors, and in some cases seizures. In fact, PKU is the most common biochemical cause of mental retardation (Diamond, Prevor, Callender, & Druin, 1997). In the 1950s, experimenters began treating infants with abnormally high phenylalanine levels (i.e., hyperphenylalaninemia, or HPA) with a low-phenylalanine diet, which was found to permit normal cognitive development (Bickel, Gerrard, & Hickmans, 1954; but see also Diamond et al., 1997); consequently, since the 1960s, infants worldwide have undergone screening to detect HPA at birth (Scriver & Waters, 1999). PKU, then, can be considered one of the major success stories in the study and treatment of present-at-birth metabolic disorders. Nonetheless, more careful consideration suggests that PKU ought not be considered simply "a genetic disorder." Instead, PKU can illuminate how genetic factors in general can best be thought of as *contributors* to both normal and abnormal phenotypes.

Because the cognitive phenotype associated with PKU does not develop in individuals who consume low-phenylalanine diets, this condition is arguably not caused by a genetic defect *per se* but is instead caused when people with a particular genotype develop in particular environmental conditions, namely the conditions wherein their diets contain ample quantities of phenylalanine. This perspective, which sees PKU-associated mental retardation developing as a result of a coaction of genetic and environmental (in this case, dietary) factors, has advantages over a perspective that sees the symptoms of PKU as simply caused by genetic abnormalities. Of most importance is the fact that an approach that focuses on developmental process instead of simply on genetic endowment effectively encourages researchers to discover all interventions that lead to desirable developmental outcomes (Moore, 2009); that is, just because a genetic abnormality might be associated with a particular abnormal phenotype does not mean that the best (i.e., easiest, least expensive, or most effective) treatment would entail genetic intervention. Understanding that phenotypes—cognitive and otherwise—are built during development as genetic factors interact (or coact; Gottlieb, 1991a) with nongenetic factors can help draw attention to the developmental processes actually responsible for the phenotypes and thereby highlight multiple points in the developmental system where interventions could be effective. Approaches that see phenotypes as effectively prespecified by people's genetic constitutions do not encourage such flexible problem solving.

As it happens, so-called "monogenic" disorders like PKU are invariably less simple than they appear at first glance. Because phenotypes do not bear simple relationships to genotypes (Summers, 1996), Scriver and Waters (1999, p. 268) concluded that "it should be no surprise that PKU can be seen to behave as a 'complex' trait when considered at its cognitive and metabolic…levels of phenotype, which are beyond the control" of the human phenylalanine hydroxylase gene (*PAH*), the gene that is missing in those with PKU. The complexity in this case is related to the facts that (1) the symptoms of PKU can appear in individuals possessing a normal *PAH* gene and (2) siblings possessing identical genetic abnormalities at the *PAH* locus can nonetheless develop different metabolic phenotypes (Treacy et al., 1996) and extremely different IQs (DiSilvestre, Koch, & Groffen, 1991); after finding that identical genotypes could lead to "major differences in intellectual phenotype," Ramus, Forrest, Pitt, Saleeba, and Cotton (1993) concluded that "there is not a simple correlation between genotype and intellectual phenotype" (p. 401). In fact, the clinical literature indicates that it is possible to be born with the genetic abnormality associated with PKU and nonetheless avoid significant mental retardation, even if a normal phenylalanine-rich diet is consumed from birth (DiSilvestre et al., 1991; Ramus et al., 1993). Thus, Plomin and colleagues' (2008) statement that "a single gene is necessary and sufficient to cause [PKU]" (p. 32)—a type of claim that is not uncharacteristic of the quantitative behavioral genetics literature—is simply false.

Huntington's disease (HD). As with PKU, genetic abnormalities do not straightforwardly cause the symptoms of other monogenic disorders such as

cystic fibrosis (Estivill, 1996), Tay-Sachs, or HD, either (Keller, 2000). HD, a progressive neurodegenerative disease, will serve as an illuminating example because it is commonly considered to reflect the workings of a single, simple genetic defect; in fact, the 1993 discovery by the Huntington's Disease Collaborative Research Group of a genetic region always associated with HD was widely considered to herald a new age in the study of the genetics of disease. However, although the abnormal HD gene appears to be present in all HD sufferers, its specific role in the development of the symptoms of HD—including behavioral, cognitive, and other symptoms—is still in doubt (Ross, 2004).

Located on the short arm of the fourth human chromosome (Walker, 2007), the gene associated with HD is an abnormal variant of a gene found in all normal people. In normal individuals, this gene contains a sequence of nucleotide bases—cytosine, adenine, and guanine, in that order (CAG)—that is repeated between 8 and 27 times. Because this triplet of bases normally codes for the amino acid glutamine, the protein that is produced when this gene is translated—called the huntingtin protein—contains multiple glutamines linked together in a long chain (Walker, 2007). In people who develop HD, CAG sequences in this region of the fourth chromosome repeat as many as 60 or more times (Huntington's Disease Collaborative Research Group, 1993), leading to the production of mutant huntingtin proteins constituted with abnormally long polyglutamine chains. The number of CAG repeats varies among individuals, but age of onset of HD symptoms—which can occur anytime during the lifespan—is inversely correlated with this number (Imarisio et al., 2008). The behavioral symptoms characteristic of HD include restlessness and loss of motor coordination, irritability, forgetfulness, and impairment in speech and in executive functions like planning and organizing (Montoya, Price, Menear, & Lepage, 2006; Walker, 2007). These symptoms are associated with abnormalities in the brains of HD patients, in particular atrophy and death of neurons in the striatum (Walker, 2007) and ultimately in the cortex as well (Montoya et al., 2006).

Thus, we have distinctive abnormal neurological and behavioral phenotypes that are associated with a distinctive genetic abnormality, but the underlying pathogenesis of HD is, nevertheless, still poorly understood (Walker, 2007). There is evidence that normal huntingtin proteins are essential for embryological development (Imarisio et al., 2008; Nasir et al., 1995) and that they are able to upregulate transcription of genes involved in the production of brain-derived neurotrophic factor (BDNF), a factor that is necessary for the survival of neurons in the striatum (Zuccato et al., 2001). Normal huntingtin has also been implicated in the transport of BDNF along microtubules within cells (Imarisio et al., 2008; Ross, 2004). In contrast, mutant huntingtin—and the accompanying downregulation of genes involved in the production of BDNF—has been associated with the onset and severity of the motor abnormalities characteristic of HD (Canals et al., 2004). Consequently, one hypothesis concerning the relationship between the symptoms of HD and the distinctive genetic characteristic associated with HD is that mutant huntingtin "initiates a cascade of different events…that converge in the specific cell death of striatal neurons" (Canals et al., 2004, p. 7728).

As with PKU, this understanding of the development of the symptoms of HD goes beyond the mere association of a genotype with a phenotype and thereby suggests possible treatments that target not the genes associated with the phenotype but abnormal processes further down the developmental pathway that leads to the disease. For example, Canals and colleagues (2004) posited that HD could be treated by administering exogenous BDNF, and Imarisio and colleagues (2008) suggested that HD could be treated by pharmacologically upregulating a natural process, known as autophagy, that clears cells of abnormal proteins. In their 2008 paper, Imarisio and colleagues wrote that "HD pathology may be a result of the cumulative effect of a variety of pathway perturbations" (p. 199), reflecting the fact that there is no simple connection between "the gene" associated with HD and its typical symptoms.

When we read about "the gene responsible for HD" (Imarisio et al., 2008, p. 191) or about "the causal HD gene" (Walker, 2007, p. 218), it is easy to imagine that normal people have a gene *X* that confers a normal phenotype and that HD sufferers have an abnormal gene *Y* that causes HD. But this is a simplistic understanding. Normal people vary in terms of the number of CAG repeats that characterize their fourth chromosome in the region implicated in HD; up to 35 repeats are not associated with HD (Walker, 2007), but repeats between 27 and 35, while not associated with HD, are nonetheless "meiotically unstable and can expand into the disease range of 36 and above, when transmitted through the paternal line" (Imarisio et al., 2008, p. 192). Even repeats in the 36 to 40 range are not invariably associated with HD; in people with repeat numbers in this range, HD is said to be incompletely penetrant, meaning that some percentage of these individuals will develop the symptoms of HD while the rest will not (for unknown reasons). Thus, the idea that there is "a gene" for HD that people either have or do not have reflects a misunderstanding. In fact, the genetic difference between normal individuals and those who will develop HD appears to be more quantitative than qualitative.

Ultimately, the important point is that genetic factors simply cannot determine phenotypic outcomes in precise ways. In the case of HD, this inability is best reflected in the fact that sets of monozygotic twins with this disorder have nonetheless been observed to develop different clinical symptoms and behavioral abilities. Despite having identical nucleotide sequences in the relevant region of chromosome 4—that is, the twins shared the same number of CAG repeats—the twins observed by Georgiou and colleagues (1999) were markedly different from one another in terms of their behavioral phenotypes. Similarly, the MZ twins observed by Anca and colleagues (2004) were obviously different from one another, both behaviorally and motorically. Of particular interest in the latter cases is the fact that although the twins shared the identical number of CAG repeats, they nonetheless experienced different ages of onset of HD symptoms.

Studying diseases like HD, PKU, and Prader-Willi syndrome can be instructive about how genetic factors contribute to behavioral/psychological characteristics because this sort of exploration can reveal what genes actually do and thereby show how genetic sequences play essential roles in the development of such characteristics, even though their effects on those characteristics ultimately depend on other factors as well. Phenotypes that have been traced to particular genes develop only as a result of complex interactions between the genes in question, other genes, RNA strands, cellular machinery responsible for processes like RNA splicing and autophagy, and a multitude of other molecules (some of which, like dietary factors, reflect organisms' behaviors and/or the environments in which development is occurring). Because the development of even these phenotypes depends on such complex interactions, it is safe to conclude that the development of *all* of our phenotypes—the vast majority of which are known *not* to be monogenic—reflect the contributions of both genetic and nongenetic factors (Meaney, 2010; Noble, 2006). If the development of symptoms of so-called "monogenic" disorders depends on the state of the complex system that contains the genes in question, the development of more complex phenotypes—whether normal or abnormal—can certainly be expected to depend on systemic factors that are at least as complicated.

Keeping the essential interdependence of genetic and nongenetic factors in mind is important for at least two reasons. First, a systems approach that

sees the gene as nondeterministic and instead as just one of many types of developmental resources that can contribute to trait development (Griffiths & Gray, 1994; Jablonka & Lamb, 2005; Moss, 2003; Oyama, 2000) encourages researchers to explore the developmental origins of any trait in question (Moore, 2009). In contrast, a conclusion that a particular trait is "genetically determined," "primarily accounted for by genetic factors," or even merely "somewhat genetically influenced" is an empty claim that effectively discourages further investigation into the actual developmental processes that built the trait (Johnston, 1987; Lehrman, 1953; Lickliter & Berry, 1990). Second, as indicated above, such an approach highlights the multiple possible points of intervention that could be targeted along a developmental pathway in order to benevolently influence development when it otherwise appears to be unfolding undesirably.

Two Meanings of the Word "Interaction"

Because systems theorists insist that nongenetic factors always play essential, causal roles in the development of all biological and psychological characteristics (e.g., Jablonka & Lamb, 2005; Lewkowicz, 2011; Lewontin, 2000; Meaney, 2010), they are often accused of holding an environmentalist position reminiscent of the position stereotypically ascribed to behaviorists. However, systems theorists are as committed to the importance of genetic factors in development as they are to the importance of nongenetic factors (in fact, their focus is on the developmental process itself, a focus that encourages rejection of a genetic/nongenetic dichotomy in the first place). Such a perspective can help make sense of findings by a number of researchers (Bakermans-Kranenburg & van IJzendoorn, 2006; Caspi et al., 2002, 2003; Fox et al., 2005; Kaufman et al., 2004) that have produced justifiable excitement about how advances in genetic sequencing technologies might contribute to understanding human behavior.

In 2002, Caspi and colleagues reported the results of a study of hundreds of adult male New Zealanders, 36% of whom had experienced maltreatment during childhood. As is the case for the general population, the participants' genomes contained variation at a genetic locus known to be involved in promoting the expression of a gene involved in producing a protein called monoamine oxidase A (MAOA). MAOA is an enzyme that metabolically inactivates several neurotransmitters, including norepinephrine, dopamine, and serotonin; thus, decreased MAOA activity is associated with increased noradrenergic, dopaminergic, and serotonergic activity, which in turn has been found to be associated with aggression and other antisocial behaviors (Caspi et al., 2002). Although Caspi and colleagues did not find that the gene associated with MAOA activity had a main effect on antisocial behavior in adulthood, a significant genotype-by-environment (G×E) interaction was revealed in their study such that the effect of childhood maltreatment on subsequent antisocial behavior was mediated by genotype: among the men with genotypes associated with low levels of MAOA activity, a history of childhood maltreatment was more predictive of later antisocial behavior than it was among the other men. Of the participants who experienced severe maltreatment during childhood and had the genotype associated with low MAOA activity, 85% exhibited some type of antisocial behavior in adulthood. In contrast, among those with the genotype associated with high levels of MAOA activity, a much smaller percentage of severely maltreated participants exhibited antisocial behavior in adulthood. Caspi and colleagues concluded that genetic variation in the MAOA-gene promoter "moderates the impact of early childhood maltreatment on the development of antisocial behavior in males" (p. 853). Clearly, focusing exclusively on the role of maltreatment *or* exclusively on the role of genetic factors in the development of antisocial behaviors would yield an unacceptably incomplete understanding of the emergence of these behaviors.

This sort of G×E interaction has since been seen in several other studies of the effects of genes involved in constructing components of the dopamine (Bakermans-Kranenburg & van IJzendoorn, 2006) and serotonin (Caspi et al., 2003; Fox et al., 2005; Kaufman et al., 2004; Kilpatrick et al., 2007) neurotransmitter systems. For example, Caspi and colleagues (2003) reported that in their prospective study, the likelihood of a person developing symptoms of depression after experiencing one or more stressful life events was influenced by the presence of particular DNA segments associated with the serotonin transporter protein (5-HTT). This protein removes serotonin from synapses, and because increasing serotonergic activity in the central nervous system through the use of selective serotonin reuptake inhibitors (e.g., Prozac) can help alleviate the symptoms of depression (Tamminga et al., 2002), alterations in transcription of the genes involved in producing 5-HTT might be expected to also have effects on mood. In 1996, Lesch and colleagues reported that people's genomes vary in the length of the DNA segment involved in promoting transcription of the 5-HTT gene and that "long" and "short" versions of this segment are associated with differing transcriptional efficiencies, differing expression of 5-HTT, and differing likelihoods of having anxiety-related personality traits. As they had predicted, Caspi and colleagues (2003) found that individuals with two "long" segments (one received from each parent) were less likely to develop depressive symptoms after experiencing life stressors than were individuals with at least one "short" segment. They concluded that this genetic feature interacts with life events such that "an individual's response to environmental insults is moderated by his or her genetic makeup" (p. 386).

G×E interactions involving 5-HTT have since been replicated with a population of hurricane-exposed individuals (Kilpatrick et al., 2007) and extended in studies with juvenile participants who were (Kaufman et al., 2004) and were not (Fox et al., 2005) experiencing psychopathology. Kaufman and colleagues (2004) found that "maltreated children with [two 'short' DNA segments—called alleles—in the 5-HTT promoter region] and no positive [social] supports had the highest depression ratings, scores that were twice as high as the nonmaltreated comparison children with the same genotype" (p. 17316); these scores were also nearly twice as high as the maltreated children with at least one "long" allele. Kilpatrick and colleagues (2007) reported that individuals with the "short" sequence in the 5-HTT promoter region and lacking social supports were at increased risk of developing posttraumatic stress disorder and/or major depression following high levels of hurricane exposure; in contrast, individuals with low levels of exposure to hurricanes—like individuals without the "short" sequence in the 5-HTT promoter region, regardless of their hurricane exposure or social supports—were at reduced risk for these conditions. Finally, Fox and colleagues (2005) discovered that behavioral inhibition in middle childhood (Kagan, Reznick, & Snidman, 1987) could be predicted with knowledge of both a child's genotype and levels of social support; as expected, children with low levels of (mother-reported) social support who also had at least one "short" 5-HTT promoter allele were more likely than other children to behave in an inhibited manner when placed in unfamiliar situations (see Fox et al., this volume 2; Kagan, this volume 2).

These sorts of findings are undoubtedly an important first step in unraveling the complex interactions of genetic and nongenetic factors in the construction of phenotypes like depression, behavioral inhibition, antisocial behavior, and posttraumatic stress disorder. However, although these findings seem to highlight gene–environment interactions, they do not actually provide adequate developmental explanations of the origins of these phenotypes. The researchers conducting these kinds of studies have adopted a theoretical framework consistent with diathesis–stress models; their

implicit belief seems to be that a person can have a genetic predisposition (a diathesis) for a behavioral phenotype that is realized only in particular (stressful) environmental contexts. Such a perspective appears to emphasize the interactive nature of development, but it nonetheless implicitly accepts a false dichotomy between evolutionarily provided (i.e., genetic) and developmentally provided (i.e., environmental) contributors to phenotypes (Johnston, 1987; Lehrman, 1953; Lickliter, 2009; Lickliter & Berry, 1990; see also Griffiths & Gray, 1994). Generally, systems theorists (e.g., Blumberg, 2005; Gottlieb, 1991a, 1992, 1997, 1998; Johnston, 2010; Lickliter, 2009; Moore, 2001) would consider predispositions to be like any other phenotypes in that they *develop* as a consequence of gene–environment interactions (Moore, 2009); one reason for thinking this way is that a genetic characteristic associated with an undesirable outcome in one context could be associated with a desirable outcome in a different context (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011). Because diatheses must arise in development, most systems theorists would not consider the G×E interactions revealed in, for example, Caspi and colleagues' (2002, 2003) studies to be the same kinds of interactions as the kinds of gene-environment interactions known to characterize phenotypic development. In fact, the word "interaction" is used in the psychological science literature in more than one way.

As Griffiths and Tabery (2008) have noted, the word "interaction" has historically been used in two very different ways when talking about how genetic and environmental factors relate to one another. Quantitative behavioral geneticists focus not on "the causal-mechanical interplay between genes and the environment during the developmental process…[but] instead on the relative contributions of genotypic and environmental differences to the total phenotypic variation of a particular trait in a particular population" (Griffiths & Tabery, 2008, p. 341). Although the studies reported by Bakermans-Kranenburg and van IJzendoorn (2006), Caspi and colleagues (2002, 2003), Kaufman and colleagues (2004), Fox and colleagues (2005), and Kilpatrick and colleagues (2007) differ from traditional quantitative behavioral genetics studies in that variations at particular genetic loci are actually observed in these studies, they are nonetheless able to inform us only about the contributions of variation at these loci to phenotypic variations; the interactions they reveal are of the sort revealed in analyses of variation (ANOVA). In contrast, the actual physical interactions known to characterize the relationships between genetic and nongenetic factors—what Griffiths and Tabery call "the causal-mechanical interplay between genes and the environment"—have only recently begun to attract the attention of scientists otherwise exploring ANOVA-style G×E interactions (e.g., Fox, Hane, & Pine, 2007; Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008; and to a lesser extent, Canli et al., 2006). Distinguishing clearly between ANOVA-style interactions and causal-mechanical interactions is important, as failing to do so can have unintended consequences worth considering here. In particular, losing sight of this distinction could inadvertently lead to the false conclusion that some phenotypes develop independently of environmental (or genetic) input.

The dual use of the word "interaction" in the biological and behavioral sciences can, in effect, suggest that we understand the origin of a phenotype when in fact we do not. ANOVA-style studies like those reported by Caspi and colleagues (2002, 2003) ask whether genetic factors interact with environmental factors to produce psychological phenotypes, and the Caspi team's published studies indicate that the DNA segments being studied do interact, somehow, with environmental factors. However, if an ANOVA-style study were to reveal only a main effect of a genetic factor and/or a main effect of an environmental factor—and no statistical interactions—it would nonetheless still be the case that the phenotype being studied was built by "causal-mechanical" gene-environment interactions. Because we know that all phenotypes are built by gene-environment interactions (Eisenberg, 2004), findings of no statistical interaction between a particular influential environmental factor and a particular influential genetic factor would mean only that the particular genetic factor being studied has its influence via interactions with some other (likely unmeasured) environmental factor(s) and that the particular environmental factor being studied has its influence via interactions with some other (likely unmeasured) genetic factor(s).

To see the importance of maintaining a systems perspective when considering ANOVA-style studies, consider the results of the following two different meta-analyses of 14 independently conducted studies on stressful life events and variations in the 5-HTT promoter region. Based on their meta-analysis, Munafò and colleagues (2009) concluded that "the interaction effect between [variations in the 5-HTT promoter region and stressful life events] on risk of depression [is] negligible" (p. 211). Similarly, an equally large meta-analysis published in the *Journal of the American Medical Association* (Risch et al., 2009) concluded that there is "no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression" (p. 2462). In discussing their findings, Munafò and colleagues wrote

> A large body of data, outside of the studies reviewed here, indicates that the [5-HTT promoter] effect on depression is very small or negligible. Indeed, the possibility that the polymorphism has no association with the disorder at all has not been excluded. The results of our meta-analysis are consistent with this and further suggest that the [5-HTT promoter region and stressful life events] interaction effect is negligible. Genetic association studies, although not unique in this respect, are notorious for non-replication and inconsistencies. Failure to replicate does not mean that an original finding is necessarily incorrect….Our results cannot demonstrate that the original report of the interaction is a false positive. However, our results do indicate that, under the assumption that there is a common variant of small effect acting at the [5-HTT promoter] locus, this finding could have arisen by chance alone. (pp. 216–217)

The point to take from the discussion above is that regardless of the statistical effects found or not found in ANOVA-style studies of G×E interactions, the fact remains that depression is a complex phenotype that, as such, necessarily emerges from "the causal-mechanical interplay between genes and the environment during the developmental process" (Griffiths & Tabery, 2008, p. 341). ANOVA-style studies can never provide evidence that a particular gene (or environment) is *un*important in the construction of a particular phenotype; at best, they can help identify genetic and environmental factors that are correlated—for any of a number of reasons—with those phenotypes. Thus, if the findings in these ANOVA-style studies ultimately prove replicable, we will have learned that different sorts of experiences and different sorts of alleles moderate one another's effects on the phenotypes being studied. But a developmental perspective demands additional work that will reveal *how* these factors interact mechanistically to contribute to, for example, posttraumatic stress disorder, inhibited behavior, and/or depression. Regarding the latter, researchers studying depression have finally started to consider the causal-mechanical influences of experiences on genes associated with depression, influences that in this case appear sometimes to be epigenetic (Mill & Petronis, 2007).

Epigenetics

The Meaning of "Epigenetics"

Much as the word "interaction" can be used to refer to two different things, the word "epigenetics," too, has been used in different ways in different contexts (Jablonka & Lamb, 2002). In his *Generation of Animals,* Aristotle argued that development entails the gradual emergence of features from earlier states in which such features were not present; in the eighteenth century, the word "epigenesis" was used to refer to such from-simple-to-complex processes. Consequently, "epigenetic" can be used to describe any process in which new forms emerge over time from interactions between different forms existing in earlier states. Thus, we can describe as *epigenetic* the emergence of, for example, a baby's first words, because words are not produced by newborn babies and instead emerge from the interactions of the baby with talking people in her environment. This sense of the word refers broadly to the development of phenotypic features that emerge via interactions occurring between any two or more levels of developmental systems, including the levels of the genes, cells, organs, organisms, etc. (Gottlieb, 1997).

In the 1940s, the developmental biologist Conrad Waddington resuscitated the word "epigenetics" to refer to the study of how *genetic* factors contribute to the *epi*genesis of developing characteristics (Van Speybroeck, 2002); thus, Waddington reintroduced this word into modern biology in a way that ensured that it would continue to refer to developmental processes (Richards, 2006). As noted above, since the mid-1990s (Jablonka & Lamb, 2002) "epigenetic" has primarily been used more narrowly to describe interactions that directly influence the functioning of DNA while not altering the genetic sequence itself (Richards, 2006). Although the word continues to be used in its broader sense as well (e.g., Canli et al., 2006), given the focus of this chapter on the molecular bases of behavior, "epigenetics" will be used hereafter to refer only to the study of interactions between DNA and other molecules in its local environment.

As described previously, nuclei in the cells of complex organisms contain chromosomes made of chromatin, which in turn is made up of DNA and the histone proteins around which DNA is wrapped (Luger et al., 1997); in fact, chromatin contains twice as much protein (primarily histones) as it does DNA (Gibbs, 2003). When a segment of DNA is tightly wrapped around histones, it is called "silent" chromatin; when it is in a state in which the order of bases constituting the segment can be accessed by other molecules in the nucleus, it is called "active" chromatin (Gibbs, 2003). Chromatin remodeling—the name used to refer to the "packaging" modifications that change the chromatin from one of these states to the other—effectively controls access to the DNA and is therefore "a key component in the regulation of gene expression, apoptosis [so-called "programmed" cell death], DNA replication and repair," and other processes (Wang, Allis, & Chi, 2007, p. 363).

Genomic Imprinting and the Epigenetic Control of Genes

The importance of this phenomenon became clear early in the 1960s as biologists began to question why female mammals, who have two X chromosomes in every somatic cell in their bodies, do not synthesize twice as much of the proteins associated with X-chromosome genes as do male mammals, who have only one X chromosome in their somatic cells (Beutler, Yeh, & Fairbanks, 1962). We now know that of the two X chromosomes in normal females' cells, one becomes inactivated extremely early in development (Cheng & Disteche, 2004; van den Berg, et al., 2009). Studies of the processes by which genetic material can be activated or inactivated led to the discovery of a variety of mechanisms by which genetic activity can be influenced (Martin & Zhang, 2007).

Among the most important of these mechanisms is a gene-silencing process known as methylation. Inactivation of genes in this case is accomplished via an enzyme-assisted process of epigenetic "marking" in which methyl groups (CH_3) are attached to cytosine nucleotide bases in a single DNA strand; strand segments that can be marked like this are characterized by a high density of CG sequences, so called because they are sequences in which a cytosine base is followed by a guanine base, which is followed by a cytosine base, and so on. When these CG-dense regions, known to molecular biologists as "CpG islands," are methylated in this way, the conformation of the DNA in that region is altered—remodeled—so that the genes near these islands become inaccessible to the cellular transcription machinery (Martin & Zhang, 2007; Weaver, 2007). Early studies of this phenomenon (Razin, 1998) led to the conclusion that "methylation plays a pivotal role in establishing and maintaining an inactive state of a gene by rendering the chromatin structure inaccessible to the transcription machinery" (p. 4905). Importantly, "sections of chromatin can condense and expand independently, effectively hiding whole swaths of the DNA from view while exposing other sections for transcription" (Gibbs, 2003, p. 113).

Although methyl groups are the only chemical elements known to epigenetically bind with DNA itself, other chemical elements can bind with histone proteins, and these, too, can effectively regulate gene expression by remodeling chromatin, thereby altering the ability of transcription machinery to access information encoded on the DNA strand (Martin & Zhang, 2007). Histones, too, can be methylated, but they can also be acetylated, ubiquitinated, and phosphorylated; these processes remodel chromatin as well, either silencing or activating genes, "depending on the nature of the modification and the specific amino acid [in the histone, which is being] modified" (Martin & Zhang, 2007, p. 266). Relative to histone phosphorylation or ubiquitination, histone acetylation has been much more extensively studied (Myzak & Dashwood, 2006). Therefore, although all of these processes influence development, the remainder of this review will focus on hypermethylation of DNA (associated with inactive chromatin, or gene silencing), on hypomethylation of DNA (associated with active chromatin, or gene activation), and on histone acetylation (typically associated with active chromatin) (Gibbs, 2003; Weaver, 2007).

Before describing some of the effects of DNA methylation and histone modification, it is worth noting that the preceding portrayal of epigenetic modifications of genetic activity might be insufficiently nuanced because it has become clear that the active and inactive states of chromatin are not as clearly defined as previously thought. Instead, epigenetic modifications now appear to sometimes have complex effects on chromatin, leading some theorists to believe "that regulation by DNA methylation or histone modification is dynamic, and that the presence of certain modifications may not indicate a unique regulatory status (that is, 'on' or 'off')" (Berger, 2007, p. 407). Furthermore, although the existence of an elaborate "histone code" has been hypothesized, our understanding of such a code currently remains incomplete at best (Bernstein & Allis, 2005; but also see Taverna, Li, Ruthenburg, Allis, & Patel, 2007).

Collectively, DNA methylation and various histone modifications contribute along with other processes to the normal inactivation of one of a female's X chromosomes early in development (Cheng & Disteche, 2004). Early work on genetic "imprinting" confirmed that because of these sorts of epigenetic

processes, maternal and paternal contributions to a new organism's genome do not function equivalently (Li, Beard, & Jaenisch, 1993; Sapienza, Peterson, Rossant, & Balling, 1987). This discovery suggested that some characteristics might develop differently if a particular gene is inherited from a father than if that same gene is inherited from a mother. Genomic imprinting disorders were subsequently discovered in which a genetic abnormality inherited from a mother produced a different phenotype than the same genetic abnormality inherited from a father.

The first genomic imprinting disorder discovered in human beings was Prader-Willi syndrome (Cassidy, 1997), discussed previously in the section on genetics. As noted there, this syndrome is associated with the deletion of genetic material on the fifteenth chromosome inherited from a patient's father (Schulze et al., 1996). The parental sex specification matters, because in normal individuals, the relevant segment of the fifteenth chromosome provided by a person's *mother* is imprinted and therefore unexpressed (Cassidy, 1997). In contrast, the same segment provided by the person's father contributes to the production of snoRNAs required for normal development (Sahoo et al., 2008). Therefore, the presence of one (or more) normal maternal fifteenth chromosome(s) cannot compensate for an abnormal (or absent) paternal fifteenth chromosome, and these individuals consequently develop the symptoms of Prader-Willi syndrome (Nicholls et al., 1989).

In contrast, a deletion in the same region of the *maternal* fifteenth chromosome leads to the development of an entirely different disorder, Angelman syndrome, which is characterized by severe developmental delay, a movement or balance disorder, frequent laughter, jerky "hand-flapping" movements, and speech impairment involving minimal use of words (Williams et al., 2006). Until relatively recently, the diagnosis of Prader-Willi syndrome was complicated by "the presence of the same chromosomal deletion in patients with Angelman syndrome, a disorder with entirely different symptomatology" (Holm et al., 1993, p. 398); that is, a deletion in a region of the maternal fifteenth chromosome is associated with a completely different phenotype than is a deletion in the same region of the paternal fifteenth chromosome, a pattern that demonstrates the importance of epigenetic imprinting in development. More recent work examining smaller genetic deletions has revealed that Prader-Willi and Angelman syndromes actually involve deletions of adjacent—not identical—genetic segments located in the same region, respectively, of paternal and maternal fifteenth chromosomes (Feinberg, 2007). But both disorders still owe their development to the fact that the segment on the normal chromosome that corresponds to the deleted segment on the other chromosome is imprinted and so unable to compensate for the deletion.

Epigenetic modifications like genetic imprinting are of interest to some psychologists simply because they are associated with disorders like Prader-Willi and Angelman syndromes, which are characterized by behavioral abnormalities. But epigenetic effects are of interest to psychologists concerned with normal behavior as well because they reflect normal organisms' day-to-day experiences, for example experiences with light that adjust our circadian rhythms (Naruse et al., 2004) and experiences that produce contextual fear learning (Levenson & Sweatt, 2005; Sweatt, 2009). As van IJzendoorn and colleagues (2011) note, some epigenetic effects are the "mechanism by which the environment affects the physiology and behavior of the developing child and [by which] development becomes literally embodied in environmentally induced signatures on the epigenome" (p. 305). In this sense, then, some epigenetic effects can be thought of as residual evidence of the interaction between genes and the environment. Moreover, some psychologists are interested in this new line of research because the epigenetic effects of some of our experiences now appear to be transmittable from ancestral generations to descendant generations. Although this possibility would be considered heretical to neo-Darwinism because the idea that "acquired characteristics" can be inherited was roundly rejected by biologists over a century ago (Varmuza, 2003), there is now some evidence that normal experiences produce epigenetic effects that can be transmitted across generations. Epigenetic inheritance will be considered below.

Epigenetic Effects of Experience, and the Epigenetics of Learning and Memory

In a remarkable series of studies, Michael Meaney and colleagues have begun to unravel the processes by which developmental events can influence gene expression via epigenetic modifications to the genome and thereby influence normal behavior (Meaney, 2010; Meaney & Szyf, 2005). These studies have revealed an extremely complex system (Curley, Jensen, Mashoodh, & Champagne, 2011). Nonetheless, the effort required to understand the work described in the next several paragraphs will be rewarded with an appreciation of how important epigenetic phenomena can be to the development and intergenerational transmission of behavioral characteristics.

By the mid-1990s, it was clear that early life stressors in rats (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999a) and nonhuman primates (Coplan et al., 1996) led to adult psychopathology via psychobiological mechanisms involving neuronal systems responsive to corticotropin-releasing factor (CRF). Following up on findings that "maternal deprivation in infancy is associated with enhanced neural CRF gene expression and increased stress reactivity [in adulthood]" (Francis et al., 1999a, pp. 1154–1155), Meaney and colleagues traced the phenomenon in rats to particular variations in maternal care, namely the frequency with which mothers lick and groom their offspring in their first week and a half of life (Liu et al., 1997). Specifically, adult rats that had been exposed shortly after birth to relatively low levels of licking and grooming were more likely than their more-groomed peers to behave in a fearful manner when exploring an open field and when eating in a novel environment (Caldji et al., 1998). These results led to the conclusion that maternal behavior toward immature offspring can "program" the offspring's neuroendocrine and behavioral responses to stress in adulthood (Caldji et al., 1998; Francis et al., 1999a).

Further work involving cross-fostering studies confirmed the hypothesis that individual differences in maternal behavioral styles can be transmitted from mother rats to their daughters (Francis, Diorio, Liu, & Meaney, 1999b). In these studies, female rat pups born to mothers known to not lick and groom their pups frequently (low-LG mothers) were cross-fostered within 12 hours of birth to mothers known to lick and groom their pups frequently (high-LG mothers); likewise, female rat pups born to high-LG mothers were cross-fostered within 12 hours of birth to low-LG mothers. The early experiences of the pups with their foster mothers were apparent when they reached adulthood, both in terms of their fearfulness and in terms of their maternal behavior. Specifically, female rats raised by high-LG mothers were less fearful in novel situations and behaved like high-LG mothers themselves once they had given birth to their own pups (Francis et al., 1999b). The mechanism by which grooming in infancy affects later maternal behavior in rats is complex and is only beginning to be understood (e.g., Champagne et al., 2006), but Meaney (2010) has written that the results of a large number of studies taken together "suggest that differences in DNA methylation may mediate the effect of maternal care on the expression of [particular genes] and thus serve as the molecular basis for the nongenomic transmission of individual differences in maternal behavior from the mother to her female offspring" (p. 63).

Regardless of how these effects are transmitted across generations, the reduced fearfulness in rats exposed in infancy to lots of licking and grooming is now known to be mediated by reduced hypothalamic CRF release (Francis et al., 1999a; Meaney, 2001; Weaver et al., 2004). In turn, reduced hypothalamic CRF release produces less activation of the neuronal system associated with fearful behaviors, namely the pituitary-adrenal system (which together with the hypothalamus is referred to as the HPA axis). However, these effects can be modulated by an animal's sensitivity to glucocorticoids (a class of steroid hormones); rats with more glucocorticoid receptors (GRs) in their brains' hippocampi experience an inhibition of CRF synthesis—and consequently, reduced reactivity to stress—relative to rats with fewer GRs (Meaney, 2001). Meaney considers this to be "a critical feature for the effect of the early environment on…HPA responses to stress, [because] reversing the differences in hippocampal glucocorticoid receptor levels eliminates the differences in HPA responses to stress" between animals exposed in infancy to high versus low levels of maternal licking and grooming (Meaney, 2001, p. 1166). This understanding is consistent with the finding that adult offspring of high-LG mothers "show increased hippocampal GR expression and enhanced glucocorticoid feedback sensitivity" (Weaver et al., 2004, p. 847), which is accompanied by reduced hypothalamic CRF expression and reduced pituitary-adrenal responses to stress.

One of the more interesting developmental questions raised by these findings asks: What sort of mechanism could allow an experience like being groomed in infancy to produce a change in stress reactivity that is mediated by changes in gene expression and that persists into adulthood? Based on additional work conducted in Meaney's lab (Weaver et al., 2004), the answer appears to be "epigenetic programming." It turns out that the DNA methylation patterns detected in rats exposed to high-LG mothers differ significantly from those detected in rats exposed to low-LG mothers. Specifically, Weaver and colleagues (2004) reported that rats exposed to less frequent licking and grooming shortly after birth had significantly more methylated cytosine bases (relative to high-LG rats) in a DNA segment involved in promoting the production of GRs. Thus, the offspring of low-LG mothers produced fewer GRs in their hippocampi by adulthood because the promoter region involved in producing these GRs had been epigenetically silenced.

To determine whether this difference was actually produced as an effect of having been licked and groomed shortly after birth, Weaver and colleagues (2004) conducted a cross-fostering study like the one described above. The results were unambiguous: independent of the characteristics of their biological mothers, rats reared by low-LG mothers had more methylated GR promoter regions than did rats reared by high-LG mothers. Moreover, cross-fostered rats reared by low-LG mothers had methylation patterns that were indistinguishable from the patterns seen in non–cross-fostered rats reared by their own low-LG mothers. Subsequent analysis of the timing of methylation revealed that the DNA region in question (the GR promoter region) was unmethylated in both groups prenatally and that the differences in methylation status between the rats reared by high- and low-LG mothers emerged between the first and sixth day after birth; these differences then remained consistent into adulthood. Consequently, Weaver and colleagues concluded that maternal care in the first week of life can "directly alter the methylation status of the exon 1_7 promoter of the GR gene…[and that therefore] a DNA methylation pattern can be established through a behavioral mode of programming" (p. 849). DNA methylation was also shown to be associated with reduced histone acetylation (which in turn is usually associated with inactive chromatin), further supporting the claim that these rats' neonatal experiences caused reduced levels of gene expression—and hence, altered stress reactivity—for the rest of their lives. Weaver and colleagues (2004) consider these findings to be "consistent with the idea that the maternal effect on GR expression and HPA responses to stress is mediated by alterations in chromatin structure" (p. 852), which themselves result from the epigenetic methylation of DNA sequences.

Importantly, these maternal effects on rats' brains are not limited to increased production of GRs in neural systems associated with stress reactions. For example, Liu, Diorio, Day, Francis, and Meaney (2000) reported that perinatal licking and grooming promote the formation of synapses in the hippocampus and contribute to enhanced spatial learning and memory. Likewise, Zhang and colleagues (2006) reviewed several findings "consistent with the idea that the tactile stimulation associated with maternal licking/grooming alters the mesocortical dopamine system and performance on attentional tests" (p. 81). To date, no evidence has been published—and perhaps none has yet been sought—indicating that maternal effects on rats' performances on tests of cognition can be mediated by epigenetic modifications to their DNA, but given the mechanism by which maternal behaviors affect stress responses in rat pups, such evidence could be discovered in the future.

In fact, Levenson and Sweatt (2005) expect future research to demonstrate an important role for epigenetic mechanisms in information storage in general, including those forms of information storage involved in learning and memory. Nature has already solved a particular information-storage problem with epigenetic mechanisms, namely the problem of how a daughter cell, produced when a differentiated cell divides mitotically, "remembers" what sort of cell its parent was, so that it can function as the same kind of cell. Levenson and Sweatt "predict that these [epigenetic] mechanisms are conserved in the adult nervous system, where they have been co-opted to…subserve changes in neuronal function in the adult that are components of memory at the behavioural level" (p. 109). In support of their claim, they note that exposing rats to aversive stimuli in novel contexts produces a form of learning known as contextual fear conditioning and that this form of learning has been shown to lead to increased acetylation of particular histones in rats' hippocampal neurons (Levenson et al., 2004). Because contextual fear conditioning produces a form of long-term behavioral memory, epigenetic mechanisms can be surmised to be involved in consolidating such long-term memories. Similarly, latent inhibition, another type of long-term memory, has been shown to be associated with a different pattern of histone acetylation. Thus, "specific types of memory [might be] associated with specific patterns of histone modifications" (Levenson & Sweatt, 2005, p. 113).

Further evidence that histone acetylation can improve formation of long-term memories has surfaced in studies of the effects of histone deacetylase (HDAC) inhibitors, chemicals that increase histone acetylation by inhibiting the enzymes that ordinarily remove acetyl groups from histones. Injecting an HDAC inhibitor into the ventricles of the brains of mice had the effect of reversing memory deficits seen in control mice undergoing contextual fear conditioning (Alarcón et al., 2004). Similarly, Bredy and colleagues (2007) found that an HDAC inhibitor was able to enhance long-term memory for extinction of a conditioned fear response, a finding that led them to conclude that "HDAC inhibitors may become a useful pharmacological adjunct to psychotherapy for human anxiety disorders" (p. 268). Coupled with a plethora of circumstantial evidence that implicates dysfunctioning epigenetic mechanisms in the production of human cognitive abnormalities, the data reported by Alarcón and colleagues (2004) and Levenson and colleagues (2004) led Levenson and Sweatt (2005) to conclude that "understanding the epigenetic regulation of neuronal function will be vital for fully understanding the molecular processes that govern memory formation and human cognition" (p. 116).

Epigenetic Phenomena in Human Populations

The relevance of discoveries about epigenetics to the development of biological and behavioral characteristics in human beings is only now beginning to be understood, as data from studies of human populations have finally begun to appear. For instance, although MZ twins have identical genomes and are commonly called "identical" twins, these individuals are virtually always distinguishable, and one possible explanation for this observation is the existence of epigenetic differences between them. In a study of 40 pairs of MZ twins, Fraga and colleagues (2005) reported that significant differences in DNA methylation and histone acetylation emerged over the course of the first few decades of life. Moreover, the greatest DNA methylation and histone acetylation differences were found among twins who spent most of their lives apart from each other. As would be expected from that finding, Fraga and colleagues also found that the gene expression profiles of the twin pairs were very similar in 3-year-old twins and very different in 50-year-old twins. Consequently, it has become clear that a lifetime of experiences leaves its marks on our genomes, altering how—and even if—our genes are expressed (Masterpasqua, 2009; Szyf, McGowan, & Meaney, 2008). Among the experiential factors either known or strongly suspected to influence an organism's epigenetic state are diet, chemicals (including some used as drugs), and metals (Gallou-Kabani, Vigé, Gross, & Junien, 2007; Junien, 2006; Singh, Murphy, & O'Reilly, 2003).

Studies of the effects of specific experiences on methylation patterns in humans are just getting under way (Curley et al., 2011), but at least a half-dozen studies have discovered phenomena that are analogous in important ways to the phenomena Meaney's team has been exploring in rats (e.g., Weaver et al., 2004). In a study of newborn human babies, Oberlander and colleagues (2008) examined methylation of a DNA segment called NR3C1, a segment that is homologous to the GR gene in rats. To look at the effects of prenatal exposure to maternal depression, Oberlander and colleagues recruited a sample of 82 pregnant women, 46 of whom were experiencing the symptoms of depression. Once the babies were born, samples of their umbilical cord blood were subjected to DNA methylation analysis. As the authors had predicted, specific locations in NR3C1 in babies born to women who had experienced symptoms of depression in their third trimesters were significantly more methylated than those locations were in babies born to symptom-free women. Importantly, babies born to depressed women did not have more highly methylated NR3C1 genes in general; the effect was limited to a region theoretically predicted to be associated with babies' HPA stress reactions later in life. And in fact, as predicted, the babies born to depressed women were found at the age of 3 months to have increased salivary cortisol stress responses relative to control babies. Although the authors statistically controlled for a number of potentially confounding variables in this study, the study was exploratory and remains correlational, of course; nonetheless, they felt comfortable concluding that their "findings suggest that increased third trimester depressed maternal mood is associated with increased infant HPA stress responsiveness, via a potential epigenetic link that involves methylation of the human NR3C1 gene" (p. 100) and that "neonatal methylation at this site might offer an early epigenetic marker of exposure to late gestational maternal depressed mood and risk for altered HPA function in humans" (p. 101). A more recent study also found a relationship between depression in pregnant women and, once their babies were born, methylation in the newborns of the serotonin transporter (5-HTT) gene promoter; these findings led the authors to conclude "that alterations in epigenetic processes may contribute to developmental programming of [childhood] behaviour by maternal depression" (Devlin, Brain, Austin, & Oberlander, 2010, p. e12201).

Another study of human NR3C1 gene expression examined hippocampal samples taken from the brains of dead adults who either had or had not experienced abuse as children. McGowan and colleagues (2009) found increased methylation of a segment of the NR3C1 promoter in the brain tissue of suicide victims who had experienced child abuse, but not in suicide victims—or in nonsuicidal adults who experienced sudden, accidental deaths—who had not experienced abuse as children. An earlier study found in several brain areas epigenetic differences between suicide victims and adults who died suddenly for other reasons (Poulter et al., 2008), but McGowan and colleagues' data revealed an effect analogous to that of Weaver and colleagues (2004), in that reduced hippocampal GR expression in adults was associated with *poor parenting* experienced earlier in development, not with suicide *per se*. McGowan and colleagues concluded their report by speculating that "epigenetic processes might mediate the effects of the social environment during childhood on hippocampal gene expression and that stable epigenetic marks such as DNA methylation might then persist into adulthood and influence the vulnerability for psychopathology" (p. 346). More recently, Beach, Brody, Todorov, Gunter, and Philibert (2010) have provided corroborating evidence that both men and women abused as children carry long-term epigenetic marks of that experience. Specifically, these researchers reported that individuals abused before the age of 16 were more likely to grow up to be adults with hypermethylated 5-HTT gene promoters.

Another study examined the effects of the *physical* environment during gestation on methylation of the gene containing information for insulin-like growth factor II (IGF2; Heijmans et al., 2008). The Dutch Hunger Winter was a Nazi-imposed famine that occurred in the Netherlands in the winter of 1944–1945; it was preceded and followed by periods in which normal food consumption was possible, thereby exposing fetuses at very specific times in gestation to extreme undernourishment. Compared to same-sex siblings conceived before or after the famine, individuals who were conceived while the famine was ongoing were found to have less methylated IGF2 genes when they were tested six decades later, even though only some of the affected individuals were born with a low birth weight. These findings indicate that "transient environmental conditions early in human gestation can be recorded as persistent changes in epigenetic information" (Heijmans et al., 2008, p. 17048), and they led the authors to publish a follow-up review article with the thought-provoking title "The epigenome: Archive of the prenatal environment" (Heijmans, Tobi, Lumey, & Slagboom, 2009).

Other researchers have assessed the effects of early life experiences on DNA methylation more broadly, across the entire genome. Borghol and colleagues (2011) studied the relationship between adults' blood DNA methylation profiles and the socioeconomic status (SES) of these individuals both in childhood and adulthood. As might not be surprising given the long-term effects reported by Heijmans and colleagues (2008, 2009), the results indicated that SES in childhood was more closely associated with adult methylation levels than was SES at the time the participants' blood was analyzed; specifically, childhood SES was associated with differences in methylation of far more gene promoters than was adulthood SES. These findings are consistent with others (e.g., Miller et al., 2009) that have demonstrated a long-term effect of low SES in childhood on the development of chronic diseases in adulthood. Borghol and colleagues concluded that their result "suggests a well-defined epigenetic pattern linked to early socio-economic environment" (p. 1).

Finally, van IJzendoorn, Caspers, Bakermans-Kranenburg, Beach, and Philibert (2010) found higher levels of methylation of a DNA segment

associated with the 5-HTT promoter in individuals experiencing “unresolved loss” of an attachment figure or some other traumatic event, but only if those individuals had two “long” alleles in the 5-HTT promoter region; such loss or trauma in individuals with two “short” alleles in the 5-HTT promoter region was associated with lower levels of methylation. Consistent with the conclusions drawn by other researchers studying epigenetic effects of experience in human beings, van IJzendoorn and colleagues wrote that “methylation may serve as the interface between adverse environment and the developing organism” (p. 405) because environmentally induced methylation patterns alter how human genotypes are associated with psychological problems.

The growing awareness of the importance of epigenetic phenomena has inspired a large-scale international research project designed to map out the human epigenome (Brena et al., 2006); this project is likely to eventually rival the Human Genome Project in terms of complexity, scope, and ultimately importance (Gomase & Tagore, 2008). Early work in this domain yielded methylation profiles of human chromosomes 6, 20, and 22 (Eckhardt et al., 2006), and additional information will undoubtedly be forthcoming. Although some of this information will be collected in the interest of understanding the role of epigenetic phenomena in the development of cancer and autoimmune diseases (Feinberg, 2007; Myzak & Dashwood, 2006; Singh et al., 2003; Taverna et al., 2007; Wang et al., 2007), much of it will eventually be useful to researchers in the behavioral sciences, too; the number of psychological phenomena now hypothesized to be influenced by an organism’s epigenetic state is growing and includes normal phenomena such as learning and memory (Sweatt, 2009) as well as abnormal phenomena such as major depressive disorder (Mill & Petronis, 2007), bipolar disorder (Feinberg, 2007; Gomase & Tagore, 2008), schizophrenia (Petronis et al., 2003; Singh et al., 2003; Veldic, Guidotti, Maloku, Davis, & Costa, 2005), posttraumatic stress disorder (Yehuda & Bierer, 2009), and the autism spectrum disorders (Persico & Bourgeron, 2006).

Work in epigenetics has inspired excitement for several reasons, one of which is the fact that it suggests possible “environmental” treatments for a variety of abnormal conditions. Because diet (Waterland & Jirtle, 2003) and exposure to certain chemicals (Crews et al., 2007) can influence an organism’s epigenetic state, controlling exposure to these stimuli—either prenatally or postnatally—could either prevent or provide targeted treatment for disorders associated with epigenetic modifications (Feinberg, 2007; Junien, 2006; Junien & Nathanielsz, 2007; Myzak & Dashwood, 2006; Raj & Mufti, 2006). In fact, Weaver and colleagues (2004) were able to use the chemical trichostatin A—a histone deacetylase inhibitor—to eliminate the pituitary-adrenal, GR expression, DNA methylation, and histone acetylation effects that had developed in adult rats previously exposed to low-LG mothers; thus, epigenetic modifications produced by life experiences have proven to be experimentally reversible. Such demonstrations have stoked hopes that dietary and/or drug regimens will be found that can modulate chromatin structure and thereby effectively treat disorders as diverse as type 2 diabetes (Junien & Nathanielsz, 2007), schizophrenia (Singh et al., 2003), major depressive disorder (Mill & Petronis, 2007), Rett syndrome (Feinberg, 2007), and other psychiatric (Narayan & Dragunow, 2010; Tsankova, Renthal, Kumar, & Nestler, 2007) or nonpsychiatric disorders such as cancer (Gomase & Tagore, 2008; Myzak & Dashwood, 2006) and the myelodysplastic (preleukemia) syndromes (Raj & Mufti, 2006).

Epigenetic Inheritance

Epigenetic research has also generated excitement among those who study evolution because it now appears that epigenetic modifications acquired during development have the potential to be transmitted to descendant generations (Franklin & Mansuy, 2010), a finding that is antithetical to neo-Darwinian orthodoxy regarding the inheritance of acquired characteristics (Varmuza, 2003). Developmental and evolutionary phenomena are conceptually distinct, but because they bear on one another, a brief discussion here of the evolutionary implications of the inheritance of epigenetic modifications is warranted (Lickliter, 2008; Moore, 2001, 2008). Studies of epigenetic imprinting have indicated that after the creation of a new organism via fertilization, epigenetic marks in the new organism’s germ cells are “erased” in the early stages of germ-cell development and then reestablished at a later stage; in this way, imprints are reset so that mature sperm and mature eggs have imprints appropriate for male and female gametes, respectively (Rakyan & Whitelaw, 2003; Reik & Walter, 2001; Richards, 2006). The erasure process occurs via “genome-wide demethylation in germ cells…in both sexes” (Reik & Walter, 2001, p. 23) and would seem to make the inheritance of epigenetic modifications to the genome impossible. Nonetheless, several studies have now shown that epigenetic modifications can, in fact, be transmitted from one generation to the next (Anway, Cupp, Uzumcu, & Skinner, 2005; Crews et al., 2007; Morgan, Sutherland, Martin, & Whitelaw, 1999; Rakyan et al., 2003; Rakyan & Whitelaw, 2003). Rakyan and Whitelaw (2003) liken this phenomenon to a sort of “memory of the epigenetic state [that persists] in the next generation” (p. R6).

The first report of intergenerational transmission of an epigenetic modification in mammals grew out of a study of fur color in a particular type of mice. Morgan and colleagues (1999) reported that fur color in these mice is influenced by the methylation of a particular DNA segment and that the fur color of the offspring of those mice is related to their mothers’ fur color (additional work by Waterland & Jirtle in 2003 also revealed an epigenetic effect in which the offspring’s coat color was caused by aspects of the mother’s diet during gestation). The maternal epigenetic effect that Morgan and colleagues (1999) observed was subsequently demonstrated to result from “incomplete erasure of an epigenetic modification when a silenced [maternal gene]…is passed through the female germ line, with the consequent inheritance of the epigenetic modification” (Morgan et al., 1999, p. 314). Rakyan and colleagues (2003) discovered a similar phenomenon in their studies of a DNA segment associated with kinked tails in mice. The kinked-tail phenotype is correlated with methylation of the DNA segment in question and was found to be transmittable from a father to its offspring, a particularly important finding because it “argues against the possibility that the effects are due to cytoplasmic or metabolic influences” since a sperm contributes virtually no cytoplasm to a zygote (Rakyan et al., 2003, p. 2538). Like Morgan and colleagues, Rakyan and colleagues found that the epigenetic modifications associated with kinked tails were not completely erased during gametogenesis, meaning that intergenerational transmission of such modifications are, in fact, possible in mammals. Other studies of the transgenerational inheritance of epigenetic states have demonstrated that pregnant rats exposed to certain industrial toxins produce male offspring that, as adults, have reduced capacities for generating viable sperm, an effect that appeared to be associated with altered DNA methylation patterns and that was then transmitted to three subsequent generations of offspring (Anway et al., 2005). A later study conducted using this paradigm found that “females three generations removed from the exposure discriminate and prefer males who do not have a history of exposure” (Crews et al., 2007, p. 5942).

Given that these sorts of phenomena have been demonstrated, it is reasonable to suspect that inheritable epigenetic effects might be found in human populations as well (Franklin & Mansuy, 2010). The possibility of intergenerational transmission of epigenetic modifications to the genome has not yet been studied extensively in human populations, but Pembrey and colleagues (2006) have reported a transgenerational effect of experience that

seems to suggest that such effects will be discovered soon. In a study of 2,121 grandparents, their children, and their grandchildren, these researchers found an effect of food availability when the grandparents were children (prepuberty) on the mortality risk ratios (RRs) of their grandchildren. Specifically, the "paternal grandfather's food supply was only linked to the mortality RR of grandsons, while [the] paternal grandmother's food supply was only associated with the granddaughters' mortality RR" (Pembrey et al., 2006, p. 159). This finding led the authors to hypothesize that these transgenerational effects were mediated by the X and Y chromosomes. Pembrey and colleagues were appropriately circumspect in their discussion of the role of epigenetic marks in this transgenerational effect because their data were suggestive only; nonetheless, they were clearly as intrigued by the possibility that this was an effect of epigenetic inheritance as were Rakyan and Beck, who wrote in the same year that an environmentally induced epigenetic modification of the X and/or Y chromosomes is "a likely mechanism underlying the…Pembrey et al. [effect]" (2006, p. 575). Approaching the question of epigenetic inheritance in human beings from a more theoretical perspective, Harper (2005) has argued persuasively that among the traits that could be considered good candidates for this sort of transmission are physical growth (i.e., body mass) and the temperamental characteristic of behavioral inhibition (Kagan, Reznick, & Snidman, 1987; Fox et al., this volume 2; Kagan, this volume 2).

Regardless, the finding that epigenetic effects can be transmitted to descendant generations in rats and mice means that we must reevaluate biologists' traditional dismissal of the idea that traits acquired through experience can be handed down to offspring (Richards, 2006). It now appears that such phenomena can occur. These discoveries suggest a need to rethink the neo-Darwinian concept of inheritance—so-called "hard" inheritance—which maintains that that which offspring inherit from their parents is impervious to changes resulting from parents' lifetime experiences. The idea of hard inheritance has guided biological thought since the end of the nineteenth century when August Weismann put forth his "continuity of the germ plasm" doctrine (Barker, 1993), but discoveries of epigenetic inheritance should encourage us to consider whether it might finally be time to abandon Weismann's principle in the interest of constructing a unified theory of phenotypes that encompasses both evolutionary and developmental phenomena (Moore, 2008). At the very least, the discovery of epigenetic inheritance should help consign to history the notion that phenotypes develop for *either* phylogenetic reasons *or* ontogenetic reasons; epigenetic inheritance can, perhaps more than any other phenomenon, draw our attention to the essential interdependence of genetic and experiential factors as they coact to build physiological, morphological, and behavioral phenotypes in development (Moore, in press; Lickliter & Berry, 1990; Lickliter, 2009, 2010).

The fact that epigenetic marks can be influenced by events experienced during development (Curley et al., 2011; Sweatt, 2009; Szyf et al., 2008) and the possibility that those marks can be inherited have the potential to make advances in molecular biology of increasing importance to psychologists (Masterpasqua, 2009). Developmentalists, in particular, are appropriately concerned with the *processes* by which behaviors and mental states emerge over time (Moore, 2009; Spencer et al., 2009), and the rising science of epigenetics opens the possibility of exploring the genetic contributions to psychological phenomena in this way. Whereas behavioral genetics and molecular biology have traditionally been, in some ways, inherently antidevelopmental because of their concern with the presence or absence of particular *structures* (i.e., genes) in the genome (Lickliter, 2008; Lickliter & Honeycutt, 2003), epigenetics is, in some ways, inherently developmental, in part because of its origins in the developmental theories of Conrad Waddington and in part because the epigenetic system is "potentially responsive to different environmental stimuli throughout life" (Szyf et al., 2008, p. 46). As our understanding of epigenetics increases over the next several years, the advances will no doubt continue to be of particular interest to developmental psychologists.

Conclusion

The information generated by molecular biologists from their detailed analyses of the genome is sure to be extremely valuable as scientists struggle collectively to understand the origins of human beings' behavioral/psychological characteristics. There can be no doubt that genetic differences contribute to phenotypic differences among individuals. Consequently, understanding how genetic and epigenetic factors contribute to the development of our characteristics will be important for coming generations of psychologists. Because of the rapid advances being made in molecular biology, this is a particularly exciting time to be a behavioral scientist.

The biological systems that generate behaviors and psychological states have been found to be extraordinarily complex. This is regrettable, in a way, because this complexity can be intimidating and in some cases can lead to attempts at simplification that are profoundly misleading. For example, the data currently available make it clear that although genetic factors contribute to the development of all behavioral phenotypes, they do not determine any of them independently of the contexts in which development occurs (Meaney, 2010); if we are talking about genes in the sense of physically detectable molecular sequences in our DNA—Moss' (2003) Genes-D—there are no such things as "genes for" particular behaviors, temperaments, eye colors, intelligence, or any other characteristics. These characteristics do not arise in development as a result of the deterministic actions of genes (Noble, 2006); rather, they emerge from the interactions among components operating at various levels of an extremely complex system (Gottlieb, 2007; Lewkowicz, 2011). Unfortunately, this kind of complexity is not easily embraced, but useful advances in our understandings of both normal and abnormal development are going to require an appreciation of this complexity. As Weiss and Terwilliger (2000) noted, "the problems faced in treating complex diseases as if they were Mendel's peas show…that 'complexity' is a subject that needs its own operating framework, a new twenty-first rather than nineteenth—or even twentieth—century genetics" (p. 156).

In retrospect, no one should have expected it to be possible to leap from an understanding of the behavior of molecules like DNA to a full-blown understanding of organisms' behaviors, any more than we should have expected an understanding of the behavior of air molecules in a concert hall to yield a full-blown appreciation for the wonder of a symphony. But the discovery of molecular factors closely correlated with phenotypes was so momentous as to have been awesome; it is no wonder that genes and their effects have captured the public's imagination in the past 50 years. Nevertheless, although sequencing the human genome was an enormous breakthrough (because we will never fully understand the development of behaviors without understanding genes), no behavior will ever be fully understood simply by understanding the function of segments of DNA, let alone knowing merely that the presence of particular genes is correlated with the presence of particular behaviors. Instead, comprehensive understanding will await the results of developmental research designed to explore the coactions of factors at the levels of the genome, the epigenome, the cytoplasm, cells, organs, bodies, and societies.

Questions for Future Research

1. What kinds of cells besides neural and blood cells might show epigenetic effects of experience?
2. Do maternal behaviors epigenetically influence stress reactivity in human infants as they do in newborn rats? What specific maternal behaviors are implicated in any such effects in human beings?
3. What are the specific roles immediate early genes play in memory and learning?
4. Can we consider the various epigenetic alterations of histones to be a sort of code that could potentially be exploited in the prevention or treatment of pathology? If so, what is that nature of the code?
5. What are the legal and ethical implications of the discovery that an individual's experiences might have biological consequences for his or her grandchildren?

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Notes:

(1) . Oyama (2000) has argued that DNA does not actually contain information but instead that information itself emerges during development, from the interaction of genetic and nongenetic factors. In this chapter, I will adopt the definition of "information" developed by communications scientists in the twentieth century: that which produces one of at least two possible states in a "receiver," or in other words, a difference that makes a difference (for more on this definition, see Johnston, 1987, Griffiths & Gray, 1994, or Jablonka & Lamb, 2005). Given this definition, DNA can be taken to contain information.

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