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Toward an Integration of Social and Biological Research

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Abstract

Accumulating evidence about the effects of genetics on mental disorders has given rise to calls to incorporate knowledge of gene-environment interactions into social work teaching, research, and practice. Social workers must become aware of the interplay between genes and environments in order to optimize research, prevention, and treatment. This article presents three conceptual frameworks for integrating genetic and environmental evidence and for organizing knowledge from once-distinct disciplines into a unified framework. Recent evidence for gene-environment interactions is presented to demonstrate the importance of integrating knowledge across disciplinary boundaries.

Decades of social research document associations between high-risk environments and poor mental health. But, despite increasing evidence for genetic influences on disorders ranging from depression (e.g., Sullivan, Neale, and Kendler 2000; Klein et al. 2001) to attention-deficit/hyperactivity disorder (e.g., Todd et al. 2001; Rietveld et al. 2003, 2004), much of this research lacks a consideration of genetic contributions to mental disorder. Recently there has been some movement toward integrating genetic considerations into social work education, practice, and research. A report titled “Standards for Integrating Genetics in Social Work Practice,” released in 2003 by the National Association of Social Workers (NASW), calls for social workers to “understand how social, behavioral, cultural, economic, and environmental factors interact with biological factors to influence health” (NASW 2003, 8). Eileen Gambrill, the outgoing editor of the *Journal of Social Work Education* in 2003, advises “social work educators to be informed about the complexity of interactions between genes and their environments, so they can alert students to controversies in the field” (Gambrill 2003, 169). Because of its interdisciplinary nature, social work is well positioned to undertake and lead an integration of social and biological research. Such an integration will contribute to a better understanding of the complex etiology of mental disorders and to improved prevention and treatment.

One impediment to an integration of knowledge is researchers’ failure to use a clearly defined conceptual framework to organize the findings from social and biological sciences around unified goals. One such goal might be to refine prevention and treatment efforts so that they suit an individual’s liability to, or experience of, a given disorder. This refinement might encourage social workers to intervene on the basis of characteristics of the disorder, individual predispositions, and the client’s accumulated life experience. Research that considers the biological and environmental antecedents to mental disorders can help to refine prevention and treatment modalities, thus improving effectiveness. This article describes three conceptual models that can be used to guide interdisciplinary research, and it demonstrates their usefulness as an integrative framework by reviewing recent evidence of gene-environment interactions.

Biopsychosocial Model

The biopsychosocial model was proposed by George Engel (1926–99), a physician and researcher who was frustrated with the dominance of the biomedical model in medicine and

psychiatry. Engel claimed that the biomedical model was so entrenched in medicine as to have become dogmatic in application, requiring that data fit within the model's parameters or be excluded from consideration (Engel 1977). The biomedical model clung to two philosophical views that Engel argued no longer suited medicine: (1) reductionism, or the idea that even complex phenomena can ultimately be explained by a single principle, and (2) mind-body dualism, or the belief in the separation of mental and physical processes and in the exclusive reliance on physical processes to explain illness and disease (Engel 1977). Engel claimed that the biomedical model's apparent success, evidenced by scientific advances that identified causes and treatments for disease, seduced the medical disciplines into "adherence to a model of disease no longer adequate for the scientific tasks and social responsibilities of either medicine or psychiatry" (Engel 1977, 129).

Engel (1977) defined six ways in which the biomedical model failed to realistically account for the origins and treatment of illness and disease:

1. Biochemical deviation from the norm is not in itself sufficient to explain the development of disease. Individuals may possess abnormalities that are never manifested as disease.
2. In order to understand and correctly interpret patient reports of symptoms, physicians must understand how psychological, social, and cultural factors influence patients' communication about their symptoms, rather than relying solely on laboratory tests and measurements.
3. Susceptibility to disease is influenced by the environmental and social conditions in which people live.
4. Individual psychology and social factors influence when a person seeks treatment for symptoms.
5. Treatment and correction of a biochemical abnormality does not always restore the patient to health. Treatment outcomes also depend on psychological and social variables.
6. The patient-physician relationship is itself influential in the treatment of illness or disease.

The theme uniting Engel's six points is the consideration of social, psychological, and environmental factors in the assessment and treatment of disease. Engel's proposed biopsychosocial model considers four factors in the design of research about and treatment of illness and disease: the individual, the social context in which the individual is embedded, the social context of the health care system, and the physician-patient relationship.

Engel used systems theory (von Bertalanffy 1968) as an organizing framework for the biopsychosocial model. This reflects the fact that systems theory assumes interdependence among all levels of organization. Interdependence fosters communication, and Engel (1977) believed that a model based on systems theory would facilitate communication among scientific disciplines. For example, physicians who treat disease would become conversant with the environmental correlates as well as the biomedical markers of disease; change in one might signal change in another.

Niall McLaren (1998) argues that Engel's model does not meet criteria for either a model or a theory. While systems theory provides a framework for modeling the relationship between abstract concepts like social context and disease susceptibility, those abstract concepts are never converted into specific variables with which to model Engel's hypothesized processes and relationships (McLaren 1998). Nonetheless, the biopsychosocial model provides a

conceptual basis for a more holistic treatment of illness and disease than that afforded by the biomedical model.

The biopsychosocial model is well suited as a framework for research in the social sciences and as a means for creating a bridge with biological science, because it is broad enough to incorporate genetic and environmental factors as potential contributors to health and illness. However, social researchers who use the biopsychosocial model must be careful not to make the same type of mistake (though opposite in intent) as researchers using the biomedical model. That is, social researchers must take care not to discount or exclude genetic effects as potential explanatory factors in their research. For example, many studies of child rearing and family socialization fail to consider that at least part of any socialization effect might be explained by the genetic correlation among family members. This failure may be because the researchers “implicitly assume that heredity lacks any agency” (Rowe 1994, 20).

Years before Engel proposed the biopsychosocial model, he pondered the relationship between psychology and biology. He mused that biological processes early in life might influence an individual’s mental health later in life and that a person’s character and mental balance are “influenced by the nature of early life experience. . . . Thus, at any later point in time, what constitutes stress to any individual will be determined to a large degree by the nature of his past experience (as well as by the character of his genic endowment)” (Engel 1960, 477). Implicit in this statement is a belief in the importance of the timing of events in the human developmental sequence and a scientific desire to examine the effects of both experiential and genetic factors on physical and psychological health.

What is most curious about the longevity of the idea that both biological processes and life experience affect mental health is the idea’s failure, despite its longevity, to take root in practical application to research designs. One reason for this slow progress may be that science has only recently advanced to the point where biological measures facilitate modeling the ideas implicit in Engel’s work. For example, measurement of brain function with neuroimaging techniques and measurement of hormones as indicators of stress response have increased knowledge about the human physiological response to environmental stimuli, allowing more explicit testing of the interactions between biology and environment than previously possible. A lack of communication and integration across disciplines might also account for the slow progress of research that examines the contributions of both biology and environment to health and illness. Because the idea that both life experience and biological factors influence health is conceptually broad, no single discipline can gather and test all the data necessary to support or refute its viability, making interdisciplinary research particularly well suited to its testing and evaluation.

Diathesis-Stress Theory

The diathesis-stress theory of mental disorder proposes that stress activates a latent diathesis, which then manifests as some form of psychopathology. Most models based on the theory assume that the diathesis alone is a necessary but not sufficient condition to produce mental disorder and that the interaction with stress activates the diathesis to increase the risk for development of mental disorder (Zuckerman 1999).

Diathesis

The first diathesis-stress model was developed to conceptualize the etiology of schizophrenia (Meehl 1962, 1989; Zuckerman 1999). The model has since been adopted for the same purpose with major depression (Monroe and Simons 1991). When the model was first proposed, the diathesis was presumed to be a genetic predisposition that was observable in biological traits. Since then, the concept of diathesis has been broadened by some

researchers, particularly those in psychology, to include such factors as cognitive and social predispositions (e.g., Monroe and Simons 1991; Abela 2001; Abela and Sullivan 2003). Under this broader concept, psychological and biological traits can both be considered diatheses, the necessary precursors to the development of disorder. Vulnerability to stress is a diathesis under this definition (Zuckerman 1999).

This broadening of the diathesis construct presents some conceptual difficulties. For example, a negative cognitive schema that makes an individual vulnerable to stress and anxiety might itself be influenced by genetic factors, social factors, or both (Zuckerman 1999). Other individual characteristics, such as temperament, social functioning, and life experiences, might also be influenced by and interact with genetic predisposition (Scarr and McCartney 1983; Rutter et al. 1997). Some studies use this broader concept of diathesis (Abela and Sullivan 2003; Schmidt and Joiner 2004), and the shifting definition complicates the interpretation of results as well as the synthesis of literatures about specific disorders.

Stress

In diathesis-stress theory, events that occur within a year prior to the onset of psychiatric disorder are considered stressors, while more distant events, such as those that occurred during an adult's childhood, are not (Zuckerman 1999). In thinking about diathesis-stress theory, it is important to maintain the distinction between proximate and distant events. Muddying that distinction threatens to merge diathesis-stress with psychodynamic theory, which considers childhood events to be predisposing factors for adult mental disorder (Freud 1943; Marmor 1968).

Prior to the 1990s, there was no consideration of the possibility that some types of stressors might have a greater effect on risk for disorder than others. Therefore, the concept of stress was nonspecific. Stress was assumed to be homogeneous and continuous, measured by ranking stress levels from low to high. Diatheses were assumed to have a threshold below which disorder would not be expressed, no matter how severe the stressor, and above which disorder would be expressed, given sufficient levels of stress to activate the latent diathesis (Monroe and Simons 1991).

However, it is now clear that the interaction between diathesis and stress can be conceptualized as additive, dichotomous, or quasicontinuous. In an additive interaction, individuals with low diathetic loading (e.g., low level of genetic risk for depression) require more extreme levels of stress to activate the diathesis and increase risk for the onset of depression than do individuals with high diathetic loading. In a dichotomous interaction, the diathesis is conceived as being either present or absent. Individuals who lack the diathesis will not develop disorder, no matter how extreme the stressor, and whether individuals with the diathesis will develop disorder depends on the degree of stress exposure. In a quasicontinuous diathesis, individuals below a minimal diathetic threshold are unlikely to develop disorder even under extreme stress. For individuals above the threshold, the diathesis has a continuous effect, and there are an infinite number of possible interactions between diathesis and stress (Monroe and Simons 1991). Increasing knowledge about genetic and environmental influences on specific disorders improves researchers' ability to design studies and interpret diathesis-stress interactions in a correct and useful manner.

Diathesis-stress theory is limited by its focus on stress to the exclusion of other aspects of the environment that might interact with biological factors. Because diathesis-stress theory was conceptualized to examine psychopathology (e.g., Meehl 1962, 1989), its environmental focus is on stressors that might contribute to the development of mental illness. Conversely, environmental factors can be examined that may prevent or delay the development of mental disorders and promote resiliency.

Cognitive ability is the focus of two recent studies that demonstrate the usefulness of diathesis-stress concepts in an arena other than psychopathology. The studies examine how genetic effects on cognitive ability vary as a function of socioeconomic status (SES), an environmental indicator often used in social research. Using a twin sample, Eric Turkheimer and associates (2003) find that, at the lower end of the SES scale, environmental effects account for a greater proportion of the variance in IQ than do genetic effects. At the higher end of the SES scale, this relationship is reversed; genetic effects account for the greatest proportion of variance (Turkheimer et al. 2003). Nicole Harlaar and associates (2005) utilize genetic markers for cognitive ability and find that mother's educational level and father's occupational class interact with genetic markers for cognitive ability at age 7. The small but significant interactions suggest that environmental risks are associated with genetic influences on cognitive ability; the higher the mother's education level, the stronger the association between genetic markers and the child's cognitive ability. So, too, the higher the father's occupational status, the greater the expression of a link between genetic markers and cognitive ability in the child. The results of these two studies (Turkheimer et al. 2003; Harlaar et al. 2005) suggest that an individual's innate cognitive ability is more likely to develop to its full potential in an environment with adequate resources.

A twin study (Johnson and Krueger 2005) examined genetic effects on physical health problems as a function of income. Wendy Johnson and Robert Krueger (2005) find that variance explained by genetic effects decreases as income levels rise, even after controlling for insurance coverage and educational level. They suggest that psychological variables associated with having a low income may help to explain the greater influence of genetics on negative health outcomes among those with low incomes (Johnson and Krueger 2005). Another possibility is that individuals with low incomes may often live in environmentally degraded situations (e.g., near toxic waste dumps). The fact that the variance in health outcomes explained by genetic effects differs by income level can help to frame questions about which environmental factors might help account for the difference.

Of course, absent the genetic data, none of this is news to social researchers. But the ability to model such effects using genetically informative data provides a counterpoint; it enables one to use measured environmental variables to help determine which particular aspects of the environment are deleterious or beneficial and which of those environmental factors interplay with genetic effects. The studies (Turkheimer et al. 2003; Harlaar et al. 2005; Johnson and Krueger 2005) also demonstrate how the concepts of diathesis-stress theory can be broadened beyond measures of stress and psychopathology to inform investigations of environmental effects on traits like intelligence and physical health.

Model of Phenotypic Vulnerability

A recent variation on diathesis-stress theory incorporates the idea from psychoanalytic theory that adverse experience in early childhood can exert lifetime effects on physical and psychological functioning (Plotsky, Owens, and Nemeroff 1998; Ladd et al. 2000; Heim and Nemeroff 2001). The variation is divergent from a strict interpretation of diathesis-stress theory that considers only genetic predisposition as the diathesis and only recent events as stressors. Under this broader interpretation of diathesis-stress theory, early, temporally distant adverse experiences would be classified as diatheses, and recent adverse events would be classified as stressors. In order to maintain a clear distinction between a strict interpretation of diathesis-stress theory and this variation, the name "phenotypic vulnerability" will be used for this model. The primary authors of the model refer to it in the context of diathesis-stress models (Plotsky et al. 1998; Ladd et al. 2000; Gutman and Nemeroff 2003) and employ the phrase "vulnerable phenotype" in describing it (Heim and Nemeroff 2001, 1,024).

The phenotypic vulnerability model emerged from the field of neurobiology, in which evidence from animal and human studies supports the hypothesis that early adversity can have long-term effects on psychological functioning (Heim and Nemeroff 1999; Heim et al. 2000; Ladd et al. 2000; Heim and Nemeroff 2001; Sanchez, Ladd, and Plotsky 2001; Gutman and Nemeroff 2003). This evidence is based on objective measurement of biological processes, such as the functioning of the central nervous system. This measurement, in combination with increasingly sophisticated neuroimaging techniques, permits “a neuro-biologic interpretation of Sigmund Freud’s psychoanalytic theory which, consonant with current theory, focused on conflicts in early life as the cardinal factor in the development of mental disorders” (Plotsky et al. 1998, 293).

The model of phenotypic vulnerability (fig. 1) illustrates the independent and interactive effects of both genes and early environment on the development of an individual’s phenotype, or observable characteristics and behavior (Plomin et al. 1997). Adverse experiences during childhood may exacerbate a preexisting genetic vulnerability to stress and disease. This can result in a phenotype that is hypersensitive to further stress exposure and that has an increased risk of developing psychopathology or physiopathology throughout the life span. Early social support and coping styles, both of which are postulated to interact with genetically endowed temperament (Scarr and McCartney 1983), may act as buffers against the effects of early adversity on the developing phenotype (Ladd et al. 2000; Heim and Nemeroff 2001).

Evidence from animal and human studies supports the model of phenotypic vulnerability, suggesting that early adversity induces neurobiological changes and that those changes inhibit the ability of the central nervous system to regulate stress and emotion. This dysregulation is accompanied by increased rates of psychiatric disorders (Heim and Nemeroff 2001; Claes 2004; Shea et al. 2005). A brief review of central nervous system function is in order before examining the evidence, which involves assessment of the function of the hypothalamic-pituitary-adrenal (HPA) axis.

The HPA axis is the center of mammalian stress and immunologic response. The hypothalamus synthesizes and releases corticotropin releasing factor in response to stress. Corticotropin releasing factor then signals the release of adrenocorticotropin hormone from the pituitary gland. In turn, adrenocorticotropin hormone stimulates the production and release of cortisol from the adrenal cortex (Gutman and Nemeroff 2003). The HPA axis function is evaluated by measuring levels of the stress hormones corticotropin releasing factor, adrenocorticotropin hormone, and cortisol. The measurement of stress hormones provides an objective means by which to compare the stress responses of individuals with histories of early trauma to those of individuals without such histories.

One study (Bremner et al. 2003) finds that cortisol levels among individuals with posttraumatic stress disorder (PTSD) related to childhood sexual or physical abuse were higher than levels among healthy, nonabused individuals during a stressful cognitive challenge test. The PTSD group had higher cortisol levels than the non-PTSD group from 1 hour before until 20 minutes after the test. Cortisol levels in both groups increased by 50 percent during the test relative to their own baseline measures. Forty-five minutes after the test, cortisol levels in both groups had fallen relative to their own peak levels. Also, 45 minutes after the challenge, there was no significant difference in cortisol levels between the groups. Douglas Bremner and associates (2003) suggest that the higher pretest cortisol levels in the PTSD group may result from anticipatory anxiety or an interpretation of the environment that differs from the control (non-PTSD) group’s understanding. Another study utilizing cortisol measures finds that children exposed to domestic violence have elevated

rates of cortisol compared to a comparison group of participants who were not exposed (Saltzman, Holden, and Holahan 2005).

Christine Heim and associates (2000) compare levels of adrenocorticotropin hormone among women who experienced severe childhood physical or sexual abuse with those of women who did not. They used four groups for comparison: (1) women with no history of abuse or psychiatric disorder (control), (2) women with current depression who experienced abuse, (3) women without current depression who experienced abuse, and (4) women with current depression and no history of abuse. The women with histories of abuse had higher measured levels of adrenocorticotropin hormone than the control group; women with both current depression and a history of abuse had the highest levels of all the groups (Heim et al. 2000). Findings such as these provide biological evidence that early environmental adversity can have a measurable effect on the human stress response and, by extension, on vulnerability to psychiatric disorder.

The evidence to date suggests that several factors play a role in determining levels of HPA axis dysfunction among people exposed to early abuse. In a review of human clinical studies examining the association between early adversity and measures of stress hormones, David Gutman and Charles Nemeroff (2003) find that the type of abuse, age at onset and duration of the abuse, the amount of intervening time since the abuse, and current psychopathology are all likely contributors to HPA axis dysfunction. In a review of animal and human studies, Stephan Claes (2004) speculates that, for humans, the developmental period during which trauma occurs, the type of stressor, the supportiveness of the environment, and the genetic liability of the individual all play a role in HPA axis dysfunction. The model of phenotypic vulnerability is further supported by animal studies. There is evidence of increased HPA axis response and behavioral disturbance among rat pups and primates exposed to early life stress in the form of maternal separation (reviewed in Heim and Nemeroff 2001; Gutman and Nemeroff 2003; Claes 2004).

While replications of existing studies and further evidence from human studies are needed in order to establish a firm connection between early adversity and increased stress response in humans, the initial findings described above support the hypothesis that the two are associated in ways that were heretofore unmeasurable. This use of biological measures as evidence that the environment affects risk for psychopathology has moved social and biological sciences toward an integration of disciplines. Such an integration has the potential to enrich inquiry and debate across previously impervious borders.

Gene-Environment Interplay

The biopsychosocial model, diathesis-stress theory, and the model of phenotypic vulnerability provide good frameworks for etiological investigations of psychopathology. Each of them is capable of incorporating six principles that can guide the exploration of the interplay between genes and environment (Rutter et al. 1997).

First, individuals differ in their reactivity to stress. Because of differences in temperament, physiology, social standing, or social environment, two people may have very different responses to the same stressful event. Only a genetic research design that incorporates well-measured environmental variables has the ability to differentiate genetically based (e.g., temperament, physiology) from environmentally based (e.g., familial or social environment) response.

Second, there is a “two-way interplay between individuals and their environments” (Rutter et al. 1997, 338). For example, while hormone levels are heritable, they are also affected by environmental circumstances. One study finds that, among humans taking part in a closely

matched chess game, testosterone levels rose in the winners and fell in the losers (Mazur, Booth, and Dabbs 1992).

Third, the interplay between persons and environments must be considered within its own environmental context. For example, in societies that prohibit the use of alcohol, individuals who are genetically predisposed to alcoholism will be less likely to develop alcoholism than similarly predisposed individuals in more permissive societies.

Fourth, people are not simply “passive recipients of environmental forces” (Rutter et al. 1997, 339) but, rather, are active participants in their environments. Two individuals’ interpretations of and responses to an event (e.g., a minor vehicle accident) may vary greatly according to temperament, even when all else is equal. For example, an individual who anticipates a negative outcome may be more likely to experience anxiety than a person who anticipates a positive outcome.

Fifth, people choose their environments and their experiences when they are able to do so. It is therefore not valid to consider events as randomly distributed in the population. For example, teenagers of ages 16 to 19 are at higher risk for motor vehicle crashes than people in any other age group. In the year 2000, these teens represented 10 percent of the U.S. population but accounted for 14 percent of vehicle-related deaths (National Center for Injury Prevention and Control n.d.).

Sixth, individual characteristics change over time as a result of maturation and genetic and environmental influences (Rutter et al. 1997). It is worthy of note that these six principles are consonant with the ideas Engel put forth in his 1960 article and in the biopsychosocial model (Engel 1960, 1977). This congruence demonstrates the longevity of the belief among some behavioral scientists that biology and environment act together to influence health and disease. The ability to measure indicators of biological response to environmental events has enhanced the power of research designed to test that belief.

The biopsychosocial model, diathesis-stress theory, and the model of phenotypic vulnerability are all conceptually broad enough to encompass the concepts of gene-environment correlations and interactions. Those concepts are integral to the six principles just described.

Gene-Environment Correlation

Research examining gene-environment correlations explores the role of genetics in exposure to the environment (Plomin et al. 1997; Rowe 2003). Gene-environment correlation is a succinct term for a phenomenon also referred to as “genetic control of exposure to the environment” (Kendler and Eaves 1986, 282; Kendler et al. 1995, 834). These terms reflect the tendency of individuals to participate in shaping and selecting their environments based on genetically influenced characteristics and behavior. Three types of gene-environment correlation are defined in the literature: passive, evocative, and active.

Passive gene-environment correlation occurs when children inherit from their parents not only a genetic makeup that may predispose them to certain abilities but also an environment that is correlated with those potential abilities (Plomin et al. 1997). For example, a child may have intellectually gifted parents who pass on to him or her a genetic tendency for intellectual curiosity, as well as a house full of books with which to inform that curiosity. Interaction between genetically related individuals is a requirement of passive gene-environment correlation (Plomin et al. 1997).

Evocative gene-environment correlation refers to the tendency for the genetically influenced behavior or temperament of individuals to elicit certain types of response from people in their environment (Plomin et al. 1997). For example, the intellectually gifted child mentioned above might be placed in advanced classes in school because of his or her perceived abilities. Or a child with behavioral problems who taunts and bullies other children may frequently end up in detention. In both cases, the behavior of the child evokes an environmental response based on his or her behavior. Any other person can be the source of environmental response in evocative gene-environment correlations (Plomin et al. 1997).

Active gene-environment correlation refers to the active seeking out of certain environments based on genetic proclivities (Plomin et al. 1997). The intellectually gifted child may seek out intellectually rich environments, while the child with a behavior disorder may seek out peers who behave similarly. Any other person or thing (i.e., books, guns, drugs, movies) can be the source of environmental influence in active gene-environment correlation (Plomin et al. 1997).

Gene-Environment Interaction

While gene-environment correlation refers to genetic exposure to the environment, gene-environment interaction refers to genetic sensitivity to the environment (Plomin et al. 1997; Rowe 2003). Once an individual is exposed to a given environment, how sensitive is he or she to the environment's potential influence on risk for psychopathology? Gene-environment interaction is implied in diathesis-stress models and the model of phenotypic vulnerability. These models posit that as individuals' vulnerability to disorder increases (owing to a high diathetic load or enhanced vulnerability to stress), the likelihood of their developing disorder also grows. As direct measurement of environmental variables in genetic designs improves, the potential for detecting gene-environment correlations and interactions will also improve (Plomin et al. 1997; Jacob et al. 2001). Gene-environment interactions, whereby the effects of genes on behavior vary as a function of the environment, provide the clearest evidence in support of the biopsychosocial model, the diathesis-stress theory, and the model of phenotypic vulnerability.

Evidence for Gene-Environment Interactions

The first study to examine the association between genetic factors and severely stressful life events finds that the relationships are consistent with a model of gene-environment interaction (Kendler et al. 1995). A genetically informative twin sample was used, and the study examined such stressful events as assault, serious financial or legal difficulties, serious marital problems or divorce, and serious illness. Consistent with each of the models described above, the effect of stressful events on risk for depression is found to be greater for individuals at high genetic risk for depression than for those who have low risk. The authors conclude that "while our findings complicate the task of understanding the etiology of mental illness, they are exciting because they force us to confront the *dynamic* nature of our genetic endowment. Gene expression as it influences risk of psychiatric illness is not static but, rather, reacts to and interacts with environmental experiences" (Kendler et al. 1995, 839; emphasis in original).

An extension of that study sought to determine why stressful events lead to depression in some people but not in others. Avshalom Caspi and associates (2003) began by testing for interactions between a specific gene and measures of life stress. The study focused on a specific gene because evidence from animal and human neuroimaging studies supports the hypothesis that the 5-HTT gene interacts with the environment to shape reactions to stress. The sample consists of 953 individuals from a representative birth cohort in Dunedin, New Zealand. The cohort was first ascertained in 1975. Individuals were assessed at ages 3, 5, 7,

9, 11, 13, 15, 18, 21, and, for this study, 26 (Caspi et al. 2003). Data about childhood maltreatment were obtained by observations during childhood, parental report, and respondent retrospective report. Stressful life events were assessed at age 26 for the period from age 21 to age 26 (Caspi et al. 2003). The events included problems in employment, finances, health, and relationships. A major depressive episode within the previous 12 months was assessed at ages 18, 21, and 26. At the same ages, researchers assessed suicidal ideation or attempt that accompanied each diagnosed episode. A DNA sample was obtained from each participant via blood draw or buccal swab. Three genotype groups were formed based on whether the gene was homozygous containing two short alleles (s/s), heterozygous (s/l), or homozygous with long alleles (l/l). Using major depression as the outcome variable, Caspi and associates (2003) tested the effect of genotype, stressful life events, and their interaction on risk for depression. Results reveal that individuals with at least one short allele were more strongly influenced by stressful events, placing them at higher risk for development of major depression, than individuals with two long alleles. They were also at increased risk for a first-onset depressive episode, for suicidal ideation, and for suicidal attempt. Childhood maltreatment predicted adult depression in individuals with a short allele but not in those with two long alleles. Ten percent of the sample was comprised of individuals with the s/s and s/l genes who experienced four or more stressful life events in the year prior to the interview, but they made up 23 percent of the diagnosed cases of major depression (Caspi et al. 2003). Based on the findings, Caspi and associates “speculate that some multifactorial disorders, instead of resulting from variations in many genes of small effect, may result from variations in fewer genes whose effects are conditional on exposure to environmental risks” (Caspi et al. 2003, 389). That view is consistent with the biopsychosocial model, the diathesis-stress theory, and the model of phenotypic vulnerability.

Three subsequent studies replicate and extend the findings of Caspi and associates (2003). One study (Eley et al. 2004) assesses environmental risk for family-related events such as serious illness, bereavement, unemployment, and financial crisis. It finds that the short allele confers increased risk for depression among adolescent girls in the high environmental risk group but not among girls at lower environmental risk. This interaction was not statistically significant for boys (Eley et al. 2004).

The findings by Thalia Eley and associates (2004) are replicated in a study of rhesus macaques (Barr et al. 2004). In the study by Christina Barr and associates, females (but not males) with a short allele had an increased response to stress only when they also had a history of adversity in the form of maternal separation. The study by Barr and colleagues (2004) extends the findings of Caspi and associates (2003) by using blood plasma levels of adrenocorticotrophic hormone and cortisol as objective measures of HPA axis function.

A third study replicates Caspi and associates' (2003) findings in a sample of children ages 5–15 (Kaufman et al. 2004). Joan Kaufman and associates (2004) extend those earlier findings by reporting that social support moderates the risk for depression associated with the short allele and childhood maltreatment in the form of physical or sexual abuse, neglect, emotional abuse, or exposure to domestic violence. Social support was measured as the child's frequency of contact with the person who provides the most support. Higher depression scores were predicted by a history of maltreatment (compared to the nonmaltreated control group), by the s/s genotype (compared to the l/s and l/l genotypes), and by low levels of social support (compared to high levels of social support). Maltreated children with the s/s genotype reportedly had the highest depression scores. When comparing the scores of children at highest risk both genetically (s/s genotype) and socially (low social support) across maltreatment groups, the scores of the maltreated children were twice as high as the scores of those who were not maltreated. However, maltreated children

who had a short allele (indicating high genetic risk) but who also had at least monthly contact with their primary support person had lower depression scores than maltreated children with the same genotype who had less frequent contact with their primary social support person (Kaufman et al. 2004). The results suggest that the availability and frequency of social support can promote resiliency even among children who possess a high genetic vulnerability to depression and who experience childhood adversity (Kaufman et al. 2004). These findings are consistent with Engel's (1977) point that susceptibility to disease is influenced by the environmental and social conditions in which people live. The findings are also consistent with the model of phenotypic vulnerability, which hypothesizes that early social support may act as a buffer against the effects of early adversity on risk for mental disorder (Ladd et al. 2000; Heim and Nemeroff 2001).

The studies reviewed above provide evidence that consideration of both environmental and genetic risk in research designs can yield results that help to clarify the etiology of specific disorders. A better understanding of etiology will make it possible for prevention and treatment studies of specific disorders to efficiently target their goals and mechanisms of change.

Implications of Interdisciplinary Research

A recent study of treatment outcome among patients with chronic depression finds that patients with a history of early childhood trauma respond better to psychotherapy than to antidepressant treatment (Nemeroff et al. 2003). That response is different from the responses among patients with no history of early trauma, who responded equally well to either treatment (Nemeroff et al. 2003). The result of the study by Nemeroff and associates (2003) suggests that a history of early trauma might signal a type of depression that is etiologically distinct from depression in individuals with no history of early trauma. Individuals who seek treatment for depression and who have a history of early trauma may benefit from a different approach to treatment than individuals with no history of early trauma. This specification of treatment according to trauma history is consistent with George Engel's (1977) view that correction of a biochemical abnormality does not always restore a patient to health and that treatment outcomes also rely on psychological and social variables.

Animal studies provide some evidence that the effects of early adversity can be ameliorated or reversed, so that the animals do not display a heightened stress response or abnormal fearfulness, even after being exposed to adverse conditions during early development (Chapillon et al. 1999; Francis et al. 2002). In an animal study of rat pups that were exposed to maternal separation during the first two weeks of life (the rat equivalent of maternal neglect), the negative effects of maternal separation were reversed when those same animals were placed in an enriched environment after weaning (Francis et al. 1999). Studies using rats also suggest that offspring born to neglectful mothers but raised by nonneglectful mothers (cross-fostered) become good mothers themselves and do not then transmit poor mothering practices to their own offspring (Francis et al. 1999; Francis 2005). This is true even when the mother and her offspring have biological markers that are correlated with neglectful behavior, providing evidence that both behavioral and biological function can be improved using environmental interventions. Although rat and human responses to interventions cannot be equated, these findings can be used to help guide the design and evaluation of early intervention and parenting programs that might reduce the incidence and effects of early adversity.

Research that incorporates biological and environmental measures can help to inform prevention efforts. However, this type of interdisciplinary research is new, and existing studies require replication. Therefore, the findings from studies that detect gene-

environment correlations (Eaves, Silberg, and Erkanli 2003) and interactions (Kendler et al. 1995; Silberg et al. 2001; Caspi et al. 2003) have not yet been used to inform prevention efforts. One can postulate how studies that include both biological and environmental measures might help to make preventive research more effective. For example, Mary Ruffolo, Rosemary Sarri, and Sara Goodkind (2004, 238) are interested in defining “areas where mental health prevention and intervention programs might prevent girls’ involvement with the juvenile justice system.” They define risk and protective factors common to unadjudicated girls in home-based settings and adjudicated girls in community-based open and closed residential settings. By comparing unadjudicated and adjudicated girls, they hope to identify areas in which mental health prevention and intervention might help the unadjudicated girls avoid eventual justice system involvement. Negative life events, childhood trauma, and depressive symptomatology are common to the unadjudicated and adjudicated groups (although there are significant between-group differences). These are measures that have been included in genetically informative studies (e.g., Caspi et al. 2003; Kaufman et al. 2004). The addition of biologic measures (e.g., cortisol or 5-HTT genotype) to a study similar to the one by Ruffolo and associates (2004) might help to stratify the group by risk level in order to target those girls at highest risk for developing chronic depression or additional comorbid disorders. Based on the findings that an interaction between stressful life events and genotype increases risk for depression (Caspi et al. 2003; Kaufman et al. 2004), girls who have both a vulnerable genotype and a history of trauma could be designated as at highest risk for chronic depression and targeted for psychotherapy. This would be consistent with Nemeroff and colleagues’ (2003) finding that psychotherapy is more effective than antidepressant treatment for patients with chronic depression and a history of childhood trauma.

In addition to providing guidance concerning the sorts of interventions that might prove most effective for individuals, genetic information can help to disentangle which factors are most salient in predicting risk for mental disorders: genetic vulnerability, environmental factors, or a combination of both. The perspective and experience of social scientists are needed in order to identify the environmental factors that interact with biological factors to increase risk and to identify which of those environmental factors are amenable to modification.

Future research about associations between high-risk environments and mental health, and about how the interplay of genes and environment affects those associations, must meet many challenges. It should increase the understanding of how environment mediates risk for psychopathology by moving beyond the identification of risk factors to identify causal risk processes. This requires a greater integration of social and biological research in order to elucidate how adversity and biology interact to increase vulnerability to mental disorder. It is also important to elucidate environmental and biological factors that provide protection against increased risk in the face of adversity or foster resilience after someone experiences adversity (Rutter 2002). As evidence continues to reveal genetic influences on behavior, it is important to think more closely about the ways in which environmental and genetic effects influence each other. The conceptual models reviewed herein provide a framework that can inform and guide these explorations.

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Fig. 1. Model of phenotypic vulnerability. PTSD = posttraumatic stress disorder. Source: Reprinted from Heim and Nemeroff 2001, with permission from the Society of Biological Psychiatry. Used with the permission of Paul M. Plotsky.