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Developmental vulnerabilities to the onset and course of bipolar disorder

ROBERT M. POST,[a] GABRIELE S. LEVERICH,[a] GUOQIANG XING,[b] AND SUSAN R. B. WEISS[ac]

[a]*National Institute of Mental Health;* [b]*Uniformed Services University of the Health Sciences; and* [c]*National Mental Health Association*

Abstract

Different types of psychosocial stressors have long been recognized as potential precipitants of both unipolar and bipolar affective episodes and the causative agents in posttraumatic stress disorder (PTSD). New preclinical data have revealed some of the neurobiological mechanisms that could convey the long-term behavioral and biochemical consequences of early stressors. Depending on the timing, quality, quantity, and degree of repetition, maternal deprivation stress in the neonatal rodent can be associated with lifelong anxiety-like behaviors, increases in stress hormones and peptides, and proneness to drug and alcohol administration, in association with acute changes in the rate of neurogenesis and apoptosis (preprogrammed cell death) and decrements in neurotrophic factors and signal transduction enzymes necessary for learning and memory. Patients with bipolar illness who have a history of early extreme adversity (physical or sexual abuse in childhood or adolescence), compared with those without, show an earlier onset of illness, faster cycling frequencies, increased suicidality, more Axis I and Axis II comorbidities (including alcohol and substance abuse), and more time ill in more than 2 years of prospective follow-up. These findings are subject to a variety of interpretations, but to the extent that the more severe course of bipolar illness characteristics are directly and causally related to these early stressful experiences, early recognition and treatment of high-risk children could be crucial in helping to prevent or ameliorate the long-term adverse consequences of these stressors.

A cohort effect for both unipolar and bipolar affective disorder has been described (Gershon, Hamovit, Guroff, & Nurnberger, 1987; Klerman & Weissman, 1989; Lasch, Weissman, Wickramaratne, & Bruce, 1990; McInnis, McMahon, Chase, Simpson, Ross, & DePaulo, 1993) such that in each generation since World War II there has been an increased incidence and earlier onset of these affective disorders. Although some investigators have questioned the validity of these observations, or have failed to replicate them (Merette, Roy–Gagnon, Ghazzali, Savard, Boutin, Roy, & Maziade, 2000), clinicians in the last 25 years are now in agreement about the existence of childhood-onset unipolar depression and are increasingly confronted with the extremely dysfunctional presentations of childhood bipolar-like disorder. Whereas adolescent onset mania had been something of a novelty (although well recognized in the 1960s and 1970s), extreme affective dysregulation resembling variants of bipolar disorder is increasingly being seen in very young children even as early as ages 2–4 years (Faedda, Baldessarini, Suppes, Tondo, Becker, & Lipschitz, 1995; Geller & Luby, 1997; Robb, 1999; Sanchez, Hagino, Weller, & Weller, 1999; Wozniak, Biederman, Kiely, Ablon, Faraone, Mundy, & Mennin, 1995; Wozniak, Biederman, Mundy, Mennin, & Faraone, 1995).

The largest number of calls to the National

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Address correspondence and reprint requests to: Robert M. Post, MD, NIMH, Biological Psychiatry Branch, 10 Center Drive MSC 1272, Bldg 10, Room 3S239, Bethesda, MD 20892-1272.

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Alliance for the Mentally Ill (NAMI) and to the National Depressive and Manic Depressive Association (National DMDA) have asked for advice on the diagnosis and treatment of very young children with bipolar-like symptoms. These children present with extreme affective dysregulation, such as temper tantrums, irritability, impulsiveness, aggression, hyperactivity, and poor attention (Chang, Steiner, & Ketter, 2000; Fergus, Leverich, Luckenbaugh, Miller, & Post, 2001; Geller & Luby, 1997; Wozniak et al., 1995). When these symptoms are the earliest presentation, some argue that the classic adult course of discrete episodes with intervening well intervals is not met and that the illness therefore does not meet the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994). However, it is also apparent that children with chronic labile presentations do go on to have classic periods of manic and depressive mood swings (Biederman, Mick, Faraone, Spencer, Wilens, & Wozniak, 2000; Fergus, Miller, Luckenbaugh, Leverich, Speer, & Post, in press), although the earliest presentations can be extreme mood lability and dyscontrol consistent with ultrarapid and ultradian cycling, as described by Geller and Luby (1997).

In this paper we attempt to circumvent the diagnostic controversy by calling these early presentations "bipolar-like" and, for brevity's sake, will refer to these early presentations as "bipolar." A variety of neurobiological mechanisms and their interactions could account for these childhood- and adolescent-onset bipolar illnesses.

Hereditary Genetic Mechanisms of Early Onset Bipolar Illness

Genetic anticipation

DePaulo and colleagues (McInnis et al., 1993) have observed a 9- to 13-year earlier age of onset of bipolar illness in the offspring of parents with bipolar illness and have suggested that this could be related to genetic anticipation. Anticipation refers to the increase in disease severity or decrease in age of onset in succeeding generations. This phenomenon is well known in a variety of neurological disorders, most particularly Huntington chorea, in which the number of trinucleotide repeats in a DNA encoding region conveys age of onset of the illness (Brandt, Bylsma, Gross, Stine, Ranen, & Ross, 1996). In Huntington chorea, individuals with fewer than 40 trinucleotide repeats of polyglutamine sequences in the protein huntingtin usually do not develop the illness, whereas those with 50–70 polyglutamine repeats become ill as adults. Those with the most extreme numbers of trinucleotide repeats have the most virulent childhood onset variety of Huntington chorea. In Huntington chorea, genetic anticipation refers to the fact that a parent may have late onset illness with 45–50 trinucleotide DNA repeats inherited from their parents, but because of the DNA replication during gametogenesis the number of DNA repeats passed to the next generation can expand considerably. Thus, there appears to be increasing severity and earlier onset of the illness that is passed from one generation to the next.

These types of observations across a variety of neurological illnesses have led to a search for expansion of trinucleotide repeats in bipolar disorder with mixed results. Some studies have been positive (Grigoroiu–Serbanescu, Wickramaratne, Hodge, Milea, & Mihailescu, 1997; McInnis et al., 1993; Mendlewicz, Lindbald, Souery, Mahieu, Nylander, De Bruyn, Zander, Engstrom, Adolfsson, Van Broeckhoven, Schalling, & Lipp, 1997; Nylander, Engstrom, Chotai, Wahlstrom, & Adolfsson, 1994; Ohara, Suzuki, Ushimi, & Yoshida, 1998), whereas others have not (Craddock, McKeon, Moorheard, Guy, Harrison, Mynett–Johnson, Claffey, Feldman, McGuffin, Owen, & O'Donovan, 1997; Merette et al., 2000).

The assortative mating effect

Another mechanism for increasing genetic vulnerability to an illness from one generation to the next is the added vulnerability of having a second parent with similar vulnerabilities genetically (Gershon, Hamovit, Guroff, Dibble, Leckman, Sceery, Targum, Nurnberger, Goldin, & Bunney, 1982; Lapalme, Hodg-

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ins, & LaRoche, 1997). If a patient with bipolar illness marries another individual with either unipolar disorder or, more problematically, bipolar disorder, the likelihood of affective illness in the offspring increases, and potentially the age of onset decreases as well.

The marriage rate involving two people with affective disorders (assortive mating) is unknown but could be substantial. In adult onset bipolar illness, or in early onset illness with a good response to treatment, many patients marry and have children. Given that some 10% of men and perhaps as many as 20% of women in the United States will have at least one lifetime episode of major depression, the chance of a bipolar individual's marrying someone with either unipolar or bipolar illness is not unsubstantial. When this occurs, there is not only additional vulnerability from hereditary genetics but also from a variety of experiential effects on gene expression that are likely to emerge in a family in which both parents are afflicted with an affective disorder. Some of these potential consequences and their neurobiological mechanisms are discussed in the following sections.

Environmentally Mediated Effects on Gene Expression: Preclinical and Clinical Studies

Repeated maternal deprivation stress in the neonatal rat pup

A vast array of environmental insults and contingencies can alter the developing brain and its subsequent growth, pruning, and responsiveness to normal processes of learning and memory. These could include the occurrence of (a) environmental deprivation or enrichment, (b) severe psychosocial stressors, or (c) viral–toxin or drug-mediated alterations. A wealth of literature now exists showing that environmental enrichment can change both neural structure and the rate of neurogenesis (Kempermann & Gage, 1999; Kempermann, Kuhn, & Gage, 1997). Environmental deprivation and its neural effects have been studied mostly in the primary sensory systems such as vision. Here, deprivation of normal sensory input by suturing one eye shut in an experimental animal, such as a cat, results in loss of the normal development of ocular dominance columns, and if it persists long enough the deprivation can result in blindness in that eye after the sutures are removed (Hubel & Wiesel, 1979). Similar consequences are just beginning to be elucidated for the effects of environmental deprivation on neural substrates important to the development of affective behavior.

A series of elegant studies by Paul Plotsky, Michael Meaney, and colleagues demonstrate the potential long-lasting effects of different periods of repeated maternal deprivation in the neonatal rodent (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Francis, Diorio, Liu, & Meaney, 1999; Ladd, Huot, Thrivikraman, Nemeroff, Meaney, & Plotsky, 2000; Liu, Diorio, Tannenbaum, Caldji, Francis, Freedman, Sharma, Pearson, Plotsky, & Meaney, 1997; Meaney, Aitken, Van Berkel, Bhatnagar, & Sapolsky, 1988; Plotsky & Meaney, 1993). If the rodents are separated for only 15 min each day for the first 7–10 of life, they appear to have benefited from this manipulation as adults, being relatively resistant to the development of stress- and aging-induced high levels of glucocorticoids, age-related loss of hippocampal structure, and associated deficits in learning and memory. Conversely, if animals undergo 3 hr of repeated maternal separation on a similar daily basis, they develop lifelong hypercorticosteronemia, increased anxiety behaviors, and a proneness to develop and sustain alcohol and cocaine self-administration compared to their littermate controls (Ladd et al., 2000; Plotsky & Meaney, 1993). All of these effects are reversed by administration of serotonin-selective antidepressants, but they return once these agents are discontinued.

The mechanisms of these biochemical and behavioral changes are beginning to be delineated. In the 15-min-separated animals, maternal attention and licking are increased upon the return of the rat pup. In contrast, in the 3-hr-separated animal the mother shows little attention to the returned offspring, and in her agitation she may not only show decreased maternal care and nurturance but may also further stress and actually trample the neonate

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in her frantic behavior (Liu et al., 1997). Meaney and associates (Francis, Diorio, Liu, & Meaney, 1999) have demonstrated that some of these effects can be transgenerational. They observed that the offspring of mothers who naturally show low levels of licking behavior toward their pups tend to be anxious and hypercortisolemic. However, if these rat pups are cross-fostered to naturally high-licking mothers they do not become hypercortisolemic and do not show high levels of anxiety-related behavior. Most interestingly, when these animals themselves have pups, the high-licking, low-anxiety behavior continues in the next generation. Thus, experiential effects can cross generational boundaries through familial, but nonhereditary, mechanisms.

One-day maternal deprivation stress paradigm in the rat pup

Mark Smith, Li Xin Zhang, and Guoqiang Xing in our laboratory have examined the effects of one 24-hr period of maternal deprivation in the 11-day-old rat pup. This paradigm has obvious advantages and disadvantages. The advantages include the ability to readily detect the acute effects of a single day of maternal deprivation stress on neurobiology and neurochemistry. The disadvantages include the potential confounds of the single day of maternal deprivation with food deprivation and other stressors implicit in the paradigm. However, temperature was maintained in these animals, and a variety of control studies by Levine and associates (Levine, Huchton, Wiener, & Rosenfeld, 1991; Suchecki, Mozaffarian, Gross, Rosenfeld, & Levine, 1993) have suggested that the majority of effects are related to the maternal deprivation stress and not the concomitant physiological effects of nutrition and fluid deprivation.

Using this paradigm, our group found that the single day of maternal deprivation significantly decreases brain-derived neurotrophic factor (BDNF; approximately 30–40%) in the hippocampus of the neonatal rat, just the way more repeated restraint stress will decrease BDNF in the hippocampus of adult animals. The number of cells undergoing preprogrammed cell death (or "apoptosis"), as revealed by radioactive ligand "apoptag" binding to broken ends of DNA, appears approximately doubled after the deprivation stress compared with handled controls (Zhang, Xing, Levine, Post, & Smith, 1997). Interestingly, whereas BDNF decreases, nerve growth factor (NGF) increases, and the degree of apoptag in white matter areas of brain is directly correlated with the degree of increase in NGF (Zhang, Xing, Levine, Post, & Smith, 1998).

These data raise the question of why neurotrophic factor increases would be associated with cell loss rather than neuroprotection. It appears that in the immature animal the receptor trkA, which usually binds and is the effector for NGF in adult animals, is not adequately developed. Instead, a low affinity p75 receptor binds NGF and occupancy of this receptor is associated with apoptosis (Barrett, 2000). These observations suggest that the inappropriate or poorly timed expression of neurotrophic and other putative positive growth factors may, potentially, be associated with adverse consequences to the organism in a fashion not dissimilar to that occurring from a failure of timely secretion of a given substance. When the apoptag cells are double-stained with appropriate markers, it appears that they represent both neurons and glia. Although these preliminary studies remain to be further explored, they are nonetheless intriguing in light of the increasing number of reports of altered neuronal or glial cell number in patients with unipolar and bipolar affective disorders (Drevets, Ongur, & Price, 1998; Ongur, Drevets, & Price, 1998; Rajkowska, Miguel–Hidalgo, Wei, Dilley, Pittman, Meltzer, Overholser, Roth, & Stockmeier, 1999).

Our preliminary preclinical data raise the possibility that, in addition to genetically preprogrammed alterations in neuronal development and migration, a variety of environmental events beyond the stressors typically considered (such as viral infection, anoxia, birth trauma) may also be able to affect neural development. Many caveats are obviously in order, including what the human equivalents may or may not be to single or repeated maternal deprivation observed in rodents and what the ameliorating factors may be as well,

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but the preclinical findings at least raise potential new directions for consideration and a series of plausible mechanisms for the long-term consequences of stress that can be further tested.

Another abnormality found after one 24-hr period of maternal deprivation is a decrease in nitric oxide synthase, a critical enzyme involved not only in signal transduction but also in neuronal growth and death (Xing, Smith, Levine, Yang, Post, & Zhang, 1998). Calcium calmodulin kinase-II (CaMKII) is also decreased 24 hr after the deprivation (Xing et al., 1998). CaMKII appears to be central to the modulation of synaptic plasticity involved in models of learning and forgetting (Frankland, O'Brien, Ohno, Kirkwood, & Silva, 2001), such as long-term potentiation (LTP) and long-term depression, respectively. Studies with partial gene knockout mice have revealed that animals deficient in CaMKII regulatory modulation are unable to demonstrate LTP and that this is likely behaviorally and physiologically relevant because they are also unable to perform adequately in the Morris water maze (Mayford, Wang, Kandel, & O'Dell, 1995; Rotenberg, Mayford, Hawkins, Kandel, & Muller, 1996; Tsien, Chen, Gerber, Tom, Mercer, Anderson, Mayford, Kandel, & Tonegawa, 1996).

These findings would be of potential clinical and theoretical interest in relation to a variety of subtle cognitive alterations manifest in patients with unipolar and bipolar affective disorders, either as state or trait findings (Post, Denicoff, Leverich, Huggins, Post, & Luckenbaugh, 2000). Recent data from our laboratory (Xing, Zhang, Zhang, Yang, & Post, 2000) revealed that autopsy specimens in the Stanley Foundation Brain Collection from patients who died with a diagnosis of bipolar illness show a selective decrement in the alpha form of CaMKII (CaMKII-α) in prefrontal cortex compared with normal controls. Patients who died with a diagnosis of unipolar depression or schizophrenia did not show these same alterations, suggesting some diagnostic selectivity in this deficit. Moreover, the assays for CaMKII beta (CaMKII-β) also failed to demonstrate a significant alteration, suggesting that nonspecific factors are highly unlikely to account for the alpha subtype finding. These data, again, raise the possibility that stressful environmental circumstances, in addition to hereditary genetic mechanisms, could be associated with acute or long-term deficiencies in a critical enzyme involved in learning and memory.

The fact that similar behavioral and biochemical alterations can be produced either through genetic or environmental–experiential mechanisms is highlighted in Figure 1. The lower part of the figure shows findings from Plotsky and colleagues (Ladd et al., 2000) and Zhang and colleagues (1998) indicating the ability of serotonin-selective antidepressants to normalize the entire syndrome. Convergently, in the top half of the figure, the findings of Barden and colleagues (Beaulieu, Rousse, Gratton, Barden, & Rochford, 1994; Pepin, Pothier, & Barden, 1992) are represented by the transgenic mouse with deficient numbers of glucocorticoid receptors (GRs). Because of the failure of negative feedback usually provided by GRs, these animals also demonstrate increased corticosterone and increased startle and anxiety-like behaviors in the open field. In this syndrome as well, an antidepressant (in this case the tricyclic desmethylimipramine) was able to reverse most of the behavioral alterations and the associated hypercorticosteronemia. These data illustrate that both hereditary genetic and experiential or stress-induced mechanisms can be involved in the pathogenesis of such behavioral syndromes.

Neurobiological consequences of stressors relevant to posttraumatic stress disorder (PTSD) versus depression

The effect of timing of the stressor on subsequent behavior, neuroendocrinology, and biology can be carefully dissected in these animal models. This is of particular relevance in the distinction between glucocorticoid regulation typically seen in PTSD versus that in primary depression (Figure 2). The classical presentation of depression is one associated with various indices of hypercortisolism, including increased 24-hr secretion of urinary-free cortisol, a blunting of the circadian rhythm of

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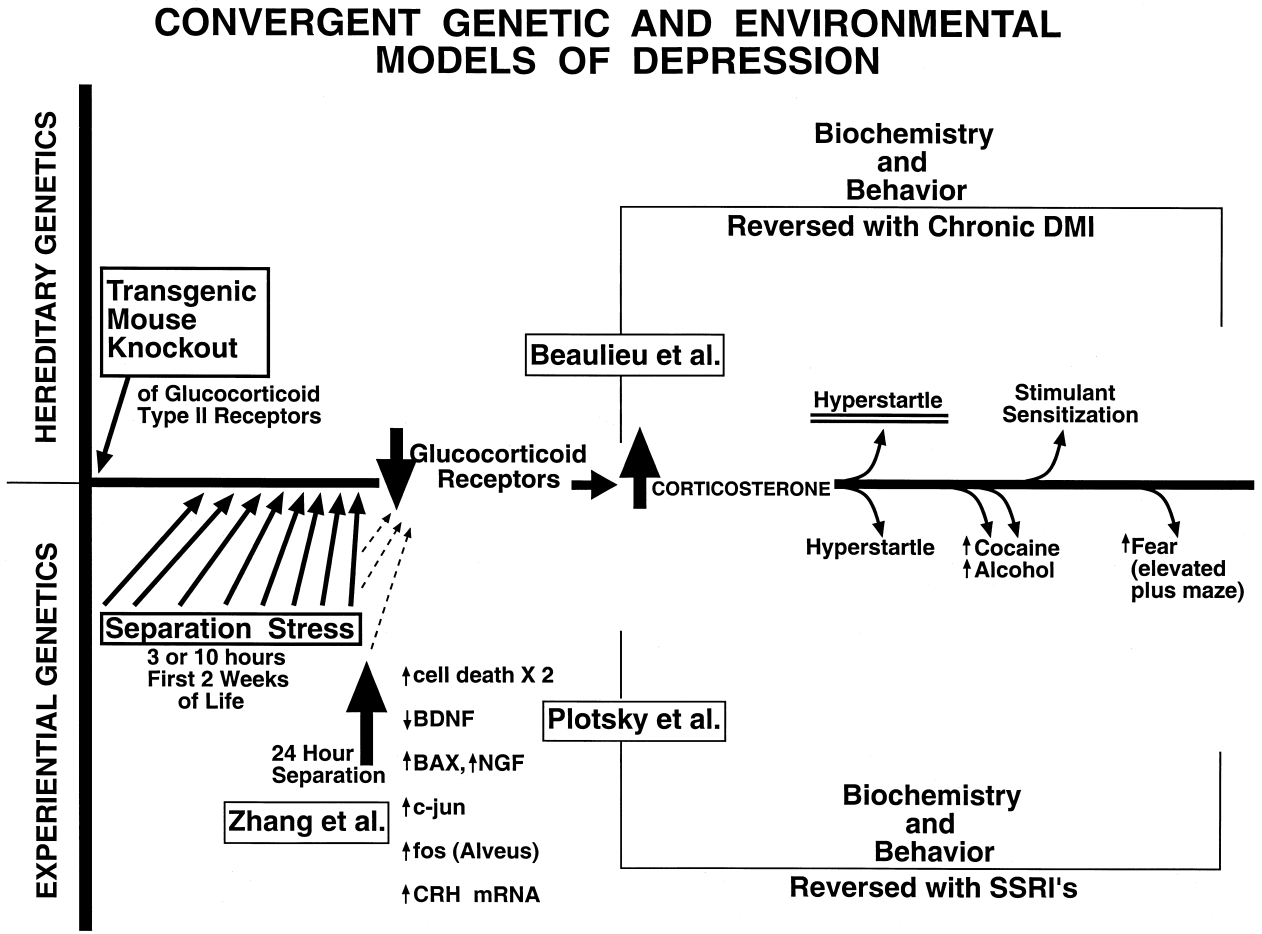


Figure 1. Convergent genetic and environmental models of depression. Either heredity or experiential genetics may lead to compounding behavioral and biochemical end points similar to those seen in depression and reversible by antidepressants. DMI, desipramine; SSRIs, serotonin-selective reuptake inhibitors; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; CRH, corticotropin releasing hormone.

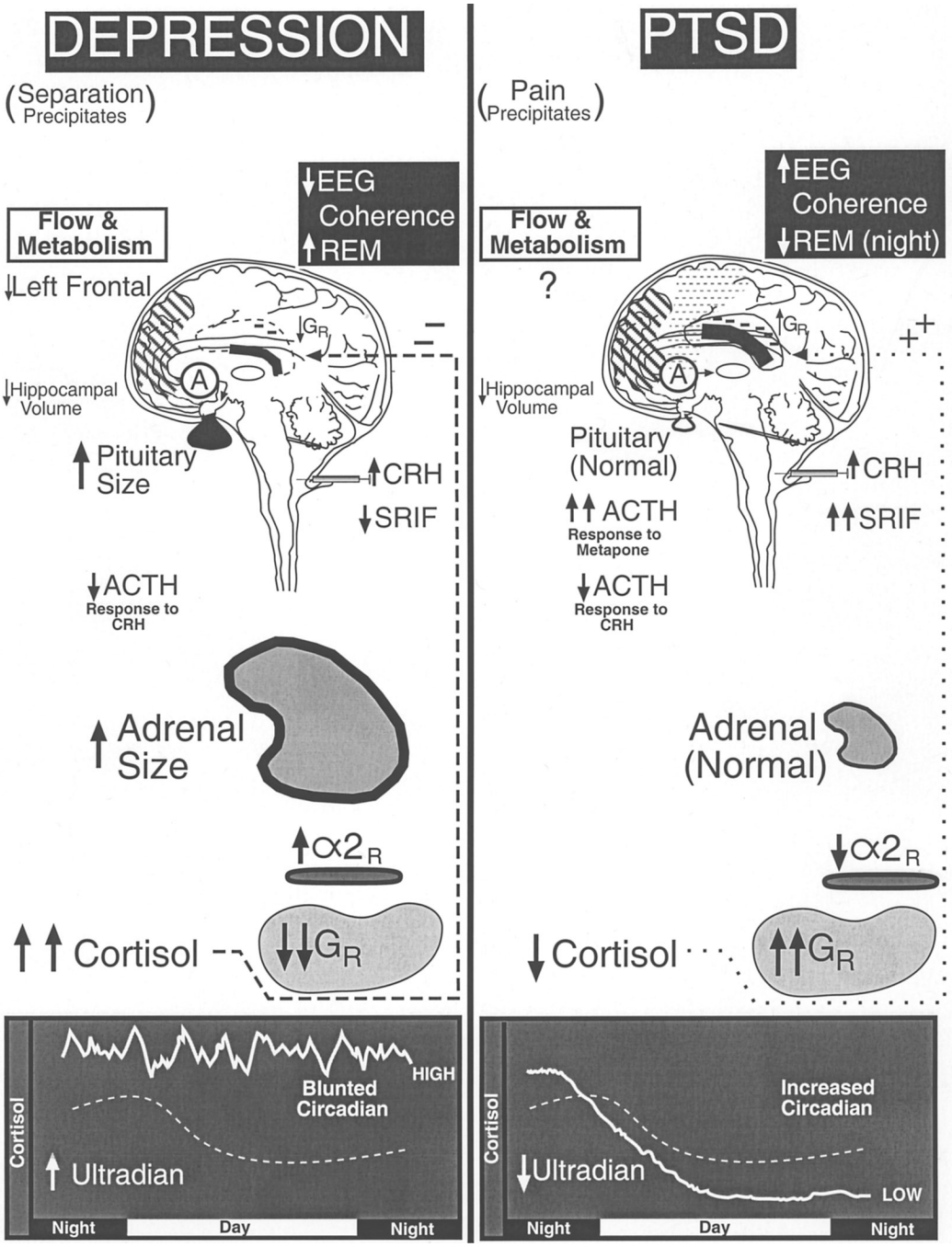


Figure 2. Schematic of differences in precipitants, neurophysiology, anatomy, peptides, endocrinology, and circadian rhythms between depression and PTSD. Much of the data illustrated are adapted from the work of Yehuda (1998, 2000). EEG, electroencephalogram; REM, rapid eye movement; CRH, corticotropin-releasing hormone; SRIF, somatostatin; ACTH, adrenocorticotropin hormone; $\alpha 2_R$, alpha-2 receptors.

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cortisol based on high levels throughout the day, a failure to suppress cortisol upon dexamethasone administration, a blunted adrenocorticotropin hormone (ACTH) response to corticotropin-releasing factor (CRF), or a hyperresponsive reaction to the combined dexamethasone–corticotropin releasing hormone test. This hypercortisolism is often associated with deficient glucocorticoid receptor numbers in the lymphocytes of patients with depression.

Conversely, the abnormalities in PTSD indicate paradoxically low levels of circulating glucocorticoids and high glucocorticoid receptor number, at least on circulating blood elements (Stein, Yehuda, Koverola, & Hanna, 1997). This appears to occur even though there is evidence of increased CRF in the spinal fluid of patients with PTSD (Bremner, Licinio, Darnell, Krystal, Owens, Southwick, Nemeroff, & Charney, 1997). Could it be that the PTSD syndrome is associated with a failure to mount an adequate glucocorticoid response to acute and repeated stressors, similar to the way that some strains of animals are more susceptible to arthritis and autoimmune reactions when they fail to mount an adequate corticosterone response (Aksentijevich, Whitfield, Young, Wilder, Chrousos, Gold, & Sternberg, 1992; Sternberg, Chrousos, Wilder, & Gold, 1992)?

Alternatively, is there some stage in development or in evolution of the syndrome itself whereby a normal or hyperactive stress response with hypercortisolemia converts to one of hyporesponsivity, as the preclinical data of Plotsky (2000) would suggest? Certainly, the behavioral consequences associated with high-dose glucocorticoids can themselves change their valence over time during the transition from acute to chronic stress or glucocorticoid administration. Acute steroids are often associated with increased energy and decreased need for sleep (i.e., a hypomanic-like syndrome) but, with more chronic administration, tend to be associated with depressive-like reactions and loss of energy and increased fatigue typical of a patient with Cushing syndrome.

Based on the clinical neurobiological data available in the literature, one can begin to address another question—that is, what happens in the individual with depression and comorbid PTSD? Do they have the neuroendocrine signature of the hypercortisolemia of depression or the hypocortisolemia of PTSD? Nemeroff and colleagues (Heim, Newport, Heit, Graham, Wilcox, Bonsall, Miller, & Nemeroff, 2000) have examined this proposition by studying four groups of women: normal volunteer controls; women who were sexually or physically abused as children with no depression (5 of 14 with PTSD), women with current depression and no history of childhood abuse, and women with current major depression who were sexually or physically abused as children (11 of 13 with PTSD). As predicted, those with depression had an elevated cortisol response to a stressor, whereas those with PTSD had a blunted response. Those who had both major depression and comorbid PTSD showed a more than 6-fold greater ACTH response to stress than age-matched controls. Thus, the set point of the corticolimbic hypothalamic–pituitary–adrenal axis appears to reach very different levels of homeostasis depending on the expression of depressive illness and early traumatic stressors (Figure 2).

Neonatal cocaine exposure and associated environmental adversity

Substance abuse can also have a long-term and even transgenerational adverse effect. There are a variety of mediators involved and some depend on the time course of exposure and impact (Figure 3). With maternal substance abuse involving cocaine, the fetus is exposed to this substance with possible adverse effects on emotional reactivity. In addition, cocaine-exposed babies are at higher risk for perinatal medical adversity, including stroke, abruptioplacentae, and seizures (Burkett, Yasin, & Palow, 1990; Chasnoff, Griffith, MacGregor, Dirkes, & Burns, 1989; Cordero & Custard, 1990).

Patients with unipolar and bipolar affective disorder by virtue of their illness are at increased risk for substance abuse. Mothers who have an affective and a substance abuse disorder may place their child at high risk be-

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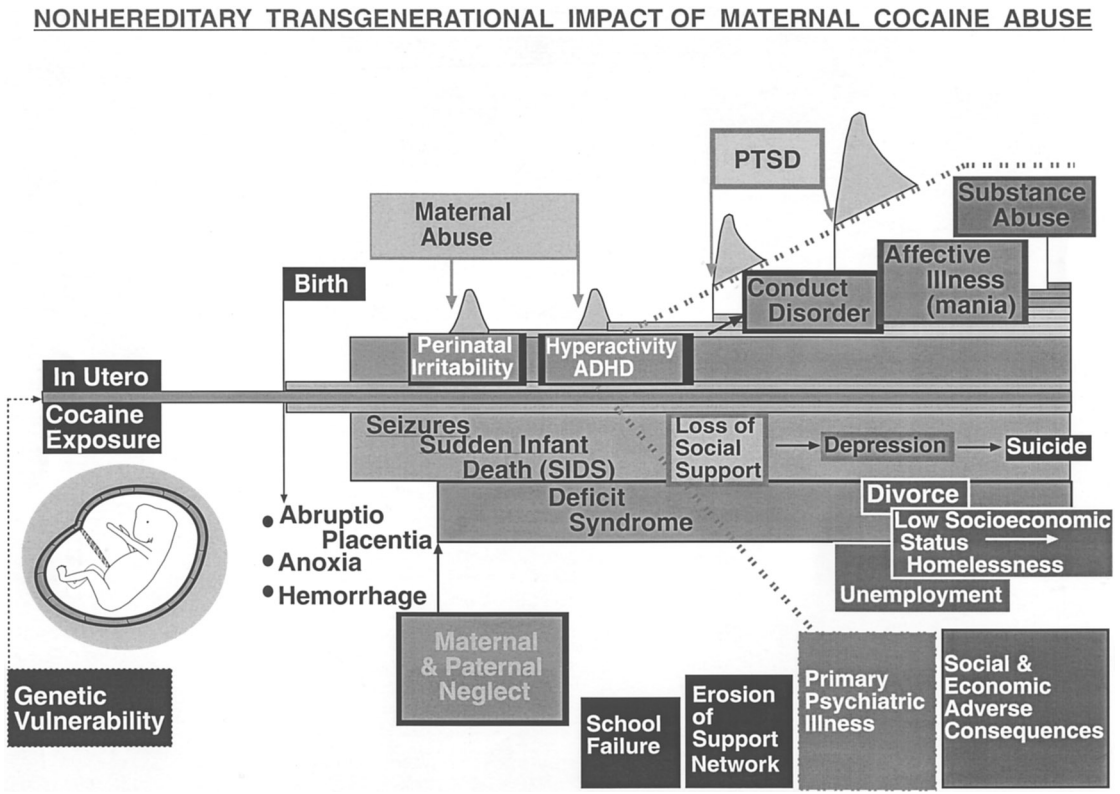


Figure 3. Schematic illustration of the potential sequential, temporal, and cumulative evolution of neurobiological and psychiatric consequences of maternal cocaine abuse during pregnancy and throughout a child's development. Although these hypothetical consequences could be ameliorated by a plethora of interventions, such a deteriorating course could occur based on the clinical literature. At the same time, corrective transgeneration effects also appear possible based on the work of Francis and colleagues (Francis, Dioro, Liu, & Meaney, 1999). ADHD, Attention deficit hyperactivity disorder.

cause of (a) genetic vulnerability, (b) decreased physical or psychological contact (because of the comorbid depressive and substance abuse disorder), and (c) the effects of the substance itself. Moreover, if a mother is addicted to cocaine, for example, and is unable to give it up during the pregnancy and perinatal period, the infant might be at increased risk of simultaneous environmental understimulation and neglect as well as superimposed acute stressors, each with their own developmental neurobiological consequences. Together, these may place the infant and child at an especially high risk for emotional dysregulation, depression, and PTSD.

To the extent that such a multiply vulnerable child does acquire the emotional lability and aggressiveness associated with bipolar illness, the associated uncontrolled behavior, which often may appear willful, can put the child at further risk for excessive verbal and physical discipline and even overt physical abuse. The degree to which the adolescent then develops a full-blown affective disorder comorbid with PTSD places him or her at further dual risk for substance abuse. This may in turn lead to increased vulnerability to emotional dysregulation in the individual's own offspring, with potential multigenerational transmission due to experiential as well as genetic mechanisms.

Impact of Early Stress on the Onset and Course of Bipolar Disorder

Stress sensitization

Data from the Stanley Foundation Bipolar Network (SFBN, or Network) patient cohort provides evidence that early psychosocial stressors can, in fact, interact with the neurobiology of bipolar illness in a variety of ways (Leverich, McElroy, Suppes, Keck, Denicoff, Nolen, Altshuler, Rush, Kupka, Frye, Autio, & Post, in press). In a patient questionnaire, bipolar probands in the Network were asked about the incidence, severity, and age at which they were verbally, physically, or sexually abused. In examining the histories of those who reported early (childhood or adolescent) physical or sexual abuse compared with bipolar patients without such a history, we found that their illness was characterized by an earlier onset, more rapid cycling patterns, and an increased incidence of serious suicide attempts. In addition, a history of physical abuse was associated with a reported increasing severity of manic episodes prior to Network entry (Leverich et al., in press).

Those patients with histories of early abuse had an increased incidence of both Axis I (McElroy, Altshuler, Suppes, Keck, Frye, Denicoff, Nolen, Kupka, Leverich, Rochussen, Hatef, Rush, & Post, 2001) and Axis II (Leverich, Altshuler, McElroy, Keck, Suppes, Denicoff, Nolen, Rush, Kupka, Frye, Autio, & Post, 2000) comorbidities. These retrospectively reported indices of an adverse course of illness and outcome were confirmed prospectively, with clinician ratings showing greater degrees of mania and depression and ultradian cycling, and fewer numbers of days euthymic in a prospective year of follow-up. Thus, these data in bipolar illness parallel those of Kendler (Kendler, Kessler, Neale, Heath, & Eaves, 1993; Kendler, Neale, Kessler, Heath, & Eaves, 1992) and others, suggesting that early adverse life events in patients with unipolar depression increase the likelihood of the development of minor and later full-blown depressive episodes and their recurrence. In Kendler's schema, these early adversities interact with both current stressors and number of affective episodes in increasing vulnerability to further depressions. A similar process may be occurring in bipolar illness as well.

Episode sensitization

Substantial evidence supports the case that the number of prior episodes is a risk factor for episode recurrence and possibly treatment resistance to lithium carbonate. At least nine studies (Abou–Saleh & Coppen, 1986; Denicoff, Smith–Jackson, Disney, Ali, Leverich, & Post, 1997; Gelenberg, Kane, Keller, Lavori, Rosenbaum, Cole, & Lavelle, 1989; Goldberg, Harrow, & Leon, 1996; Maj, Pirozzi, Magliano, & Bartoli, 1998; O'Connell, Mayo, Flatow, Cuthbertson, & O'Brien, 1991; Prien, Caffey, & Klett, 1974; Sarantidis & Waters, 1981; Swann, Bowden, Calabrese,

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Dilsaver, & Morris, 1999) report that patients with a greater number of affective episodes prior to the institution of lithium prophylaxis have a less favorable prognosis than those who begin prophylaxis after fewer episodes. The dividing line was 3 or 4 prior episodes in several studies (Gelenberg et al., 1989; Goldberg, Harrow, & Leon, 1996; O'Connell, Mayo, Flatow, Cuthbertson, & O'Brien, 1991), although it was 10 prior episodes in the study of Swann and colleagues (1999).

Kraepelin (1921) observed an overall trend in his clinic for the well interval between successive episodes to decrease as a function of episode number. These findings have been replicated even in the modern psychopharmacological era, particularly in treatment-resistant patients (Post, 1992) and perhaps most robustly by Kessing and colleagues (1998). In a study of more than 20,000 patients from the Danish case registry hospitalized for depression or mania, the rate of recurrence increased with the number of previous episodes in both unipolar and bipolar disorder. These data were partially replicated by Angst and Sellaro (2000) who reported a decreasing well interval, at least over the first four episodes of affective illness, with a leveling out thereafter.

In addition to the impact on lithium responsivity, the number of prior episodes may play a role in overall pharmacological responsivity. In the study of Calabrese, Woyshville, Kimmel, and Rapport (1993), an accelerating course of illness was a negative prognosticator for response to valproate. In a National Institute of Mental Health (NIMH) series of treatment-refractory patients, those patients hospitalized in the decade of the 1970s were able to be discharged with a high rate of response on monotherapy, whereas in the 1990s the number of medications at discharge had increased to 3.3 on the average (Frye, Ketter, Leverich, Huggins, Lantz, Denicoff, & Post, 2000). It is not clear what factors mediated these increases, and it is possible that they reflect referral biases rather than real trends in the community. However, we noticed that patients in the more recent admissions (1990s) had a significantly earlier onset of illness and a greater number of prior depressions, as well as a much greater incidence of a rapid-cycling course, than the patients requiring fewer medications in the 1970s and 1980s.

Early onset of affective disorder could also have a variety of adverse consequences for social and educational development. In a subcohort of patients in the SFBN studied at the NIMH, those with a greater number of prior episodes performed more poorly on a variety of neuropsychological tasks when they were tested in the relative euthymic state compared with those with fewer prior episodes (Denicoff, Ali, Mirsky, Smith–Jackson, Leverich, Duncan, Connell, & Post, 1999). Thus, early onset, whether or not it was associated with early stressful life events, would appear to place the patient at greater risk for substance abuse, increased numbers of Axis II disorders, social and employment disabilities, and even increased risk for neurophysiological impairment.

Clinical and Therapeutic Implications

It is highly disappointing that there is an approximate 5- to 10-year lag between the onset of first symptoms that would meet criteria for a major affective disorder and first treatment in patients with bipolar illness in many different settings (Egeland, Hostetter, Pauls, & Sussex, 2000; Leverich et al., in press; Lish, Dime–Meenan, Whybrow, Price, & Hirschfeld, 1994; Suppes, Leverich, Keck, Nolen, Denicoff, Altshuler, McElroy, Rush, Kupka, Bickel, & Post, in press). To the extent that recurrent episodes of major depression or dysfunctional mania are occurring during this interval in the absence of adequate treatment, the effects are potentially devastating on multiple levels. The experience of considerable illness morbidity and its costs to the individual on their social, educational, or occupational roles can be substantial. The illness can also have a lethal outcome, with adolescent and early adult suicide a major and underestimated reason for cause of death in individuals in this age range, exceeding that of cancer, heart disease, and many other illnesses, and trailing only accidents and homicide (Jamison, 2000).

In addition to this devastating potential for morbidity and mortality, there is also the pos-

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sibility that the mechanisms underlying long-term illness expression are being transformed. As noted above in the data of Kessing et al. (1998), the well interval between initial episodes appears to decrease and vulnerability to recurrence increases as a function of episode number (Kendler, Thornton, & Gardner, 2000). Thus, in the initial untreated interval, patients are likely becoming more prone to relapse. Since episode number is a negative prognosticator, at least for lithium, in many studies in the literature (Abou–Saleh & Coppen, 1986; Denicoff et al., 1997; Gelenberg et al., 1989; Goldberg et al., 1996; Maj et al., 1998; O'Connell et al., 1991; Prien et al., 1974; Sarantidis & Waters, 1981; Swann et al., 1999), it is also possible that lack of treatment during this time is rendering the illness less likely to respond to one of its major treatments. Since lithium tends to normalize not only the incidence of suicide in the primary affective disorders, but also the risk of death from other medical causes (Ahrens, Muller–Oerlinghausen, Schou, Wolf, Alda, Grof, Grof, Lenz, Simhandl, & Thau, 1995; Muller–Oerlinghausen, Ahrens, Grof, Grof, Lenz, Schou, Simhandl, Thau, Volk, & Wolf, 1992; Muller–Oerlinghausen, Muser–Causemann, & Volk, 1992; Nilsson, 1995), losing the opportunity for lithium responsivity has enormous implications for illness prevention and long-term outcome. Even if a patient with first onset major depression is treated, but residual depressive symptoms remain short of a complete remission, they too are at increased risk for a major recurrence and more chronic course (Judd, Paulus, Schettler, Akiskal, Endicott, Leon, Maser, Mueller, Solomon, & Keller, 2000).

Recent data also suggest that lithium has stress counterregulatory mechanisms at a variety of levels. It increases neurotropic or cell survival factors such as BDNF and Bcl-2 and decreases cell death factor Bax and p53 (Chen, Zeng, Yuan, Huang, Jiang, Zhao, & Manji, 1999; Chen & Chuang, 1999; Manji, Moore, Rajkowska, & Chen, 2000). Stress decreases the rate of neurogenesis (Gould & Tanapat, 1999), and lithium increases it (Manji, Moore, & Chen, 2000). Similarly, whereas stress decreases the expression of BDNF in the hippocampus, antidepressants and electroconvulsive seizures increase BDNF, and the presence of antidepressants during a stressor will moderate some of its effects on neurotrophic factor gene expression (Duman, 1998; Smith, Makino, Altemus, Michelson, Hong, Kvetnansky, & Post, 1995; Smith, Makino, Kvetnansky, & Post, 1995; Smith, Zhang, Lyons, & Mamounas, 1997). Thus, to some extent lithium and antidepressants may be stress counterregulatory.

Another possible liability of prolonged expression of untreated illness is that of accumulating other comorbid illnesses. To the extent that one tries to treat one's own low mood or high anxiety with alcohol or other substances of abuse, a decade of untreated affective illness in adolescents and young adults gives them considerable additional risk for acquiring other serious conditions such as substance abuse or alcohol addiction. This in turn can influence gene expression in the central nervous system (Post, Weiss, Leverich, George, Frye, & Ketter, 1996) and further confound treatment and convey a negative prognosis (Brady & Lydiard, 1992; Brady & Sonne, 1995; Strakowski, DelBello, Fleck, & Arndt, 2000).

All of these considerations make the lack of early treatment a potentially devastating individual and family burden, and the situation is even more serious for those with histories of childhood or adolescent physical or sexual abuse. These individuals have a significantly longer interval from onset of first symptoms meeting diagnostic thresholds to first treatment than other bipolar patients without such a history (Leverich et al., in press). Thus, the patients who are the most vulnerable and in need of greatest support and medical intervention are precisely those who are currently the least likely to have adequate illness recognition and treatment in the community.

It should be reemphasized that the incidence of physical and sexual abuse reported in the SFBN patients is not very different from that reported in the general population (Hyun, Friedman, & Dunner, 2000). Thus, we are not suggesting that patients with bipolar disorder are at unique risk for the occurrence of these severe stressors compared with the

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general population but only that if they do occur in the context of bipolar illness they convey an increased likelihood for an early onset and adverse outcome compared with those without such a history.

Public Health Implications

Families, pediatricians, and general practitioners need to become increasingly aware of the risks, signs, and symptoms of major affective disorder and PTSD in children. In this regard, current statistics are highly disappointing. Even for adults seen in the general medical practice, there is often little direct effort at depression screening, and even more troubling is the high rate of absence of treatment recommendations even if a serious depression is uncovered. Depression is a much more immediate direct and indirect health risk than is smoking, yet it receives relatively little public attention compared with the current focus on and expenditures for smoking education and prevention. In coronary artery disease, for example, depression increases the likelihood of a heart attack and, if one has a heart attack, a lethal outcome is 4–7 times more likely for an individual who is depressed compared to one who is not (Musselman, Evans, & Nemeroff, 1998). What are the similar figures for the risk of acquiring a substance abuse problem or dying from a suicide attempt in adolescents and young adults with a history of depression compared with those without? From the published statistics, it would appear that the risk for acquiring a substance abuse problem might be increased similarly 2- to 4-fold over that of the general population, and the risk for suicide more than 10-fold.

Increased public awareness and treatment should be targeted for depression similarly to that of hypertension and hyperlipidemia, whereby specific numbers describing norms are available to patients who are thereby more likely to become aware of the considerable risks associated with their values. We suggest that a rating scale be developed so that individuals could have ready access to their depression quotient. High numbers on this scale might then trigger further action, including an increased treatment seeking and case identification even in general practice settings. Similarly the potentially devastating consequences of early stressors, especially when unameliorated by many potential modifying factors, need greater attention, direct case exploration, and the institution of appropriate treatment. Because appropriately targeted treatment can be highly effective (Cicchetti, Rogosch, & Toth, 2000; Luthar, Cicchetti, & Becker, 2000), the need for early recognition is even more pressing.

Several attempts at developing screening devices for the bipolar spectrum disorders have recently been developed (Hirschfeld, Williams, Spitzer, Calabrese, Flynn, Keck, Lewis, McElroy, Post, Rapport, Russell, Sachs, & Zajecka, 2000; Speer & Post, 2001), and these may ultimately be used in an effort to help individuals with higher scores to seek appropriate evaluation and consultation. In addition to general attempts at education of physicians and the community at large, it might also be particularly fruitful to focus attention on those groups who are at the highest risk. This would include those in whom there is a positive history of bipolar illness on one side of the family (unilineal vulnerability or high risk) and especially those with another individual on the other side of the family with either unipolar or bipolar illness (bilineal vulnerability or very high risk). Instead of the usual < 10% prevalence of unipolar or bipolar affective disorder in the community for the combined group of males and females, this may double and quintuple, respectively, in those with a unilineal or bilineal family history of affective disorder (Gershon et al., 1982; Lapalme et al., 1997; Mendlewicz et al., 1997). When this familial risk interacts with the occurrence of early adverse environmental events, the chances of early onset bipolar disorder appear greatest (Leverich et al., in press).

Given the very high risks for an affective disorder in children from a family in which there is bilineal vulnerability for bipolar affective illness, this may be the ideal population for further developing better methods of early recognition, identification of clinical cases, and early institution of treatment. If these

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very high risk children are also entered into acute and long-term prophylactic clinical trials, the hope is that there would be more rapid identification not only of which agents might be effective in the treatment of childhood and adolescent-onset bipolar illness but also which would hold the best promise for preventing the onset of full-blown illness altogether.

Thus, it would appear highly productive when clinically treating adults with bipolar disorder to ask about the health of children in these very high risk families and encourage a child's appropriate evaluation rather than ignore the potential problem in the hope that the offspring will be spared the illness and its stigma. Moreover, support and therapeutic efforts offered in a positive way to the high-risk parent with active affective illness should be redoubled in further hopes of avoiding any potential for undesirable behavior toward their children (Cicchetti et al., 2000). To the extent that this is achieved, it could even have an extended multigenerational impact like that observed in preclinical studies.

In a child at high risk who has begun to develop affective dysregulation, it would appear that the ultimate consequences of having a major illness missed or ignored far outweigh that of the possible stigma involved. Children with early signs of heart disease, epilepsy, rheumatoid arthritis, infectious diseases, and malignancies are studiously evaluated and treated as early as possible in the hope of achieving complete remissions and preventing even more severe illness in the future. The empirical and theoretical rationales for similarly approaching those at highest risk for affective disorders are also cogent and should further drive the exploration of the efficacy of early intervention.

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