

CHAPTER 15

The Social Environment and Life Stress in Depression

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It has long been suspected that the social environment plays an important role in depression. Depressed individuals, clinicians, and theorists commonly assume that depression is intimately intertwined with the stressors and strains of people's social worlds. There can be little doubt about the general truth of these assumptions. However, such views are far too sweeping and nonspecific. There are many forms of life stress, numerous "roles" for life stress in depression, and a number of pathways via which depression and stress may be intertwined. It is within these more refined relations between particular dimensions of life stress and aspects of depression that theoretically trivial and fertile effects can be distinguished.

This chapter examines these important issues and related topics. We begin by breaking down the nonspecific notions of *social environment* and *life stress* into more explicit and useful concepts. In a similar manner, we disaggregate depression into its specific features and clinical course to then distinguish the various "roles" that life stress may play with different aspects of the disorder (e.g., the onset vs. clinical course of an episode). We next provide an overview of empirical findings, and key theoretical and methodological issues involving life stress and depression. Throughout this discussion, we emphasize requirements for satisfactorily handling an expanding framework of dynamic interrelations between life stress and depression over time. Then, having reviewed the general research literature on life stress and depression, we venture on to topics that are more debatable and controversial in nature, and discuss unresolved issues, empirical gaps, and emerging themes. By approaching these topics from a life stress perspective, we are able to advance lines of inquiry that may be useful in resolving the issues and closing the gaps. We conclude with a discussion of directions for future theory and research.

PRELIMINARY CONSIDERATIONS AND CLARIFICATIONS

People tend to think very globally about the *social environment*, *adversity*, and *life stress*, and about how such factors relate to *depression*. It is helpful to begin by restricting what is to be considered within the broad scope of these terms. First, what aspects of the social environment are relevant for depression? At a *distal level*, the social environment reflects aspects of cultural variation and differences in socioeconomic status (SES); at a more *proximal level*, the social environment reflects individual differences in exposure to major life events (e.g., deaths, relationship breakups) and chronic difficulties (e.g., ongoing health, financial, or relationship problems); and at the most *immediate level*, the social environment reflects the quotidian details and vicissitudes of everyday life. Which of these levels might be most relevant for understanding depression? Second, what aspects of depression are under the influence of the social environment and life stress? Does life stress contribute to the onset of depression in general, to the development of different types of depression, or to the clinical course of depression? By attending first to these distinctions, we can focus attention on the most promising areas for understanding which elements of the social environment and life stress play particular roles with regard to specific features of depression.

What Features of the Social Environment Are Relevant for Depression?

The social environment encompasses a variety of concepts of potential relevance for depression, such as SES, geography, and cultural factors. Research on SES and screening scale scores of depressive symptoms, for example, has consistently demonstrated an inverse linear association, with lower SES correlating with higher depressive symptomatology (Kohn, Dohrenwend, & Mirotznic, 1998). Findings for SES and major depression have been more complex, possibly varying by gender, geography, ethnicity, and diagnostic interview procedures (cf. DSM-IV-TR; American Psychiatric Association, 2000). However, in a recent meta-analysis including both symptom and diagnostic measures of depression, low SES individuals were at greater risk initially for incurring depression (odds ratio [OR] = 1.24) and at even greater risk for persisting depression (OR = 2.06; Lorant et al., 2003). Furthermore, quasi-experimental research has tried to disentangle competing explanations for the association between SES and psychopathology by attempting to determine whether adversity related to lower SES leads to depression (i.e., social causation), or whether depression leads to lower SES over time (i.e., social selection). Here, the findings point convincingly toward social causation of depression, at least for women (Dohrenwend, 2000). Finally, recent research on changes over time in socioeconomic circumstances also implicates low SES as a causal factor for increases in depressive symptoms and caseness of major depression (Lorant et al., 2007).

These general lines of research linking SES and depression provide clues about proximal and more specific mechanisms that account for the SES–depression relationship. A favored interpretation is that low SES inherently involves greater life stress, which represents a process through which SES translates into individual risk (Dohrenwend, 2000). But *life stress* is a term that is overly general and nonspecific. Based on research and theory over the past several years, we make the case for a critical role of major life events in the onset of major depression (Hammen, 2005; Mazure, 1998; Paykel, 2003; Tennant, 2002).

In What Ways Is Depression Influenced by the Social Environment?

Social factors and life stress may influence the onset, clinical course, and clinical characteristics of a depressive episode. These separate relations may be of interest on their own; yet if they are not taken into active consideration, they may obscure or confuse the causal picture between social factors and depression. A comprehensive account of the role that life stress plays in depression requires attention to these broader issues involving depression and its dynamic nature over time.

LIFE STRESS AND DEPRESSION: RESEARCH ISSUES AND EMPIRICAL FINDINGS

Reviews of research on life stress and depression unanimously conclude that major life events precede the onset of many, if not the majority of, depressive episodes (Hammen, 2005; Kessler, 1997; Mazure, 1998; Paykel, 2003; Tennant, 2002). Despite strong consensus about the consistency of these findings, however, questions remain about what the findings indicate specifically about the nature of depression (Hammen, 2005; Kessler, 1997). For example, do major stressors lead to particular types of depression, or can less major forms of adversity trigger a depressive episode? Some intriguing methodological challenges are posed when we try to resolve such questions. How these challenges have been handled in the past has implications for evaluating the reported findings, particularly with respect to the sensitivity and potential biases of the procedures employed.

Conceptualization and Measurement of Life Stress

Attributing illnesses of unknown origins to stress, adversity, and negative emotions is a recurrent theme in the history of medicine and psychiatry, and should give one pause when invoking psychosocial factors as causes of disorders of unknown origin (Sontag, 1978). It is against this backdrop of psychological preconceptions that modern research on life stress must be examined and evaluated. Psychological stressors are very popular explanations for unwanted emotional and physical states. As a result of their intuitive appeal and social legitimacy, they possess unwarranted explanatory power that exceeds their scientific utility. These tendencies to rely on life stress explanations often infiltrate the procedures adopted by researchers to measure and test hypotheses, permitting biased results to elude critical commentary. The challenge is to translate the productive ideas about psychological stress into more precise concepts, definitions, and operational procedures, thereby providing an appropriate empirical platform for scientific inquiry (Monroe & Slavich, 2007).

Self-Report Checklist Procedures

Research on life stress proliferated in the late 1960s and 1970s as a result of methodological innovations in measurement of life events (Paykel, 2001). Holmes and colleagues' development of the Schedule of Recent Experiences (SRE) (Hawkins, Davies, & Holmes, 1957; Rahe, Meyer, Smith, Kjaer, & Holmes, 1964) introduced the idea of measuring individual differences in exposure to life stress, with the potential to do so in a standard and objective manner. The SRE was a brief 43-item self-report checklist of common life events "empirically observed to occur just prior to the time of onset of disease" (Holmes, 1979, p. 46).

These investigators later developed standard weights for the degree of readjustment required by these events and subsequently published the well-known Social Readjustment Rating Scale (SRRS; Holmes & Rahe, 1967).

Innovation and expediency, however, outweighed rigor in the early development of these methods, and eventually serious deficiencies in the self-report checklist approach were recognized, including confounds between life events and actual symptoms of depression (e.g., inclusion of items such as sexual difficulties, changes in sleeping and eating habits) and between life events as consequences (not causes) of depression (trouble with a boss, divorce, marital separation, being fired at work, change in recreation, etc.). Despite early recognition of these major limitations (Brown, 1974; Paykel, 2001), as well as mounting empirical evidence that documented many other problems with self-report checklists (Dohrenwend, 2006; McQuaid et al., 1992; McQuaid, Monroe, Roberts, Kupfer, & Frank, 2000), measures of this type continue to predominate in research on life stress and depression (Grant, Compas, Thurm, McMahon, & Gipson, 2004; Monroe, 2008).

Investigator-Based Methods

Fortunately other researchers developed more scientifically sound procedures for assessing life stress (Brown & Harris, 1978; Dohrenwend, 2006; Hammen, 1991; Paykel, 2001). Probably the most elaborate system for assessing, defining, and rating life stress is the Life Events and Difficulties Schedule (LEDS), developed by Brown and Harris. Using a comprehensive manual, the LEDS incorporates explicit rules and operational criteria for defining acute and chronic stressors, for distinguishing between complex constellations of such stressors, and for rating these experiences (Brown & Harris, 1978). The unique biographical circumstances of the person are taken into account when rating each life event, so that the stressor experience is judged in light of what it might mean for that person given the context. The interview-based information can be presented in a separate meeting to raters who are blind to the subjective reactions of the particular individual to prevent confounding of reaction with possible depression status.

Other investigators have developed or adapted stress assessment procedures that are consistent with the LEDS philosophy and incorporate many of the same methodological advantages (Dohrenwend, 2006; Hammen, 1991; Paykel, 2001). Importantly, these investigator-based approaches have been found to be superior to self-report measures with respect to their psychometric properties, ability to control for potential sources of bias, and capacity to predict depression (Brown & Harris, 1989; Hammen, 2005; Mazure, 1998; McQuaid et al., 1992, 2000; Paykel, 2003; Tennant, 2002).

Life Stress and the Onset of Depression

As recent reviews of the topic uniformly indicate, there is a strong relation between major life stress and the onset of depression, with little doubt about the consistency or theoretical importance of the basic finding (Hammen, 2005; Mazure, 1998; Paykel, 2003; Tennant, 2002). In one review of over 20 studies, Mazure (1998) noted that the consistency and strength of the association between life stress and depression is not simply a generic stress effect; rather, it is specifically related to the “occurrences that are defined as *undesirable, major* life events” (p. 294; original emphasis). Kessler (1997) came to a comparable conclusion that “there is a consistently documented association between exposure to major stressful life events and subsequent onset of episodes of major depression” (p. 193), and that life stress

associations are “generally stronger when ‘contextual’ measures are used rather than simple life event checklists” (p. 193).

In particular, one class of contextually rated life events, termed *severe events*, has been found to predict the onset of depression most consistently (Brown & Harris, 1989). These events represent highly aversive experiences, generally involving serious threats to core relationships or occupation, and sometimes involving acute economic or health changes (Brown & Harris, 1989). Indeed, the presence of a single, severe life event has been found to predict depression in the majority of cases; when these major events are taken into account, the less severe stressors, alone or in combination, are typically not predictive of depression (Brown & Harris, 1978, 1989; Monroe & Simons, 1991). Although more minor forms of life stress may on occasion play a role in depression (Hammen, Henry, & Daley, 2000; Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Monroe et al., 2006), a strong case can be made that the dominant effect is attributable to a major, severe life event.

If major negative life events are of particular relevance for depression, then these forms of stress can provide a focal point and clues about the processes that eventuate in an episode of the disorder. The general and nonspecific idea of stress obviously is narrowed considerably. However, further specification of the nature and qualities of particular types of severe life events could enhance the prediction of the onset of depression. Indeed, recent findings suggest that particular types of major stress are especially potent in precipitating depression. Such events include humiliation and entrapment (Brown, Harris, & Hepworth, 1995; Kendler et al., 2003), social defeat (Gilbert, Allan, Brough, Melley, & Miles, 2002), loss and danger (Kendler et al., 2003), and targeted rejection and social exclusion (Allen & Badcock, 2003; Slavich, Thornton, Torres, Monroe, & Gotlib, in press). Progress along these lines could ultimately provide a conceptual basis for a taxonomy of life stress in depression (Allen & Badcock, 2006; Nesse, 2000).

Life Stress and the Clinical Characteristics of Depression

A major issue facing depression researchers is how to explain the substantial heterogeneity in the clinical presentation of depression. Why do individuals with depression exhibit such different combinations of signs and symptoms? Clearly a full account of depression must be capable of explaining such variability in phenotypes across, as well as within, depressed persons over time. Several lines of research have attempted to explain individual differences in clinical characteristics of depression in relation to life stress, and this research can be categorized into (1) studies of symptom severity and symptom profiles, and (2) studies of depressive subtypes.

Life Stress, Symptom Severity, and Symptom Profiles

Depressed people with major life stress have been found to have more severe depressive symptomatology compared to depressed people without such stress (e.g., Monroe, Harkness, Simons, & Thase, 2001; Tennant, 2002). Interestingly, these effects have been primarily attributable to preonset, as opposed to postonset, major life events (e.g., Monroe et al., 2001). That the preonset events are more removed in time relative to the postonset events suggests that the effect reflects matters of etiological relevance.

Few explanations have been offered as to why life stress is related to greater overall symptom severity in depressed people. Are individuals with prior stress elevated “across the board” for all depressive symptoms? Or are the associations with stress primarily accounted

for by particular types of symptoms (e.g., cognitive–affective vs. somatic)? Research suggests that stress–severity associations often hold for symptoms assessed with the Beck Depression Inventory (BDI; Beck, Steer, & Garbin, 1988), but not for those assessed with the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Due to the different loadings of cognitive (BDI) versus somatic (HRSD) symptoms on the two instruments, these findings suggest some degree of symptom specificity. Alternatively, method variance may account for the differences between the self-reported BDI and the interview-based HRSD. Monroe and colleagues (2001) found life stress to be associated principally with cognitive–affective symptoms. Across different assessment methods there also was a consistent positive association between severe life events and suicidal ideation. Overall, research on life stress and the symptoms of depression is relatively sparse, and this is especially true for chronic stressors and depression symptoms. However, the existing clues suggest that a better understanding of such associations may be of use for clarifying the role of life stress in depression.

Life Stress and Subtypes of Depression

Many of the earliest accounts of depression refer to a syndrome of “sadness without reason” (Klibansky, Panofsky, & Saxl, 1964; Monroe & Depue, 1991). Kraepelin (1921), and others suggested that some forms of depression “may be to an astonishing degree largely *independent of external influences*” (p. 181, original emphasis). Others, addressing similar concepts, invoke terms such as *excessive depression*, *unjustified depression*, and *depression disproportionate to causative factors* (Jackson, 1986, p. 316). All of these observations reflect the central idea that social circumstances cannot fully explain the onset of *some* forms of depression. As a result of these observations and writings, it is often assumed that there exists an *endogenous* subtype of depression that is biologically based and arises independent of environmental circumstances. This viewpoint simultaneously implies that other forms of depression are due to adverse social circumstances, indicating a nonendogenous, or reactive, form of depression (Jackson, 1986).

The general distinction between stress-related and biologically based subtypes of depression has stimulated a number of related classification schemes and distinctions. Dichotomies such as *endogenous–reactive*, *neurotic–psychotic*, and *endogenous–neurotic* have been proposed and investigated. Many other terms loosely reflect one or the other of the two hypothesized etiological distinctions (e.g., situational, secondary, and nonendogenous for the stress-based concept; melancholic, retarded, and vital for the biologically based concept). Unfortunately, adding to the confusion, such terms have been used to describe differences between depressed persons in their presenting symptomatic and syndromal features, irrespective of social versus biological assumptions about cause. For instance, people exhibiting psychomotor retardation, unreactive mood, and pervasive anhedonia have been considered to represent an endogenous or melancholic subtype of the disorder (Rush & Weissenburger, 1994). Overall, despite the appeal of such typologies, inconsistency and confusion in their usage have hampered progress toward identifying potential subtypes of depression (Hammen, 2005; Katschnig, Pakesch, & Egger-Zeidner, 1986; Monroe & Depue, 1991).

Notwithstanding definitional difficulties, attempts to validate subtype distinctions based on the presence of life stress have been numerous over many decades, producing an extensive and often contentious debate (Mapother, 1926). Several reviews of literature from the past 25 years have suggested that life stress appears to be more common prior to the onset of almost *any* depressive subtype based on symptomatic differences (relative to the rate

for nondepressed populations; Mazure, 1998). Yet some of these studies also suggest that there is a weak relationship between life events and a particular symptom pattern or depressive subtype (Katschnig et al., 1986; Mazure, 1998; Monroe & Depue, 1991; Tennant, 2002). Again, some of these inconsistencies can be ascribed to the lack of standardization for defining both stress and the endogenous and nonendogenous forms of depression (Hammen, 2005; Katschnig et al., 1986). Also, the relation of major life stress to different subtypes of depression may depend on whether the depressive episode is a first onset or recurrence. For example, patients with a recurrence who presented with an endogenous symptom pattern reported fewer severe events relative to first-onset patients, recurrence patients with nonendogenous symptoms, and community controls (Brown et al., 1995; Frank, Anderson, Reynolds, Ritenour, & Kupfer, 1994). Further work incorporating other symptoms or factors that distinguish subtypes may be of use to clarify the utility of such distinctions (Parker et al., 1999).

Life Stress and the Clinical Course of Depression

A number of studies have examined the association between life stress and the course of a depressive episode. Owing to the dynamic and changing nature of both stress and depression over time, this area of study is methodologically challenging. Whereas research on life stress and the onset of depression has one focal point for prediction, research on life stress and the clinical course of depression has many possible points of interest over time (e.g., remission, relapse, recurrence). And whereas the timing of life stress vis-à-vis onset is fixed by the nature of the question (i.e., stress precedes onset), important questions about the clinical course of a depressive episode involve stress at any point in time, pre- and postonset.

Compared to research on life stress and the onset of depression, research on life stress and the clinical course of depression has not been as common, mostly due to a general lack of attention to clinical course issues, as well as to diffusion of the existing attention across the different components that comprise the topic (i.e., remission, relapse, recurrence). Variations in design (e.g., definitions of the relevant outcomes for remission, relapse, recurrence), populations (community depressives, patients in different forms of treatment), and methods (self-report checklists and investigator-based stress assessments) further reduce the number of studies within any topic area, despite considerable potential for this area of research to uncover and resolve important clinical and conceptual matters.

Remission

With regard to remission, two related considerations are apparent: the timing of recovery and the absolute likelihood of recovery. Do stress-related depressions remit more or less quickly than depressions that are unrelated to major stress? And, do stress-related depressions have a better or worse overall likelihood of recovery? Although a few studies have addressed these issues, once again, the variability in methods and the heterogeneity of depressed populations complicate the interpretive picture. The major concerns are the timing of life stress (preonset vs. postonset), the nature of life stress (severe life events vs. other indices of stress), the nature of the population of participants studied (first onset, recurrences, severity, age), and the presence or type of treatment (natural course, psychotherapy, pharmacotherapy).

In terms of events prior to onset and *time to recovery*, inconsistent findings have been reported. Whereas some studies suggest a more rapid resolution of depression following

preonset stress (e.g., Kendler, Walters, & Kessler, 1997; Parker & Blignault, 1985), other data suggest a slower response time to remission (Karp et al., 1993). In terms of life events following onset, recovery appears to be delayed considerably when stressors occur during treatment (e.g., Monroe, Roberts, Kupfer, & Frank, 1996). Again, however, caution is warranted owing to the relatively few studies on the topic, the diversity of methods; and the definitions, designs, and populations employed.

Research on life stress and the overall *likelihood of recovery* from depression has been somewhat more plentiful. Reviews underscore the inconsistent findings across studies, with some reporting that life events prior to onset forecast a better outcome, and others reporting a worse outcome (Mazure, 1998; Paykel, 2003; Tennant, 2002). Occurrence of major events during the course of the episode appears to prevent recovery (Mazure, 1998). Some of the discrepancies in this literature, again, may be due to differences in methods and populations studied. For example, some studies suggest that life stress prior to onset forecasts a lower likelihood of recovery for people with severe forms of depression (e.g., recurrent depression) compared to those with less severe forms (e.g., first onset; Monroe et al., 1996). Also, although the presence of chronic stressors has rarely been taken into account (Hammen, 2005), such forms of stress have been found to make recovery less likely (Tennant, 2002). Overall, whereas questions about preonset events, chronic stressors, and clinical course remain unanswered, there is more consistency about the adverse effects of concurrent stressors on overall recovery.

Relapse

Once recovery is achieved, previously depressed persons are at risk for slipping back into the previous episode. Can life stress help to explain why some individuals relapse and others do not during this vulnerable period? With regard to preonset stressors (i.e., Does stress prior to onset predict vulnerability to relapse?), the evidence is mixed (Mazure, 1998; Paykel, 2003; Tennant, 2002). Theoretically, however, the question is central to understanding depression over the life course: Does a stress-related episode imply that, once recovered, the psychobiological system will be more or less vulnerable to depression reemerging? This question hinges on two additional questions, which we address in turn. First, does the initial stress abate or continue? And second, does the psychobiological system change as a consequence of prior stress or depression?

Life stress occurring prior to the onset of a depressive episode may signify the likelihood of continuing stress given that depressed persons often generate life events, even when they are not actively depressed (Hammen, 2005). In light of this evidence for stressors occurring concurrently with an episode of depression, it seems reasonable to consider that continuation of stress after remission represents a proximal and potent trigger of relapse. Thus, the continuation of preonset stressors, the occurrence of new stressors, and the presence of chronic stressors after remission is achieved all might contribute to a social vulnerability to relapse. Research to date has not taken into consideration these dynamic, interactive stress processes over time, even though such information might be of considerable theoretical and clinical value.

In addition to changes in life stress over time, there may be psychobiological changes consequent to major stress or depression that render the person more susceptible to recurrence (Monroe & Harkness, 2005; Post, 1992). These social and biological processes may be especially important for understanding individual differences in the lifetime course of major depression and the problem of recurrence. We address this topic in detail next.

Recurrence

Over the past several years, concern about the long-term course of depression over the lifespan has moved from the periphery to the center of research and clinical interests. In one of the early reviews of the topic, Belsher and Costello (1988) concluded that about 50% of patients have a recurrence within 2 years following successful treatment. Since then, estimates of long-term morbidity owing to recurrence have steadily risen. Most recently, DSM-IV-TR (American Psychiatric Association, 2000) reported, "At least 60% of individuals with Major Depressive Disorder, Single Episode, can be expected to have a second episode. Individuals who have had two episodes have a 70% chance of having a third, and individuals who have had three episodes have a 90% chance of having a fourth" (p. 372).

In terms of clinical observations, Kraepelin remarked many years ago that one of his patients became depressed "after the death first of her husband, next of her dog, and then of her dove" (1921, p. 179). This suggests that repeated exposure to losses and experiences of depression result in a progressive lowering of the threshold for stress needed to trigger subsequent recurrences. More recently, Post (1992) provided a more formal conceptual premise for such observations, developing the *kindling* hypothesis for life stress and the recurrence of depression. The relation of stress to subsequent episodes of depression is hypothesized to change over time, such that progressively less severe doses of stress are required to bring about onset; eventually, after many episodes, recurrences may appear apparently spontaneously, independent of psychosocial origins. These intriguing ideas are derived from animal laboratory work on electrophysiological kindling and behavioral sensitization, paradigms that demonstrate the plausibility of transitions from precipitated episodes to episodes independent, or autonomous, of psychosocial origins (Post, 1992).

There is ambiguity, however, about the implications for understanding the role of life stress within this conceptual premise. For example, does stress become *more* or *less* relevant for successive recurrences? On the one hand, one might reason that stress becomes progressively less important over time, with nonstress factors beginning to predominate in causing a recurrence episode (the *stress autonomy hypothesis*). On the other hand, one might reason that life stress becomes progressively *more* important in triggering recurrence episodes as vulnerability to stress increases over successive episodes (the *stress sensitization hypothesis*); that is, with an accruing history of prior episodes, less severe life events acquire the capability to trigger a recurrence of depression. Because severe life events occur relatively infrequently compared to events of lesser magnitude, these latter, more frequent and common stressors increase the probability, and hasten the onset, of recurrence (see Monroe & Harkness, 2005).

Fortunately, the stress sensitization and stress autonomy hypotheses can readily be tested. For example, if severe stress is essential for the onset of early episodes, it seems probable from the stress sensitization point of view that severe stress would still bring about recurrence in a sensitized system (see Monroe, Slavich, Torres, & Gotlib, 2007a). Thus, although proportionately fewer people with many episodes of depression will have experienced a severe event before the onset of their most recent recurrence, those people who do incur severe stress should have a very high likelihood of breakdown. Alternatively, if longitudinal studies of life stress and recurrence of depression find that people with more lifetime episodes are less likely to succumb following a major life event, then the evidence would support the stress autonomy premise (Monroe & Harkness, 2005).

There are noteworthy gaps between these ideas about life stress and depression recurrence, and epidemiological data on the recurrence of depression. If depression researchers are indeed largely studying samples of people with recurrent depression, then why do severe events remain the strongest stress-related predictor of episode onset? Specifically, if 91% of depressed persons in the community report a prior episode of depression (Kessler, 1997), then how do we account for up to 80% of depressed persons in the community reporting a recent, major life event (Mazure, 1998)? Why is there relatively little firm evidence available for lesser severities of stressors triggering onset of a recurrence (cf. Monroe et al., 2006)? Researchers have begun to study different facets of these ideas (Hammen et al., 2000; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Monroe et al., 2006), and the relations also may be moderated by genetic or other factors (Kendler, Thornton, & Gardner, 2001).

EMPIRICAL INCONSISTENCIES AND RESEARCH GAPS

Compared to other risk indices, major life events represent one of the strongest predictors of the onset of depression (Kendler, Gardner, & Prescott, 2002, 2006). Major life events also have significant implications for understanding the clinical course of an episode and the lifetime course of the disorder. These wide-ranging findings provide the foundation for moving toward a better understanding of the nature and course of depression. However, there is relatively little discussion about what these findings specifically suggest about depression. We suspect that part of the problem harkens back to the intuitive appeal of stress as a culturally accepted and nonspecific explanation. Stress “makes sense” and possesses high face validity, which can deflect attention from asking deeper questions about the processes involved (Monroe, 2008). Without further analysis, however, such an unquestioning attitude undermines the search for underlying mechanisms, and leads investigators to overlook important inconsistencies and research gaps. Yet by considering more fully the research on life stress and depression, there is considerable potential for researchers to develop insights into central questions about the nature of this disorder.

Despite consensus about the broad diagnostic status of depression, its variations, and public health significance, less agreement exists concerning its core features, possible subtypes, and underlying causes. That debate continues about the dimensional versus categorical nature of the disorder alone, despite decades of extensive research and deliberations, underscores the complexity of the problem and the challenges facing investigators (Kendell, 1976). Attempts to explain the causes of depression are particularly hindered in light of problems in understanding the basic nature of the disorder. It is in this context that the magnitude and consistency of findings for major life events in relation to the onset of an episode of depression are useful for expanding thinking about the disorder's origins and its many features, and for addressing inconsistencies and gaps in current knowledge.

Not all people with depression report prior severe events, and not all people who experience severe events develop depression. Approximately 50% or more of depressed patients have experienced recent stress, as have about 80% of community depressives (compared to approximately 24% in nondepressed samples; see Table 1 in Mazure, 1998); between 20 and 50% of persons experiencing a recent major life stress succumb to depression (Brown & Harris, 1989; Monroe & Simons, 1991). From a life stress perspective, then, one needs to explain why some people become depressed following major life events, whereas others do not, and why some depressed persons apparently have not experienced a recent major life

event. The most readily apparent explanations include the following: (1) Depression is a heterogeneous class of disorders with regard to clinical and presentation etiology; (2) stress is one factor in a multifactorial model of depression; and finally, and less obviously, (3) depression is a dimensional disorder in which stress plays a graded role.

Life Stress, Clinical Heterogeneity, and Depression Subtypes

Although the available evidence for a distinct subtype of stress-related depression is modest, creative approaches may yet uncover a form of depression that is largely, if not uniquely, linked to major life stress. This optimism is warranted by findings that indicate the following: (1) A substantial proportion of (but not all) depressed people relative to nondepressed controls experience severe stress prior to depression; (2) preonset severe stress predicts the clinical course of depressed persons; and (3) preonset severe stress predicts greater levels of depressive symptoms, specificity of symptoms, and, possibly, symptom profiles. Whereas one can debate the findings within any of these three literatures, the broad and emerging picture is that major stress is an intrinsically important causal factor for a large proportion of depressed persons.

One obstacle to isolating a hypothetical, stress-induced subtype of depression is the significant heterogeneity of the signs, symptoms, and presentations of major depression. Different people diagnosed with major depression often present with different symptoms and permutations of the requisite criteria and features. Life stress may influence the presenting features of depression, and these influences may occur in addition to any etiological role for stress. For instance, stress might have a causal role for one subtype of depression and a *pathoplastic* (i.e., symptom modification) role for another. Awareness of such *dual roles* associated with life stress may be required to explain individual differences in depressive features and the detection of distinctive syndromes.

There are additional sources of clinical heterogeneity that, if taken into account, could enhance our ability to detect unique patterns of stress influences on specific syndromes or particular symptom expressions. With respect to psychosocial factors, the early loss experiences of separation from or death of a loved one have been reported to distinguish between neurotic and psychotic depressive features (Brown & Harris, 1978). Personality characteristics also have been implicated as creating variability in symptomatic expression of depression (Clark, Vittengl, Kraft, & Jarrett, 2003; Hirschfeld & Shea, 1992). Another intriguing possibility is that severe life events are equally important for people incurring a first episode of depression, regardless of whether they meet symptom criteria for endogenous or nonendogenous depression. However, for subsequent recurrences of depression, severe events may be associated predominantly with nonendogenous presentations of depression (Brown et al., 1995; Frank et al., 1994).

Finally, an underappreciated advantage of a life stress perspective on the heterogeneity of depression is the potential for isolating a non-stress-related form of the disorder. The classic endogenous depression subtype has been distinguished throughout time by a stark and severe clinical presentation in people who otherwise appear to be relatively stress-free and to have advantaged situations and attractive social worlds (Jackson, 1986; Monroe & Depue, 1991). Cases of classic endogenous depression may be easily overlooked in contemporary society, with ubiquitous and specious explanation of "stress" helping to obscure the true origins of the disorder. These superficial and biased explanations based on life stress are minimized when rigorous stress assessment procedures are adopted, with precise definitions of major stressors and accurate dating of preonset stressors. Use of such methods would in-

crease capability to isolate a hypothetical subtype of depression that develops independent of life circumstances.

Life Stress, Multifactorial Models, and Depression Subtypes

The etiology of depression has long been thought to be due to a variety of factors operating together to precipitate a depressive episode (Jackson, 1986). The central importance of life stress has typically been formalized within these conceptual schemes (e.g., diathesis–stress models of depression; Abramson, Metalsky, & Alloy, 1989; Monroe & Simons, 1991; Zuckerman, 1999). Within these approaches, life stress is an important component in the cause of depression (or subtype of depression), yet necessarily operates in concert with other vulnerability factors (or *diatheses*). Major life stress activates, or interacts with, the underlying diathesis, transforming predisposition into manifest depression. Returning to the theme of severe events as a pivotal focus for depression onset, we pose the following questions: What other forms of vulnerability do severe events require to precipitate depression? What additional susceptibilities are sufficient to allow severe stress to eventuate in depression?

Investigators might proceed in a number of ways to determine how severe life stress operates with other vulnerability factors in depression. Initially, a better understanding of how severe stress is related to other vulnerability factors would be useful. For example, how are severe events related to cognitive vulnerability, or to genetic and familial liability? Patient samples provide a useful starting point for testing severe stress associations with other vulnerability factors, and for testing predictions in relation to other validating considerations (e.g., clinical characteristics, clinical course, and outcome). Because patient samples typically report approximately 50% incidence of recent severe stress, there is an optimal level of variability in severe stress occurrence to probe associations with other vulnerability factors. Next, interactions between severe stress and other risk factors can be evaluated within depressed samples to determine whether there are further associations of particular theoretical interest. Does the pairing of severe events with other vulnerability factors predict a distinctive symptom profile or clinical course (see Monroe, Slavich, Torres, & Gotlib, 2007b)? Once the nature of severe stress, other risk factors, and their interactions are better modeled and validated, the groundwork will be laid for research on the stress processes that influence depression onset and course.

Along these lines, it is helpful to distinguish between two different models for life stress and diatheses coactions. On the one hand, traditional diathesis–stress theory posits an ipsative or inverse relationship between severe stress and the diathesis: The greater the allotment of one factor, the less of the other is required (Abramson et al., 1989; Ingram & Price, 2001; Monroe & Simons, 1991). The sum of the two factors is critical, not the relative loading of either. This additive model parsimoniously accounts for many diverse findings in the research literature, including the concerns that (1) not all people with severe stress develop depression, and (2) not all depressed people report recent life stress.

On the other hand, if there is something of particular etiological importance about severe life events, then a second model is important to consider. Recognizing, again, that not all people with severe stress succumb to depression, other factors are required to explain why some people break down under stress and others do not. Within this conceptualization, severe life events are associated with one (or more) additional vulnerability indices in a *permissive* manner. In direct contrast to the ipsative model, severe stress is associated with *heightened* cognitive vulnerability, or with *greater* genetic predisposition. Consistent with

this *interactive* or *multiplicative model*, Kendler and colleagues (1995) found that the likelihood of depression onset was greatest for women with heightened genetic liability *and* a recent major life event. There are two noteworthy implications of this model. First, it implicitly specifies that the class of major depression is heterogeneous. Because not all people with major depression have prior severe life events, alternative causal explanations are required for the nonstress depressive conditions. Second, this perspective readily incorporates many popular concepts as moderators of the impact of stress in the genesis of depression (Hammen, 2005). Thus, social support (or lack thereof), coping efficacy, personality attributes, biological factors, and so on, all are easily integrated into the framework, further explaining why some people may succumb to stress and others do not.

Of course, variants of these two basic models also might be considered. For example, one could extrapolate to three or more subtypes of depression, each with different arrangements of vulnerability factors and interrelations. The two models proposed, though, provide a reasonable starting point for testing competing hypotheses and for learning about how severe stress interacts with other indicators of risk.

Life Stress and Dimensional Models of Depression

Categorical models of psychopathology possess many advantages. They simplify thinking about the disorder in question (i.e., it is either present or absent), have clinical benefits (e.g., facilitate treatment decisions), and provide distinct practical benefits (e.g., public health planning, treatment reimbursement). Indeed, this perspective has been extraordinarily successful in leading to the discovery of the causes of many diseases, thereby alleviating sundry scourges of humankind (Gordon, 1993). With such victories and virtues in its favor, it is easy to understand why a categorical approach continues to dominate conceptual systems in psychopathology.

Alternatively, dimensional approaches to depression have their advocates, and there has been a recent resurgence of interest in such models of disorder (Ruscio & Ruscio, 2000; Widiger & Clark, 2000). These models assume that disorder is distributed along a continuum, without natural *break points*, or thresholds for differentiating people with and without the problem (Kendell, 1976; Lewis, 1934). In this context, the debate between categorical and dimensional viewpoints has stimulated thought and controversy, but little research has been aimed at resolving the matter. Might the particular importance of severe life events in depression be useful for moving research on this topic along productive lines?

Perhaps, most generally, a basic misunderstanding about life stress in relation to psychological disorders biases thinking in subtle ways against dimensional approaches. From DSM-III through DSM-IV-TR, the criteria for mental disorders require that the “syndrome or pattern must not be merely an expectable and culturally sanctioned response to a particular event” (American Psychiatric Association, 2000, p. xxi). There are at least three major concerns with this criterion. First, it presumes knowledge about what constitutes the range of expectable responses under particular environmental and cultural conditions (as well as a reliable means for evaluating the matter). Second, it is not theoretically clear why an expectable response to an event—if the response meets the indicated diagnostic criteria and impairment requirements—would *necessarily* be dismissed on such a basis alone (Wakefield, Schmitz, First, & Horwitz, 2007). Finally, the addition of the dismissive adverb *merely* to the official diagnostic nomenclature undermines the clinical gravity and perceived importance of an event-related psychological problem.

These matters may be complicated by the overvalued explanatory potential of life stress and major events. Comments and attitudes, such as those in DSM, imply that clinical science possesses firm knowledge about the range of human reactions to the vicissitudes of life, that for a given situation X the range of normal responses is Y , and the range of abnormal responses is Z (and that Y and Z do not overlap). While the argument possesses plausibility at the extremes (e.g., depression emerging under completely tranquil circumstance or under extreme trauma), many people—and quite possibly the majority of people with major depression—inhabit social worlds filled with dilemmas and hardships that exist in a gray area of suspected environmental determination for which the “expectable” responses are simply not known (or are so varied as to render meaningless the notion of *expectable*). By directly addressing the issue conceptually and empirically, researchers might develop (1) better ways of thinking about adversity, emotion, and depression and (2) an empirical basis for specifying the expectable response range to diverse forms of life stress (Wakefield et al., 2007).

Traditional thinking based on a categorical model may obscure alternative ways to consider the matter. Viewing the stress process in terms of a more finely tuned fit between environmental challenge and individual response, however, suggests the possibility of graded reactions in proportion to varying degrees of challenge (Weiner, 1992). In other words, depression may not represent a dichotomous breakdown under major stress, but a complex and graded mixture of adaptation and maladaptation to specific, psychologically meaningful environmental challenges (Allen & Badcock, 2006; de Kloet, Joëls, & Holsboer, 2005; Nesse, 2000). This way of viewing the stress process in depression is more consistent with the dimensional approach to depression.

At first glance, though, such speculation appears to contradict a central premise of our discussion that something particularly useful about major life events can lead to fresh insights about depression. But, again, by focusing on major events as a pivotal piece of information, novel directions for research may be brought to light. For example, the findings for major life events and depression onset could inform us about a possible artifact of the categorical systems used to define major depression; that is, by arbitrarily constraining the information on depression into two categories (depressed or nondepressed), the role of life stress in depression may be underestimated. Could the “average” reaction to a severe event simply be what is needed to push most people over the definitional threshold for a diagnosis of major depression? Could less severe life events perhaps precipitate psychobiological responses that typically fall just below what is required for a clinical diagnosis? It may be, as well, that other factors moderate the average reaction range between life stress and depression in a dimensional manner (e.g., early life stress increases the likelihood of exceeding the threshold in the face of major stress, or availability of social support lessens the likelihood of exceeding the threshold). Pursuing this line of thinking further, we note that there has been little systematic study of people with severe stress who do *not* meet full criteria for major depression; available information suggests that these people suffer, too, yet from somewhat milder forms of the disorder (Brown, 1991). More generally, it is noteworthy that these ways of thinking about relations between stress and depression help to explain why not all people who have experienced severe events necessarily develop depression; a substantial proportion suffer from debilitating, but subthreshold, depressive conditions (Gotlib, Lewinsohn, & Seeley, 1995).

Last, it is worth considering why an expectable response to adversity would be summarily dismissed with the adverb *merely*, suggesting that it does not merit full consideration as a syndrome or mental disorder. In addressing this point, we hesitantly shift from matters of science to matters of values in the recognition and remediation of human suffering. What

forms of misery and malady are sanctioned by a society? Which dysphoric and debilitated groups are accorded social legitimacy and allowed to be considered “ill,” to adopt the sick role, and to not be held accountable or blamed for their incapacity? From this vantage point, a categorical approach to defining psychopathology lends a shorthand legitimacy to depression: It is consistent with a medical viewpoint and, importantly, provides the appearance of clearly demarcating the normal from the abnormal. A dimensional approach is less desirable in this regard: It is difficult to discern who is deserving of the sick role from who is undeserving, and there is no “natural” reference point or cultural anchor to guide important decisions. When and where depression shades into demoralization—when and where clinical entities and subsyndromal conditions merge into, or overlap with, expressions of the miseries of everyday life—are poorly understood at present, perhaps are ultimately indeterminate. It is the frank reluctance of clinical science to address directly the question of “an expectable response” to adversity in its many forms that belies a great gap in our understanding of so-called “normal responses,” the limits of normal functioning, and the beginnings of psychopathology. Without such a knowledge base, discussions and definitions of the abnormal, demarcating the boundaries of the pathological, possess an inevitably arbitrary element that is grounded both in society’s values and in current science (Wakefield, 1992).

Our intent is not to advocate for a categorical or dimensional model of depression, but to provide examples of life stress research that might be useful for research on these models of depression. It is quite conceivable that the dimensional issues play into the previously discussed problem of subtypes of depression, yielding even more complex frameworks that incorporate distinct categorical subtypes and dimensional typologies (Kendell, 1976). In all likelihood, the category of depression, as currently defined, will turn out to be a complex and cumbersome mélange of categorical and dimensional subgroup distinctions, with different, yet possibly overlapping, etiological factors and arrangements. Finding solutions to the riddle of depression’s causes may depend as much on intelligent and creative probing of the boundaries of the disorder as on seeking answers within the currently accepted definition of the phenotype.

FUTURE DIRECTIONS

Although psychosocial and biological approaches to depression often emphasize the central importance of stress, there is remarkably little common ground in what actually constitutes “stress” and relatively few efforts to draw linkages across the two levels of analysis. The paucity of translational ideas and research between the literatures, however, is by no means a necessary state of affairs. Each perspective can inform the other, and bridging the psychosocial and biological approaches represents one of the most promising areas for understanding how social adversity impacts biological processes in ways that may lead to major depression. Three topics for future research possess particularly strong potential for integrating ideas across these two levels of analysis, and for furthering understanding of the causal pathways leading to depression.

Translating the Psychology of Stress into the Biology of Depression

One of the most consistently replicated biological findings in psychiatry is the overactivity of the hypothalamic–pituitary–adrenal (HPA) axis in depressed patients (Goodwin & Jamison, 2007). At a very general level, the human life stress and human neuroendocrine research ap-

pear to converge: One might expect cortisol, a key stress hormone, to be elevated in depressed persons suffering from recent major stress. Indeed, the approximate proportion of the depressed samples with prior stress (50%) nicely parallels the approximate proportion of patients with HPA axis dysregulation and excessive cortisol secretion (50%; Young, Lopez, Murphy-Weinberg, Watson, & Akil, 2000). However, there are fundamental gaps and inconsistencies in the literature for determining how research on naturally occurring major life events translates to the research on HPA axis dysfunction in depression (van Praag, de Kloet, & van Os, 2004).

In fact, few studies have examined directly the association between major life events and cortisol dysregulation in depressed patients. Of the little work conducted, at least one study reported elevated cortisol in depressed persons with recent major stress (e.g., Dolan, Calloway, Fonagy, De Souza, & Wakeling, 1985) whereas another study reported HPA axis dysfunction for depressed persons *without* recent stress (Roy, Pickar, Linnoila, Doran, & Paul, 1986). Other, more recent studies also have yielded discrepant findings regarding cortisol's relation to life events and depression onset (Hammen, 2005). Inconsistencies in this literature may be attributable to differences across studies in the measurement of life stress or in the method of assessment for HPA functioning. Clarifying how major life stress and HPA axis disturbances operate in relation to one another is an obvious next step, the results of which will guide further inquiry into the nature of the associations involved with regard to depression. For example, if the high-stress group exhibits HPA irregularities, is it due to continuation of the environmental stress or to more centrally mediated "breakdown" in regulation of the HPA axis? Given the theoretical importance of stress and cortisol, as well as the adverse effects of excessive cortisol on brain structure and function, all possible contributing factors to HPA axis overdrive are worthy of exploration (Sapolsky, 2000).

Finally, HPA disturbance has been associated with poor treatment response and risk of relapse (de Kloet et al., 2005). Greater risk of relapse has also been reported in patients with residual symptoms (Judd, Schettler, & Akiskal, 2002), as well as patients with life stress (Mazure, 1998). A tempting interpretation is that these separate findings work in a unified manner: Continued social adversity and life stress drive HPA activity and symptomatology, which collectively eventuate in relapse. More generally, these observations point to the need to evaluate each domain of risk, and their independent and combined contributions to treatment response, relapse, and recurrence.

In general, there are several empirical gaps with respect to HPA axis functioning, current environmental stress, and depression. This raises further questions as to what factors influence the integrity of the HPA regulatory system, particularly with regard to the sensitivity of HPA function and susceptibility to dysregulation. We address this topic next.

Early Adversity and the Developmental Neurobiology of Stress Regulation

Recent animal laboratory research has highlighted the formative influences of prenatal and early life experiences for the development of individual differences in HPA axis function and stress sensitivity. Differences in early stress exposure also forecast the development of behavioral problems in the animals as they mature (Huizink, Mulder, & Buitelaar, 2004; Meaney, 2001). These animal laboratory studies complement a literature implicating early adversity as a general vulnerability factor for a wide range of problems later in life for humans, including depression (Heim, Plotsky, & Nemeroff, 2004).

An integration of these findings may suggest that early stress exposure renders the organism more vulnerable to the deleterious effects of subsequent stressors by setting in mo-

tion alterations in stress-sensitive neurobiological systems. For example, individuals exposed to early adversity may be more likely to develop hyperresponsive threat/stress systems, which may in turn sensitize them (or increase susceptibility) to subsequent stressors. Alternatively, the vital biological regulatory systems of individuals exposed to early adversity may be more prone to dysregulation as a result of repeated activations of these systems (Repetti, Taylor, & Seeman, 2002). Overall, exposure to early adversity points toward changes in key neurobiological regulatory systems that may modulate adaptation to stressful circumstances, which may in turn help to explain further why some people faced with major stressors develop depression and others do not.

Recent work has begun to explore the intervening mechanisms linking early adversity to later morbidity, with advances in understanding how early adversity contributes to stress sensitization and the pathophysiology of depression (Gunnar & Quevedo, 2007; Heim et al., 2004). Noteworthy, too, is that early adversity broadens and adds another layer to the types of stress that can explain depression. Future studies on early development, neurobiological indicators of stress regulatory systems, and current life events may help to specify better the pathophysiology of depression and the possibility of distinctive subtypes (Heim et al., 2004). The reliable measurement of early adversity in adults adds another challenging area given that these experiences occurred far back in time (Brewin, Andrews, & Gotlib, 1993).

Life Stress and the Molecular Genetics of Depression

Another explanation for why only some people develop depression in the face of life stress involves the role of specific vulnerability genes. This area of research recently has become quite attractive given topical advances in the mapping of the human genome and the development of powerful molecular genetics techniques for detecting specific allelic variations in genes. In a landmark study, Caspi and colleagues (2003) reported that individuals with one or two copies of the short allele of the serotonin transporter (*5-HTT*) gene promoter polymorphism are especially susceptible to developing depression following stressful life events. As a result of these and other findings, a new generation of studies is emerging on life stress, genes, and depression. One can anticipate considerable effort and output over the next several years testing interactions between life stress and specific genes in depression.

In this context, a major challenge for future research will be to ensure that the life stress component of the gene–environment interaction is assessed in as sophisticated and competent a manner as is the genetics component. It is quite possible that techniques for addressing the genetics will overshadow those for life stress, and that careful conceptualization and measurement of stress will be neglected. For instance, to date, the majority of studies attempting to replicate the original findings of Caspi and colleagues (2003) have used varied procedures for indexing life stress, with no two studies using the same or, arguably, even similar measures; only one of 11 studies to date (i.e., Kendler et al., 2005) has adopted measurement procedures in keeping with preferred practices for life stress assessment (Monroe & Reid, in press).

The promise of research on gene–environment interactions depends on proper specification of both the genetic and environmental components of the interaction. Optimal measurement of the particular environmental factor, though costly at times, enhances the statistical power of the research design and increases the ability to discover genes of causal relevance (Moffitt, Caspi, & Rutter, 2005). The successful replication by Kendler and colleagues (2005) of an interaction between major life events and the serotonin transporter

gene in depression onset bears testimony to the importance of taking the assessment of life stress as seriously as the assessment of genetic vulnerability. More generally, these studies provide exciting leads for future research on life stress and its role in the development of major depression.

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