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Major depression and the stress system: A life span perspective

STEPHANIE E. MEYER,[a,b] GEORGE P. CHROUSOS,[c] AND PHILIP W. GOLD[a]
[a]*National Institute of Mental Health;* [b]*University of Minnesota; and* [c]*National Institute of Child Health and Human Development*

Abstract
From a transactional developmental perspective, the authors review findings from studies of animals and humans regarding a proposed relation between stress system abnormalities and major depression. The stress system has evolved to promote successful adaptation across the life span, but disruptions in its functioning may increase the risk of pathological outcomes. Emphasis is placed on the role of prenatal and early postnatal experience in contributing to individual differences in postnatal stress reactivity, which may interact with cognitive and psychosocial vulnerabilities to increase susceptibility to later onset of depression. Findings regarding cognitive, psychosocial, and medical sequelae of depression are also reviewed, with a focus on the possible mediating role of the stress system. The authors highlight the importance of multidisciplinary, longitudinal studies in attempting to gain a deeper understanding of the complex developmental processes involved in the onset and course of depression.

Major depression is a clinically and biologically heterogeneous disorder of adaptation that impacts development in a myriad of ways. Depression darkens memory, diminishes hope, and alters perceptions of oneself and others. Depression also intrudes upon fundamental biological processes that regulate sleep, appetite, sexual activity, autonomic function, and neuroendocrine regulation. In taking into account the natural history, mental suffering, and medical morbidity associated with major depression, the World Health Organization ranked this disorder as the fourth cause of disability and premature death worldwide (Murray & Lopez, 1996). Although there is clear evidence that depression runs in families, there is growing consensus that genes cannot entirely account for the transmission of depression across generations. Indeed, there is widespread agreement that complex psychiatric illnesses, such as depression, are heterogeneous in their etiology and course (Cicchetti, 1993; Cicchetti & Toth, 1995). The well-replicated finding that many individuals with depression exhibit abnormal stress system functioning has led to transactional models (Cicchetti & Schneider–Rosen, 1984) that emphasize the role of development, environment, and genotype in shaping pathways to affective illness. In particular, studies of animals and humans have suggested that exposure to prenatal or early postnatal stress may interact with genetic predisposition to increase an individual's risk of developing depression. In addition, depression itself may alter the course of development by interfering with cognitive, psychosocial, and physiological functioning, and by increasing the risk of medical mortality and morbidity. In this article, we will attempt to bring together findings from across the life span, highlighting the complex ways in which multiple systems interact to shape individual pathways toward ill-

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Address correspondence and reprint requests to: Stephanie E. Meyer, Clinical Neuroendocrinology Branch, National Institute of Mental Health, 10 Center Drive (MSC-1284), Building 10, Room 2D-46, Bethesda, MD 20892-1284; E-mail: meyer104@gold.tc.umn.edu.

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ness and health. We will begin by describing normative functioning of the mature stress system, then proceed by discussing the role of prenatal and postnatal experience in increasing susceptibility to stress system dysfunction and pathology, and finally present findings regarding the impact of depression on subsequent development, emphasizing the possible mediating role of the stress system.

The Core Stress Response System

The stress response consists of a repertoire of relatively automatic physiological and behavioral changes that promote survival during acutely threatening situations. The physiological adaptations have been well delineated and consist of increased pulse rate and blood pressure, breakdown of tissue in the mobilization of fuel, redirection of energy to the brain, and inhibition of vegetative functions, such as food consumption, sleep, and sexual behavior. Relatively stereotyped fear-related and defensive behaviors predominate during stressful situations. Emotional memories of past traumatic events emerge to inform the present context, and they influence the intensity and duration of biochemical, metabolic, and behavioral responses. At the same time, working memory becomes less accessible, and the capacity or readiness to plan and set into motion carefully planned novel or complex behavioral sequences is held in relative abeyance. Instead, behavioral repertoires emerge that have been associated with previous efforts at coping with stressful situations (Gold, Goodwin, & Chrousos, 1988a, 1988b).

The core stress system consists of the corticotropin releasing hormone (CRH) and locus coeruleus–norepinephrine (LC-NE) systems and their peripheral components, the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS; Gold & Chrousos, 1999). CRH and NE are the principal central regulators of the HPA axis and LC-NE system and are responsible for stimulation of these two centers. The neuroanatomical and functional interactions among the central components of the stress system are summarized in Figure 1. Activation of the CRH and LC-NE systems stimulates behavioral arousal, increases cardiovascular and metabolic activity, and interferes with vegetative functions. These two systems also interact multidirectionally with neural substrates such as the amygdala, mesolimbic dopaminergic system, and the medial prefrontal cortex. The amygdala mediates fear, anxiety, and emotional memory, the mesolimbic dopamine system mediates reward and pleasure, and the medial prefrontal cortex controls behavioral and affective flexibility (Gold & Chrousos, 1999). We shall first describe the CRH and noradrenergic systems and their peripheral components in some detail.

The CRH system, the HPA axis, and the role of cortisol during stress

CRH was first isolated in 1981 as a neurohormone synthesized by neurons of the paraventricular nucleus (PVN) of the hypothalamus. It is released into a specialized bloodstream circuit conveying it to the anterior pituitary gland, where it triggers the production of adrenocorticotropin hormone (ACTH). Elevated ACTH levels, in turn, activate glucocorticoid secretion from the adrenal gland (Vale, Spiess, Rivier, & Rivier, 1981). Arginine vasopressin (AVP), also released from PVN neurons, plays an important role in potentiating CRH-mediated ACTH release, but it is a relatively weak direct stimulus of ACTH (Raadsheer, Hoogendijk, Stam, Tilders, & Swaab, 1994). During acute stress, the HPA axis exerts important adaptive activational and inhibitory effects through the release of glucocorticoids, including increased pulse rate, blood pressure, and metabolism. Glucocorticoids (along with CRH) also inhibit programs for growth and reproduction (Gold et al., 1988a, 1988b). For the most part, the adaptive advantages conferred by glucocorticoid secretion during stress are limited to their acute rather than chronic release. Chronic elevation in plasma cortisol is almost always deleterious. Specifically, hypercortisolemia is associated with excessive fear, insulin resis-

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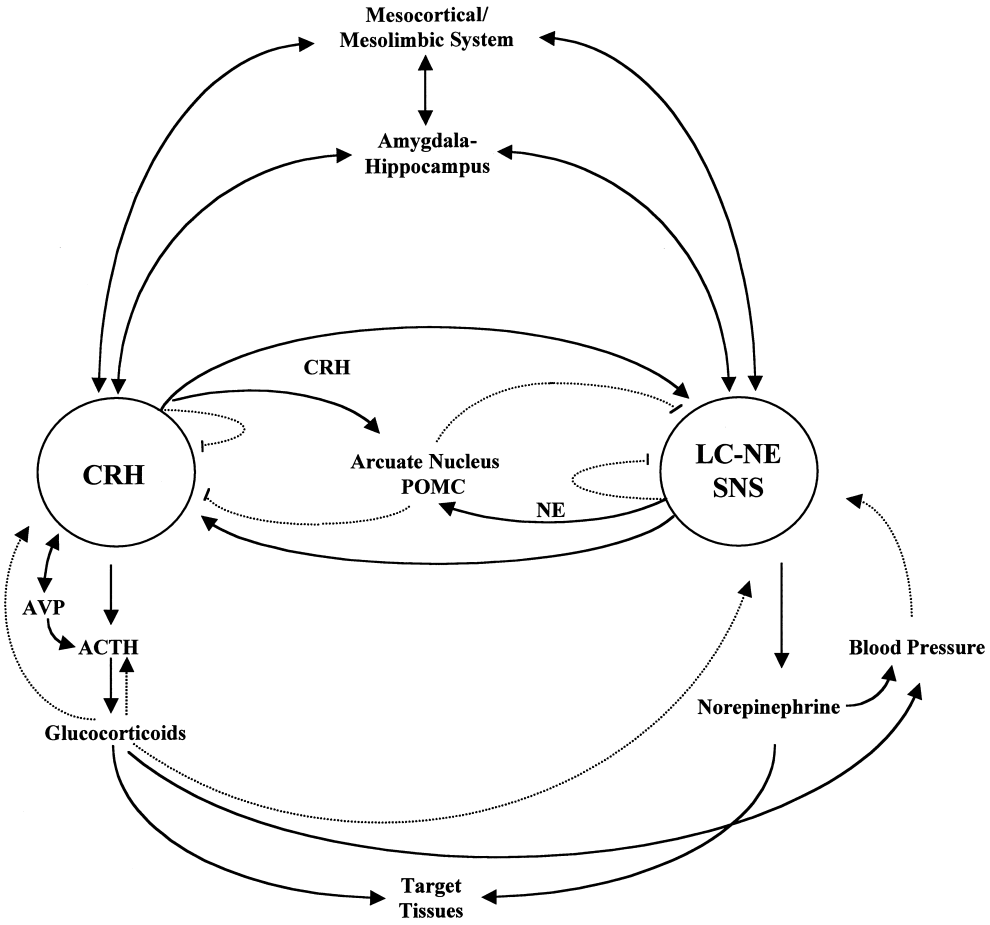


Figure 1. A simplified representation of the central and peripheral components of the stress system, their functional interrelations, and their relations to other central systems involved in the stress response. CRH, corticotropin releasing hormone; LC-NE, SNS, locus coeruleus–norepinephrine–sympathetic nervous system; POMC, pro-opiomelanocortin; AVP, arginine–vasopressin; ACTH, adrenocorticotropin hormone. Activation is represented by solid lines; inhibition is represented by dashed lines. *Note:* Adapted from "The Concepts of Stress and Stress System Disorders: Overview of Physical and Behavioral Homeostatis," by G. P. Chrousos and P. W. Gold, 1992, *Journal of the American Medical Association, 279,* p. 1247. Adapted with permission.

tance, visceral fat deposition, atherosclerosis, reduced growth, bone loss, and chronic suppression of the mesolimbic dopaminergic reward system (Gold & Chrousos, 1999).

CRH and its receptors in brain

CRH is a major contributor to the behavioral, neuroendocrine, neurovegetative, and autonomic components of the stress response (Smith, Aubry, Dellu, Contarino, Bilezikjian, Gold, Chen, Marchuk, Hauser, Bentley, Sawchenko, Koob, Vale, & Lee, 1998; Sutton, Koob, Le Moal, Rivier, & Vale, 1982; Valentino, Foote, & Aston–Jones, 1983). In addition to its role in HPA axis activation, CRH released from the hypothalamus has been found to promote behavioral arousal and SNS activation and to inhibit the release of growth hormone and reproductive hormones (Ri-

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vier & Vale, 1983). Furthermore, CRH neurons activate proopiomelanocortin-containing cells in the arcuate nucleus, which are involved in inhibiting the LC and thus in reducing arousal and anxiety (Weinstock, 1997). Finally, there is an extrahypothalamic CRH system in the amygdala that plays a key role in classical fear conditioning (Chrousos & Gold, 1999).

CRH binds to receptors throughout the brain. Two types of receptors have been identified. The CRH Type 1 receptor appears to play a role in the escalation of fear-related behaviors (Behan, Grigoriadis, Lovenberg, Chalmers, Heinrichs, Liaw, & De Souza, 1996; Heinrichs, Lapsansky, Lovenberg, De Souza, & Chalmers, 1997). Evidence comes from studies of CRH Type 1 receptor knockout mice that show decreases in indices of arousal and anxiety. On the other hand, CRH Type 2 receptor knockout mice manifest increased arousal and anxiety, as well as diminished food intake. This suggests that CRH Type 2 receptors may counterregulate the anxiogenic effects mediated by CRH Type 1 receptor activation (Perrin, Donaldson, Chen, Blount, Berggren, Bilezikjian, Sawchenko, & Vale, 1995).

The LC-NE system

The CRH and LC-NE systems are closely linked, stimulating one another's activity. The LC is located in the mid pons and contains the greatest number of noradrenergic neurons in brain (Aston–Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996). It sends an exceptionally dense network of ascending terminal fields to billions of neurons in the cerebral cortex as well as to the amygdala, hippocampus, and other brain sites. Activation of the LC-NE system serves globally as an emergency or alarm system, leading to a decrease in vegetative functions such as grooming, eating, and sleeping, either directly or via NE-induced CRH release, and contributing to accompanying increases in autonomic outflows in the periphery (Goldstein, 1995). While the LC-NE is not synonymous or necessarily contiguous with the SNS, the activity of the two systems is fairly closely coupled. Activation of the SNS during emotional or physical stress increases blood pressure and pulse rate, as well as the availability of glucose, via suppression of insulin secretion (Aston–Jones, 1985).

The Impact of Prenatal Stress on the Developing Stress System

During prenatal and early postnatal development, the stress system undergoes dramatic changes (Ng, 2000), with various components developing at different rates. ACTH has been detected in fetal life as early as 7 weeks, and by 26 weeks levels are comparable to those of a newborn. CRH is produced in the fetal hypothalamus, as well as in the placenta, and appears during Weeks 12 and 13 (Graham, Heim, Goodman, Miller, & Nemeroff, 1999). In response to stress, the fetal hypothalamus increases production of CRH, triggering heightened secretion of ACTH, which in turn stimulates the production of adrenal cortisol, which inhibits the activity of the hypothalamus and pituitary (Ng, 2000). While the prenatal endocrine stress response involves the same elements as in later life, exposure to stress in utero is unique in its contributions to subsequent development. Chrousos and Gold (1999) have suggested that exposure to environmental stress in prenatal and early postnatal life is likely to result in permanent biological changes. Similarly, Benes (1994) has hypothesized that prenatal stress exposure may permanently alter neural circuitry, thus increasing susceptibility to stress in postnatal life. The mechanisms accounting for the impact of prenatal stress on brain development are not fully understood. However, there is growing evidence that exposure to elevated levels of maternal glucocorticoids may be important. Findings from animal studies suggest that increased glucocorticoid levels may be related to a stress-induced decrease in activity of placental 11β-hydroxysteroid dehydrogenase (11β-OHSD) (Benediktsson, Lindsay, Noble, Seckl, & Edwards, 1993; Langley–Evans, Phillips, Benediktsson, Gardner, Edwards, Jackson, & Seckl, 1996). 11β-OHSD is a critical agent in prenatal development, in that it converts glucocorticoids to inactive

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products, thereby reducing harmful effects to the fetus (Benediktsson et al., 1993).

Several studies have provided evidence supporting the role of glucocorticoids in translating prenatal stress into permanent behavioral and biological changes. Barbazanges, Piazza, Le Moal, and Maccari (1996) conducted an experiment in which rat dams were subjected to an adrenalectomy in order to block the release of glucocorticoids. Dams were then exposed to repeated restraint stress during the final week of pregnancy. The authors found that stress exposure without accompanying glucocorticoid release did not lead to stress system abnormalities normally seen among offspring exposed to prenatal stress. In particular, there was no decrease in hippocampal Type I corticosteroid receptors, which are involved in the inhibition of the HPA axis during stress (Weinstock, 1997). Moreover, when the investigators administered corticosterone to pregnant dams, in order to compensate for the effects of adrenalectomy, offspring did show a reduction in hippocampal Type I receptors. Further evidence that maternal glucocorticoids play a role in altering the development of prenatally stressed organisms comes from findings that prenatally stressed adult rats have elevated CRH (Cratty, Ward, Johnson, Azzaro, & Birkle, 1995) and CRH receptors (Ward, Johnson, Salm, & Birkle, 2000) in the amygdala, a region that has been implicated in emotional and behavioral responses to stress.

Changes associated with exposure to prenatal stress have important implications for individual development. Optimal functioning of the stress system is central to adaptation across species and across the life span (Chrousos & Gold, 1992). Furthermore, the effects of prenatal stress have been shown to negatively impact cognitive, emotional, motoric, and physical health, all of which can interfere with the mastery of salient developmental tasks. Delays in the achievement of early developmental milestones have also been associated with prenatal stress. Schneider (1992a) found that prenatally stressed rhesus monkey infants were delayed in various aspects of neuromotor development, including learning to self-feed. Furthermore, these monkeys experienced significant psychosocial delays. Specifically, under novel conditions, they engaged in fewer gross motor and exploratory behaviors than did control animals. They also manifested increased clinging and self-directed behaviors (Schneider, 1992b). Attentional deficits and distractibility are also seen in animals exposed to prenatal stress (Schneider, 1992b; Weinstock, 1997).

Several authors have speculated that the cognitive and memory deficits in humans that have been associated with prenatal stress result from decreases in hippocampal cells, secondary to glucocorticoid exposure (Benes, 1994; Graham et al., 1999). Impairment of stress system feedback mechanisms may also contribute to learning difficulties in humans (Benes, 1994), as well as poor coping strategies (Weinstock, 1997). Because of its negative impact on biological, emotional, and cognitive development, prenatal stress is thought to increase individual vulnerability to stressful stimuli in postnatal life (Benes, 1994). Although difficulties may not be evident at birth, these individuals are thought to be at increased risk for developing later psychiatric problems (Fride, Dan, Feldon, Halevy, & Weinstock, 1986; Seckl & Meaney, 1993). Prenatal stress has also been linked to physical health problems in adult life (Seckl & Meaney, 1993). Epidemiological studies have found evidence of an association among prenatal stress, low birthweight, high placental weight, and heightened rates of heart disease and hypertension (Ashton, 2000). While the mechanism is not clear, there is experimental evidence in animal models that relative glucocorticoid excess may be a key factor. Benediktsson et al. (1993) showed that rats with low birthweight and high placental weight had been exposed to heightened fetal glucocorticoid levels as a result of attenuated placental 11β-OHSD activity. Additionally, studies of pregnant rats treated with dexamethasone (a synthetic analogue of cortisol) have shown that increased glucocorticoid action reduces fetal growth (Langley–Evans et al., 1996). In turn, low birth weight and high placental weight are strongly predictive of later hypertension and ischemic heart disease in these animals (Benediktsson et al., 1993).

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It is important to note that, although acute prenatal stress can yield permanent alterations across systems, these changes may be counteracted by early postnatal experience (Weinstock, 1997). Maccari, Piazza, Kabbaj, Barbazanges, Simon, and Le Moal (1995) conducted a study in which rats that had been exposed to prenatal stress were either "adopted" or raised by their biological mother. Initially, they found that prenatally stressed animals had impaired counterregulatory mechanisms compared to controls. However, those rats that were adopted at birth showed a significant postnatal increase in hippocampal Type I receptors, resulting in normalization of HPA axis functioning. This effect seemed to result from differences in rearing behavior between previously stressed mothers and nonstressed adoptive mothers.

The Impact of Postnatal Experience on the Developing Stress System

The importance of the attachment relationship

In his 1958 paper, "The Nature of the Child's Tie to His Mother," John Bowlby described a series of instinctual responses that develop during the 1st year of life, which he termed attachment behaviors. The purpose of these behaviors, in his view, was to bind the infant to his or her mother. Unlike many of his contemporaries, Bowlby believed that social interaction was a primary drive that had evolved to ensure the survival of immature members of a species. He recognized that, under extreme conditions, the attachment relationship could be disrupted, thus increasing the risk of pathological development. In a similar vein, D. W. Winnicott (1965) wrote of the importance of a reliable caregiving environment in which the mother's supportive presence protected the child from external threat. He believed that the young infant and the caregiver were both essential in regulating the child. Like Bowlby, Winnicott viewed infancy as the period in which the seeds were sown for future development. More recently, Hofer (1984, 1987, 1994) has elaborated a theory that focuses on biological processes that exist in the early relationship between caregiver and infant. He considers attachment to be a genetically programmed mechanism for maintaining the homeostasis of the developing infant, through the process of coregulation. According to Hofer (1987), this early experience is also critical in determining the actualization and timing of gene expression. In this way, early postnatal experience makes a major contribution to individual differences across biological and behavioral systems.

Studies of rats during the stress hyporesponsive period (SHRP) have provided an animal model for exploring the regulatory function of early maternal care. The SHRP, from approximately Postnatal Day 4 through 14, is characterized by relative inactivity of the stress response (Levine, 1994; Suchecki, Nelson, van Oers, & Levine, 1995). This downregulation of the stress system, which is thought to serve a protective function in brain development, appears to be dependent upon maternal proximity (Gunnar, 1998). Evidence comes from studies showing that infant rats that are separated from their mothers display stress system reactivity that resembles that seen in adult rats following acute stress (Graham et al., 1999; Suchecki et al., 1995; van Oers, de Kloet, Li, & Levine, 1998). Furthermore, repeated and prolonged separations during infancy lead to long-term alterations in HPA axis responses to stress. In a study of Brown Norway (B-N) rats, who are genetically predisposed to developing stress system abnormalities, Workel, Oitzl, Ledeboer, and de Kloet (1997) illustrated the importance of the early caregiving environment in shaping the expression of genetic liabilities. B-N rats were raised under deprived (DEP) or nondeprived (NDEP) caregiving conditions. At Postnatal Day 18, DEP rats exhibited lower basal ACTH levels than did NDEP rats. However, exposure to stress resulted in significantly higher levels of ACTH among DEP rats. Furthermore, there was evidence that DEP rats were less responsive to glucocorticoid feedback than were their NDEP counterparts. Levine (2000) reported on findings illustrating the importance of alternative caregivers in the event of disrupted attachment. In a study of squirrel monkeys, he showed that the presence of familiar "com-

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panions" at the time of separation reduced behavioral and endocrine responses to this stressful event. The opposite effect was found if separation took place in isolation.

In keeping with a transactional developmental perspective (Cicchetti & Toth, 1995, 1998), studies of human infants suggest that disturbances in a child's primary attachment relationship not only contribute to abnormal physiological processes (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996; Hertsgaard, Gunnar, Erickson, & Nachmias, 1995; Spangler & Schieche, 1993) but also to the development of maladaptive cognitions about the self and others (Sroufe, 1989), a fragile sense of internal security and low self-esteem (Cummings & Cicchetti, 1990), impaired self-regulatory skills (Zahn–Waxler, Mayfield, Radke–Yarrow, McKnew, Cytryn, & Davenport, 1988; Zahn–Waxler, McKnew, Cummings, Davenport, & Radke–Yarrow, 1984), and poor social support networks (Cummings & Cicchetti, 1990), all of which are resistant to change and may interact to increase an individual's risk for depression across the life span (Cummings & Cicchetti, 1990). Many of these findings have come from studies of children whose parents suffer from affective illness. There is evidence that the extended periods of psychological unavailability that accompany mood disorders may have a more powerful impact on the attachment relationship than does physical separation or loss (Cicchetti, Toth, & Lynch, 1995; Cummings & Cicchetti, 1990; Radke–Yarrow, Cummings, Kuczynski, & Chapman, 1985).

Despite evidence linking maternal affective illness and insecure attachment, the development of a secure attachment relationship is still possible under these high-risk conditions (Cicchetti et al., 1995). Indeed, findings suggest that it may be the inability to provide sensitive and responsive care, rather than the manifestation of psychopathology per se, that interferes with the formation of a secure attachment relationship (Egeland & Sroufe, 1981). For example, Spangler, Ilg, Maier, and Ackermann (1994) found that maternal psychological unavailability, irrespective of psychopathology, had a deleterious impact on children's developing behavioral and endocrine systems. Specifically, 3-month-old infants of highly insensitive mothers exhibited increased negative emotionality and behavioral disorganization during a play session. At 9 months, these infants showed difficulty adapting to novel situations. At 3, 6, and 9 months, children of insensitive mothers showed elevated cortisol levels, as compared to children of mothers who were moderately sensitive.

Longitudinal evidence indicates that attachment history is not only important during infancy, but its effects are carried into future stages of development (Sroufe, 1979, 1989). Waters and Sroufe (1983) reported that quality of attachment predicted effective problem solving behavior in toddlerhood, preschool social competence, and future capacity for empathy and adaptive emotional expression. Moreover, attachment security is predictive of adaptive coping responses (Cicchetti & Toth, 1995) and optimal stress system functioning well into adulthood (Adam, 1999; Scheidt, Waller, Malchow, Ehlert, Becker–Stoll, Schulte–Moenting, & Luecking, 2000). Alternatively, a history of insecure attachment has been associated with higher risk for mood disorders in adolescence and adulthood (Cicchetti et al., 1995).

Late infancy through adolescence

Even as infants become increasingly autonomous, parenting continues to serve an important regulatory function. Our research team has been involved in a 20-year follow-up study of children whose mothers were diagnosed with unipolar depression, Bipolar I or II disorder, or had no history of psychiatric illness. Two children from each family have been followed since early childhood. Information regarding mothers' Axis I and Axis II symptomatology has been collected at each visit. Furthermore, during the early years of the study, families were observed and videotaped in a research apartment that was designed to simulate home conditions (Radke–Yarrow, 1998). Ratings of mothers' parenting style were made based on these videotaped interactions. During adolescence, 63 children from these families underwent a CRH challenge procedure. Analysis of these data have

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shown that adolescents whose mothers displayed a highly angry or irritable parenting style during childhood were more likely to exhibit exaggerated ACTH activation in response to CRH challenge. On the other hand, mothers who used "considerate control" strategies imparted a significant buffering effect on their children's stress responsivity, as evidenced by a lesser increase in ACTH levels following CRH challenge (Martinez, Ronsaville, Laney, Municchi, Chrousos, Radke–Yarrow, Meyer, & Gold, manuscript in preparation). While cross-sectional studies of depressed adolescents have largely failed to find group differences in HPA axis activity (Dahl & Ryan, 1996; Dorn, Burgess, Susman, von Eye, De Bellis, Gold, & Chrousos, 1996; Ryan & Dahl, 1993), our study suggests that there *are* individual differences in stress responsivity during this period of development and that these seem to be shaped, in part, by early life experiences. What remains to be seen is whether individual differences in our sample are indicative of vulnerability to later onset psychopathology. Interestingly, in a retrospective study of women who had been physically or sexually abused during childhood, Heim, Newport, Heit, Graham, Wilcox, Bonsall, Miller, and Nemeroff (2000) found a similar pattern of elevated ACTH levels, but normal cortisol levels, among women with a history of abuse who had not developed depression. The authors speculated that increased pituitary activity in response to stress might represent a vulnerability to the development of psychiatric disorder.

Our findings indicate that enriched parenting styles may enhance children's long-term adaptive capacities. Similar findings have come from animal studies that have used a handling paradigm (Ader & Grota, 1969; Denenberg & Whimbey, 1963). The effects of handling on newborn rats appear to be mediated by the positive impact on parenting behaviors (Liu, Diorio, Tannenbaum, Caldji, Francis, Freedman, Sharma, Pearson, Plotsky, & Meaney, 1997; Plotsky & Meaney, 1993). Nonhandled rats have been found to be cognitively and emotionally impaired under stress (Levine, 2000), whereas handled rats display low levels of inhibition when exposed to novel situations (Graham et al., 1999). Furthermore, handled rats show increases in glucocorticoid receptors in the hippocampus and frontal cortex, thus increasing feedback sensitivity (Levine, 2000; Liu, Caldji, Sharma, Plotsky, & Meaney, 2000; Plotsky & Meaney, 1993). In addition, they exhibit lower NE and CRH levels in the PVN of the hippocampus (Liu et al., 2000; Plotsky & Meaney, 1993) and reduced CRH and AVP in the median eminence than do nonhandled and maternally separated rats.

There have been several studies that have focused on the impact of chronic stress in childhood on later behavioral and biological adaptation. However, the difficulty in controlling for measurement issues, genetic factors, and the specific nature and timing of the stress has led to varying results (Hart, Gunnar, & Cicchetti, 1996). In our study, exposure to chronic family stress was associated with hypoactivity of the adrenal glands in response to CRH challenge. This pattern of HPA axis underreactivity may also be found among offspring of parents who suffer from posttraumatic stress disorder (Yehuda, Bierer, Schmeidler, Aferiat, Breslau, & Dolan, 2000). Other studies that have focused on child maltreatment as a form of chronic stress have shown dysregulation of the adrenal system, but the pattern of dysfunction varies across studies. For example, Hart et al. (1996) found that maltreated children had elevated afternoon cortisol levels, with morning levels comparable to nonmaltreated children, whereas F. W. Putnam and his colleagues found that sexually abused girls showed elevated morning and reduced afternoon cortisol levels (as reviewed in Hart et al., 1996). De Bellis, Chrousos, Dorn, Burke, Helmers, Kling, Trickett, and Putnam (1994) reported that girls who had been sexually abused showed no differences in basal or stress-induced cortisol levels, but both basal and CRH-stimulated ACTH levels were reduced compared to matched controls.

Because of the ability to control for genetic and environmental variables, animal studies have provided important information regarding the impact of early chronic stress on the developing stress system. Coplan, Andrews,

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Rosenblum, Owens, Friedman, Gorman, and Nemeroff (1996) studied monkeys who were raised by mothers who were forced to spend a great deal of time and effort foraging for food. They found that these infants exhibited emotional dysregulation, as well as elevated levels of CRH, in response to challenge. As adults, they continued to display adjustment problems, as well as heightened CRH and NE activity. King and Edwards (1999) explored the impact of early stress and genetic composition on the long-term reactivity of the endocrine system in rats. The investigators studied rats that had a genetic vulnerability to develop learned helpless behaviors (cLH) and rats that were congenitally resistant to developing learned helpless tendencies (cNLH). They found that the timing of stress exposure, along with genetic composition, were both important in shaping neuroendocrine response to future challenge. Early stress had a larger influence on future functioning when it occurred after, rather that during, the stress hyporesponsive period. There was also a clear interaction between genes and experience. Specifically, cLH animals who had been exposed to early stress showed hyperreactivity of the pituitary in response to challenge, with a marked decrease in corticosterone levels compared to nonstressed cLH controls, while the cNLH animals exhibited hyporeactivity of the pituitary and adrenal systems compared to their nonstressed peers.

As with prenatal experience, exposure to stress during early postnatal life may interact with genetic predisposition to increase individuals' susceptibility to psychopathologic outcomes (De Bellis et al., 1994; Meaney, Diorio, Francis, Widdowson, LaPlante, Caldji, Sharma, Seckl, & Plotsky, 1996), including depression (Plotsky, Owens, & Nemeroff, 1998), as well as chronic medical illness (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999).

Melancholic Depression and the Stress System

Thousands of papers have been written on the hypercortisolism of melancholic depression in adulthood. Several lines of evidence suggest that this represents a central nervous system defect at or above the hypothalamus, presumably resulting in the hypersecretion of hypothalamic CRH. The first data to support a role for CRH in the hypercortisolism of major depression came from studies in which ovine CRH (oCRH) was given as a stimulus to ACTH secretion (Gold, Chrousos, Kellner, Post, Roy, Augerinos, Schulte, Oldfield, & Loriaux, 1984; Gold, Loriaux, Roy, Kling, Calabrese, Kellner, Nieman, Post, Pickar, Gallucci, Avgerinos, Paul, Oldfield, Cutler, & Chrousos, 1986; Holsboer, Vonbardeleben, Girken, Stalla, & Muller, 1984). This test represented an assessment of the functional integrity of glucocorticoid negative feedback at the pituitary. Adult patients with melancholic depression showed basal hypercortisolism and normal basal plasma ACTH levels. In response to oCRH, they exhibited blunted plasma ACTH, and their cortisol responses were proportionally greater than were those of nondepressed controls. The more hypercortisolemic the patients, the more blunted were the ACTH responses to oCRH (Gold et al., 1986). These data suggested that a stimulus such as sympathetic innervation of the adrenal in melancholic depression either directly released NE independent of ACTH or led to hypertrophy and hyperplasia of the adrenal cortex and glucocorticoid hyperresponsiveness to ACTH. Some of the blunting may also have been due to a CRH-mediated down-regulation of pituitary CRH receptors. Several other lines of indirect evidence are compatible with a role for CRH in the hypercortisolism of melancholia in adults. For example, when healthy controls were given a continuous infusion of oCRH for 24 hr, they showed the pattern and magnitude of plasma ACTH and cortisol levels that typically occur in patients with melancholic depression (Schulte, Chrousos, Gold, Booth, Oldfield, Cutler, & Loriaux, 1985). Additionally, a postmortem study of brains taken from individuals who had a history of major depression during their lifetimes showed an increase in CRH-containing neurons in the hypothalamus (Raadsheer, van Heerikhuize, Lucassen, Hoogendijk, Tilders, & Swaab, 1995). Another study conducted on brains taken from individuals who had died of suicide showed a significant decrease in frontal

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cortex CRH receptors (Nemeroff, Owens, Bissette, Andorn, & Stanley, 1988). This finding was interpreted to reflect increased CRH release in the frontal cortex resulting in a down-regulation of CRH receptors. Finally, Brady, Whitfield, Fox, Gold, and Herkenham (1991) found evidence that antidepressants produce a down-regulation of the CRH system. Specifically, they showed that chronic, but not short-term, administration of an antidepressant (imipramine) to rats caused a significant decrease in PVN CRH mRNA levels in association with a significant increase in Type I glucocorticoid receptor mRNA levels in the hippocampus, which are thought to play an important role in restraining the HPA axis.

Norepinephrine is perhaps the more widely studied neurotransmitter in biological studies of major depression. The first significant biological hypothesis regarding major depression, the catecholamine hypothesis, stated that major depression resulted from reduced levels of available NE (Schildkraut, 1965). This theory was based on clinical observations that drugs, such as tricyclic antidepressants and monoamine oxidase inhibitors, which apparently increased NE in the synapse, had antidepressant effects. More recently, many conflicting studies have appeared in the literature regarding noradrenergic function in depression. This most likely reflects diagnostic heterogeneity and the fact that studies have measured CSF NE at a single time point. On the other hand, we recently measured CSF NE every hour for 24 hr in patients with melancholic depression. Results indicated that these patients exhibit chronic elevations in NE, even during sleep (Wong, Kling, Munson, Listwak, Licinio, Prolo, Karp, McCutcheon, Geracioti, De Bellis, Rice, Goldstein, Veldhuis, Chrousos, Oldfield, McCann, & Gold, 2000). The elevated NE levels in melancholic patients are compatible with their pathological hyperarousal, anxiety, and physiological hyperreactivity. As noted, NE serves as an alarm system in the brain and inhibits neurovegetative functions such as sleep, feeding, and sexual behavior. NE also activates the amygdala fear system (Le Doux, 1992) and inhibits the medial prefrontal cortex, which ordinarily changes mood from one state to another based on internal or external cues (Arnsten, Mathew, Ubriani, Taylor, & Li, 1999). Finally, recent data indicate that the increase in available NE that results from antidepressant use gradually results in a decrease in the firing rate of the LC, which then reduces anxiety and arousal (Wong et al., 2000).

Developmental Sequelae of Major Depression

At any age, the onset of depression appears to result in longlasting functional impairment, even beyond that associated with chronic illness (Judd, Akiskal, Zeller, Paulus, Leon, Maser, Endicott, Coryell, Kunovac, Mueller, Rice, & Keller, 2000; Wells, Stewart, Hays, Burnam, Rogers, Daniels, Berry, Greenfield, & Ware, 1989). Coryell, Scheftner, Keller, Endicott, Maser and Klerman (1993) reported that adults with unipolar depression were less likely to get married, and those who did get married were twice as likely to get separated or divorced. Furthermore, the authors found that psychosocial impairments that were associated with depression persisted even after a significant period of remission. Adolescents who suffer from depression are more likely to quit school (Kandel & Davies, 1986) and to have difficulty adjusting to adult roles. Specifically, Kandel and Davies (1986) found that women who had suffered from adolescent depression were more likely to divorce than were their never-depressed peers, and men who were depressed in adolescence experienced more periods of unemployment than did their never-depressed counterparts. In terms of direction of causality, Cole and Milstead (1989) showed that, in children, depression preceded social skill deficits, as well as a decline in self-perceived competence. Granger, Weisz, McCracken, Ikeda, and Douglas (1996) found evidence that the stress system may play a role in this association. Specifically, they showed that, among children who had been referred for treatment, continuity of internalizing problems predicted subsequent HPA axis reactivity to psychosocial challenge, which in turn predicted a sig-

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nificant decrease in perceived self-competence.

There is growing evidence that the physiological changes associated with depression may also contribute to heightened risk for premature physical morbidity (Vaillant, Orav, Meyer, McCullough Vaillant, & Roston, 1996) and mortality (Barefoot & Schroll, 1996; Black, Winokur, & Nasrallah, 1987; Ford, Mead, Chang, Cooper–Patrick, Wang, & Klag, 1998; Glassman & Shapiro, 1998; Lee & Murray, 1988; Murphy, Monson, Olivier, Sobol, & Leighton, 1987). In particular, it has been suggested that the prolonged and recurrent dysregulation of the endocrine system that is associated with depression may play a role in the development of medical illnesses such as osteoporosis and heart disease (Barefoot & Schroll, 1996; Chrousos & Gold, 1998; Glassman & Shapiro, 1998; Gold & Chrousos, 1999). Hippisley–Cox, Fielding, and Pringle (1998) showed that men with a history of depression were 3 times more likely than age-matched controls to develop heart disease, even when smoking was controlled for. Glassman and Shapiro (1998) reported that, after controlling for potentially mediating risk factors, men and women with depressive symptomatology were still more likely to develop heart disease. Similarly, a prospective study by Anda, Williamson, Jones, Macera, Eaker, Glassman, and Marks (1993) showed that individuals with depressed affect or hopelessness were at risk for heart disease after controlling for socioeconomic status, alcohol use, preexisting physical illness, and smoking. However, there was evidence that smoking increased the risk for developing heart disease among depressed persons.

Endocrine changes associated with melancholic depression may partly account for its association with heart disease. Hypersecretion of insulin triggers chronic SNS activation (Reaven, 1995), which is profoundly deleterious to cardiac well-being. Excessive SNS activation increases heart rate and blood pressure and has an independent effect on decreasing left ventricular compliance, a risk factor for congestive heart failure (Gold & Chrousos, 1999). Moreover, increased NE secretion is arrythmogenic in patients with established heart disease (Goldstein, 1995). This may account for the fact that heart disease patients who suffer from depression are more likely to have died a cardiac death at 6- to 18-month follow-up than are their nondepressed counterparts (Frasure–Smith, Lesperance, & Talajic, 1995; Glassman & Shapiro, 1998). Cortisol hypersecretion and increased production of insulin stimulate accumulation of visceral fat, a highly metabolically active tissue that exerts profound effects on lipid metabolism, coagulation, inflammation, and blood pressure regulation. Decreased levels of growth hormone and sex steroids, which have been found among patients with melancholic depression, also lead to increased visceral fat deposits. In addition, growth hormone deficiency, in itself, significantly increases the risk of cardiac morbidity, in part by leading to a loss of cardiac mass. Finally, excessive visceral fat leads to increased secretion of PAI-1, a potent inhibitor of clot dissolution and increased endothelial inflammation, presumably accelerating atherosclerosis (Reaven, 1995).

In recent years, there have been a handful of studies that have looked at the relation between depression and osteoporosis. Michelson, Stratakis, Hill, Reynolds, Galliven, Chrousos, and Gold (1996) demonstrated that women with current or a past history of depression had reduced bone mineral density. More recently, Coelho, Silva, Maia, Prata, and Barros (1999) found higher rates of depression among women with osteoporosis, even after controlling for risk factors such as age, menopause, hyperthyroidism, calcium imbalance, alcoholism, smoking, anorexia nervosa, drugs, diet, sunshine exposure, and immobility. The cause of premature osteoporosis in patients with major depression has not been definitively determined. However, hypercortisolism has been associated with bone loss (Michelson & Gold, 1998; Michelson et al., 1996), and steroid-induced bone loss in patients receiving glucocorticoid treatment is well recognized (Lukert & Raisz, 1990). It may be that steroids decrease bone formation significantly, while increasing resorption. The effects seem to be most pronounced in areas

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of woven bone, a bone with a high turnover rate that is a predominant constituent of the hip and vertebral bodies. Glucocorticoid-induced estrogen deficiency also results in a high turnover state, with resorption predominating over production (Marcus, Feldman, & Kelsey, 1996). Ordinarily, all bone is broken down and reconstituted in phases of production and resorption. Normally these phases are coupled so that if formation rises, resorption rises, and vice versa. Bone loss occurs if decreased production occurs with a corresponding increase in resorption.

Conclusion

It seems ironic that the stress system, which has evolved to promote successful adaptation, may interfere with health and well-being, if it is disrupted at various points in development. However, there is increasing evidence that, in certain individuals, exposure to stress during pre- and early postnatal life may interfere with subsequent stress system functioning, thus increasing susceptibility to the development of depression and other forms of chronic illness. It is important to emphasize, however, that at this point most of the evidence to support this model comes from retrospective and cross-sectional studies of humans following the onset of depression. From these studies we can conclude that a significant portion of adults who manifest depressive symptoms also display a particular pattern of stress system dysfunction. There is less of an understanding of normal and abnormal stress system functioning among children and adolescents. Studies of depression in young people tend to utilize methods that have produced significant findings in adults. Furthermore, patterns of reactivity are measured against adult norms. It is possible that measures that have been effective in detecting individual differences in stress system functioning among adults may not be appropriate at earlier stages in development. Experiments with animals represent an important complement to human studies, in that they have provided elegant data regarding developmental processes that render organisms vulnerable to later disordered behavior and physiology. However, the degree to which these findings may be generalized to humans is unclear.

At this juncture, longitudinal investigations of humans are critical if we are to better understand the transactional processes involved in the development of depression in humans (Cicchetti & Toth, 1995; Cicchetti & Toth, 1998). This principle is inherent to a developmental psychopathology perspective, which emphasizes the need for interdisciplinary studies of individuals over time in order to deepen our understanding of the reciprocal relations among cognitive, biological, psychosocial, and psychopathological processes in development (Cicchetti, 1993; Rutter & Sroufe, 2000). Another central consideration in this endeavor is the vast heterogeneity of depressive syndromes and the various developmental pathways that can lead to identical symptoms (Cicchetti, 1993; Cummings & Cicchetti, 1990; Sroufe & Rutter, 1984). For example, Gold and Chrousos (1999) have isolated a group of depressed patients who manifest hypoarousal of the stress response. Unlike patients with melancholic depression, which is associated with activation of the LC-NE and CRH systems, patients with so-called atypical depression exhibit hyposecretion of hypothalamic CRH. Furthermore, Heim et al. (2000) identified a subgroup of depressed individuals who had no history of early stress, and among whom stress system functioning was normal. Thus, it would seem that the nature, course, and treatment of these individuals would be very different from depressed individuals with a history of early trauma and signs of HPA axis dysfunction.

A great deal of progress has been made in elucidating the relation between stress and melancholic depression. This has much to do with the collaborative efforts of researchers from various disciplines, including psychiatry, endocrinology, epidemiology, and developmental and experimental psychology. However, at this point, as efforts are being made to translate findings into effective treatments, it is important to move away from cross-sectional and animal models to a more process-oriented, long-term follow-up approach to the study of depression in humans.

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