


The ascendance of emotion theory, recent advances in cognitive science and neuroscience, and increasingly important findings from developmental psychology and learning make possible an integrative account of the nature and etiology of anxiety and its disorders. This model specifies an integrated set of triple vulnerabilities: a generalized biological (heritable) vulnerability, a generalized psychological vulnerability based on early experiences in developing a sense of control over salient events, and a more specific psychological vulnerability in which one learns to focus anxiety on specific objects or situations. The author recounts the development of anxiety and related disorders based on these triple vulnerabilities and discusses implications for the classification of emotional disorders.

Editor’s Note

David H. Barlow received the Award for Distinguished Scientific Applications of Psychology. Award winners are invited to deliver an award address at the APA’s annual convention. This award address was delivered at the 108th annual meeting held August 4–8, 2000, in Washington, DC. Articles based on award addresses are not peer reviewed, as they are the expression of the winners’ reflections on the occasion of receiving an award.
The phenomenon of anxiety, to some prominent philosophers and psychologists, is at the very root of what it means to be human (Kierkegaard, 1844/1944; May, 1979). To the well-known early psychologist Howard Liddell, anxiety was the shadow of intelligence:

The planning function of the nervous system, in the course of evolution, has culminated in the appearance of ideas, values, and pleasures—the unique manifestations of man's social living. Man, alone, can plan for the distant future and experience the retrospective pleasures of achievement. Man, alone, can be happy. But man, alone, can be worried and anxious. Sherrington once said that posture accompanies movement as a shadow. I have come to believe that anxiety accompanies intellectual activity as its shadow and that the more we know of the nature of anxiety, the more we will know of intellect. (Liddell, 1949, p. 185)

In this sense, anxiety reflects our important capabilities to adapt and plan for the future (Barlow, 1988).

Yet, individuals spend billions of dollars yearly to rid themselves of anxiety. The cost of visits to primary care physicians and the use of health care services by individuals with anxiety disorders are double what they are for those without anxiety disorders, even if the individuals seeking treatment are physically ill (Simon, Ormel, VonKorff, & Barlow, 1995). Many take away prescriptions from their physicians for various drugs to treat anxiety, making these drugs among the most widely used in the world. In fact, over the past decade individual drugs introduced for the treatment of anxiety by the major pharmaceutical companies have routinely yielded billions of dollars per year in revenue for each product (Greenberg et al., 1999; Hofmann & Barlow, 1999). For individuals availing themselves of these anxiolytics, anxiety is a curse—something they could live without.

Is anxiety the shadow of intelligence or a curse on mankind? Our greatest thinkers have pondered these questions. Freud spent much of his life confronting the mysteries of anxiety and concluded at one point, "One thing is certain, that the problem of anxiety is a nodal point, linking up all kinds of most important questions; a riddle, of which the solution must cast a flood of light on our whole mental life" (Freud, 1917/1963, p. 401). In 1950, the great psychologist O. Hobart Mowrer described what is perhaps the fundamental contradiction of the experience of severe anxiety:

[It is] the absolutely central problem in neurosis and therapy. Most simply formulated, it is a paradox—the paradox of behavior which is at one and the same time self-perpetuating and self-defeating! . . . Common sense holds that a normal, sensible man, or even a beast to the limits of his intelligence, will weigh and balance the consequences of his acts: if the net effect is favorable, the action producing it will be perpetuated; and if the net effect is unfavorable, the action producing it will be inhibited, abandoned. In neurosis, however, one sees actions, which have predominantly unfavorable consequences; yet they persist over a period of months, years, or a lifetime. (Mowrer, 1950, p. 486)

This self-perpetuating and self-defeating paradox is a universal experience. At the beginning of this century, Danish travelers to Greenland reported observing a condition in which Eskimo hunters, alone in kayaks on a perfectly still sea for hours on end waiting for seals to emerge, would experience sudden difficulty breathing, accompanied by a racing heart, trembling, and other strange bodily sensations. Subsequently, these hunters would be unable to venture far from their villages. This condition, well-known among the Eskimo tribes of Greenland, was referred to as kayak angst (Katschnig, 1999). In more recent times, Khmer refugees have presented in large numbers to clinics complaining of trembling, weakness, sudden dizziness, fatigue, and a "sore neck." The Khmer attribute these symptoms to kyol geou, or wind overload, a condition that, when occurring in the neck and limbs, may signal impending death. Thus, a selective attention and exquisite sensitivity develop to sensations in the neck, followed by feelings of impending doom and thoughts of possible death (Hinton, Ba, Peou, & Um, in press-a, in press-b). Kayak angst and Khmer “sore neck” seem to be culturally diverse expressions of panic disorder.

Phobias and, to a lesser extent, other anxiety disorders have one additional mysterious characteristic: a selective association with being female. For example, over 90% of individuals suffering from a phobia of insects or small animals severe enough to keep them from moving to rural areas, or even visiting friends in places where small animals or insects might be present, are female. Data from a large survey conducted by the World Health Organization in primary care settings revealed a consistently high proportion of women with panic disorder with or without agoraphobia (odds ratio 1.63; 95% confidence intervals 1.18–2.20), and this is a consistent finding around the world (Gater et al., 1998). Similarly, a large sample of over 1,000 adolescents revealed a strong preponderance of female participants among those experiencing an anxiety disorder. This gender imbalance emerged early in life, with retrospective data indicating that by the age of 6, girls were already twice as likely as boys to have experienced anxiety (Lewinsohn, Gotlib, Lewinsohn, Seeley, & Allen, 1998).

Anxiety disorders are shockingly common, far exceeding the prevalence of affective disorders or substance use disorders (Kessler et al., 1994), and these disorders may last for decades or even a lifetime in the absence of effective treatment, making them among the most chronic of the mental disorders (Goisman et al.,
1998; Hirschfeld, 1996; Keller & Baker, 1992; Marks & Lader, 1973; Noyes, Clancy, Hoenk, & Slymen, 1980; Pollack et al., 1990). In this article, I summarize my own view of what research has uncovered in the past decade about the nature of anxiety and panic and discuss the classification and development of anxiety and related disorders.

The Ascendance of Emotion Theory

In the 1980s, I made the then somewhat radical proposal that to understand emotional disorders in general and anxiety disorders in particular, it was necessary to more fully appreciate the nature of emotion (Barlow, 1988), a subject that has long been absent from psychology's curriculum. It now seems clear that the experience of emotion (and the development of emotional disorders) cannot be reduced to dry cognitive attributions and appraisals on the one hand, or to specific actions of neurotransmitters and the intricacies of cell physiology on the other (Barlow, 1991c). The growing recognition of the necessity of focusing on emotional experience and expression as a scientific subject in its own right is highlighted by the appearance of the new APA journal Emotion. The model of emotional disorders I presented in the 1980s and 1990s (Barlow, 1988, 1991a, 1991b; Barlow, Chorpita, & Turovsky, 1996) highlights the role of fundamental emotions in the great tradition of the emotion theorists (Darwin, 1872; Ekman & Davidson, 1994; Izard, 1994).

The underlying premise of this approach is that emotions are innate patterns of reaction and responding that have evolved in many life forms because of their functional significance. Although clearly modifiable by learning and maturation, these basic patterns of emotion are present in humans and animals at birth and show a remarkable consistency both within and across species. The primary function, or adaptive value, of emotional behavior is not only preparation for action, but also communication from one member of the species to another. As Öhman (1996; Öhman, Estéves, & Soares, in press) pointed out, the function of emotions in this sense can be understood as a clever means, guided by evolution, to ensure that people do what they have to do to successfully pass their genes to coming generations. In other words, emotions are now conceptualized by most theorists as fundamental action tendencies whose purpose is to motivate behavior related to survival of the species. A theory of the nature of emotional disorders based on discrete emotion theory as applied to depression, anger (stress), and excitement (mania) has been described elsewhere (Barlow, 1988, 1991a, 1991b, in press; Barlow et al., 1996). The focus of this article is on the defensive emotions of fear and anxiety, and their pathological expression.

With this new focus on the study of emotion, the mysteries of anxiety are giving way, grudgingly, to a new appreciation of the richness and complexity of behavioral and cognitive patterns associated with defensive emotions. One of the more important developments is the recognition of substantial and fundamental differences in the behavioral expression of anxiety, on the one hand, and fear, on the other, which have only recently come to light. Thus, on a phenomenological, behavioral expressive, psychometric, and neurobiological level, the emotions of fear and anxiety seem to be fundamentally different emotions (Barlow, in press; Barlow et al., 1996; Bouton, Mineka, & Barlow, in press). On the other hand, these emotions are closely related, and the intimate dance of these two action tendencies within our defensive motivational system (Lang, Cuthbert, & Bradley, 1998) can be observed not only at the level of behavior and cognition, but also in closely related but unique brain circuits underlying these action tendencies. Fear is our emergency defensive reaction (Cannon, 1929), our flight–fight response, enabling us to respond to present danger with instantaneous, sometimes superhuman efforts. To make the response system as rapid as possible, underlying neural circuits bypass the cortex in favor of direct connections from the retina to the emotional brain (LeDoux, 1996). The topic of fear is taken up below. The nature of anxiety is somewhat more complex.

The Nature of Anxiety

In 1988 and in recent updates (Barlow, 1988, in press; Barlow et al., 1996), I described anxiety as a unique and coherent cognitive-affective structure within our defensive motivational system, and I outlined a model of the interaction of the various components of anxiety. At the heart of this structure is a sense of uncontrollability focused largely on possible future threats, danger, or other upcoming potentially negative events, in contrast to fear, where the danger is present and imminent. Thus, anxiety could be characterized roughly as a state of helplessness, because of a perceived inability to predict, control, or obtain desired results or outcomes in certain upcoming personally salient situations or contexts. Accompanying this negative affective state is a strong physiological or somatic component that may reflect activation of distinct brain circuits such as the corticotropin releasing factor system and Gray’s behavioral inhibition system (Chorpita & Barlow, 1998; Gray & McNaughton, 1996; Sullivan, Kent, & Coplan, 2000). These systems may be the physiological substrate of readiness, underlying a state of preparation to counteract helplessness. Vigilance (hypervigilance) is another characteristic of anxiety that suggests readiness and preparation to deal with potentially negative events. If one were to put anxiety into words, one might say, “That terrible event could happen (again), and I might not be able to deal with it, but I’ve got to be ready to try.” For these reasons, I have suggested that a better and more precise term for anxiety might be anxious apprehension. This conveys the notion that anxiety is a future-oriented mood state in which one is ready or prepared to attempt to cope with upcoming negative events. Another term often paired with anxiety is anticipatory. However, in the present definition, all anxiety is anticipatory, so this qualifying adjective is
not necessary. The process of anxiety as described above is presented in Figure 1.

In this model, a variety of cues or propositions, to use the terms of Lang (1985, 1994a, 1994b), would be sufficient to evoke anxious apprehension. It is important to note that this process could occur without the necessity of a conscious, rational appraisal (Bouton et al., in press; Öhman, 1997; Öhman, Flykt, & Lundqvist, 2000). For example, one might experience anxiety without realizing the specific trigger or cue, such as an object or situation that represents an earlier trauma or an internal somatic sensation. These cues may be broad based or very narrow. For example, test anxiety and sexual dysfunction each have a narrow set of cues, which signal the necessity of imminent performance and evoke a state of anxious apprehension with its associated heightened tension and arousal and negative valence. This state, in turn, is associated with a shift to a self-evaluative focus of attention (or a rapidly shifting focus of attention from an external potentially threatening context to an internal self-evaluative content) in which evaluation of one’s (inadequate) capabilities to deal with the threat is prominent. Evidence suggests that this shift to a self-focused attentional state further increases arousal and negative affect, thus forming its own small positive feedback loop (Barlow, 1988, in press). This subsystem is also represented in Figure 1.

Continuing on in the larger system or feedback loop, attention narrows to sources of threat or danger, setting the stage for additional distortions in the processing of information, either through attentional or interpretive biases, reflecting preexisting hypervigilant cognitive schemata. In any case, one becomes hypervigilant for cues or stimuli associated with sources of anxious apprehension. This process in humans is analogous to and may represent Gray’s (1987; Gray & McNaughton, 1996) stop, look, and listen state of behavioral inhibition, although the actual state of inhibition is not as readily apparent in clinical examples of human anxiety as it is in animals. At sufficient intensity, this process results in disruption of concentration and performance. The process of anxiety is seldom pathological, even when intense, until it becomes chronic.

When this happens, one or both of two prominent consequences of the process of anxiety ultimately develop in an attempt to cope with negative affect and its triggers. First, a tendency to avoid entering a state of anxious apprehension is always present. This tendency becomes more pronounced

**Figure 1**

*The Process of Anxious Apprehension*

<table>
<thead>
<tr>
<th>Dysfunctional Performance and/or lack of concentration on task at hand</th>
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<tbody>
<tr>
<td>Evocation of Anxious Propositions (situational contexts, unexplained arousal or other cues)</td>
</tr>
<tr>
<td>Negative Affect</td>
</tr>
<tr>
<td>A sense of uncontrollability and unpredictability (perceived inability to influence personally salient events and outcomes)</td>
</tr>
<tr>
<td>Preparatory coping set accompanied by supportive physiology and activation of specific brain circuits (e.g., CRF system, Gray’s Behavioral Inhibition System)</td>
</tr>
<tr>
<td>Hypervigilance and Cognitive Biases</td>
</tr>
<tr>
<td>Attentional Biases: Enhanced Recognition of Threat</td>
</tr>
<tr>
<td>Attention Narrowing on Sources of Threat</td>
</tr>
<tr>
<td>Interpretative Biases</td>
</tr>
<tr>
<td>Memory Biases</td>
</tr>
<tr>
<td>Attentional Shift to self-evaluative focus (on physiological or other aspects of responding)</td>
</tr>
<tr>
<td>Intensification</td>
</tr>
<tr>
<td>Additional Increases in Arousal</td>
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<tr>
<td>Attempts to Cope Characterized By:</td>
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<tr>
<td>(Possible) Avoidance of situational context or other aspects of negative affect (e.g., arousal) if feasible</td>
</tr>
<tr>
<td>Process of Worry</td>
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<tr>
<td>Heightened verbal-linguistic capabilities and restricted autonomic activity to support (often futile) attempts to plan and problem solve</td>
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<tr>
<td>Avoidance of Core Negative Affect</td>
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</tbody>
</table>

and observable, depending on the severity or intensity of the state and the specificity of the contextual cues that set the occasion for anxious apprehension. Thus, test-anxious individuals will avoid tests to the extent that this is possible, and sexually dysfunctional individuals will eventually avoid sex. However, this rather maladaptive coping skill may not be available to individuals whose anxious apprehension has diffused to many different situational contexts (or across many different networks in memory). In these individuals, subtle avoidance behaviors, rituals, or superstitious behavior may become established. Second, worry driven by the process of anxiety, which (at intense levels) is very difficult to control (Brown, Dowdall, Côté, & Barlow, 1994), seems best construed as an additional, most often futile, attempt to cope with chronic anxiety. In the DSM–IV (American Psychiatric Association, 1994), lack of control over the worry process is a defining feature of generalized anxiety disorder (Brown, Barlow, & Liebowitz, 1994). Worry, or concern over future events, is of course not problematic and may even be adaptive under some circumstances, unless it is so driven by anxiety that it becomes intense and uncontrollable. It is in this sense that worry can become chronic and maladaptive. Chronic anxiety also is characterized by persistent central nervous system tension and arousal, autonomic inflexibility (Thayer, Friedman, & Borkovec, 1996), and functional brain asymmetry (Heller, Nitschke, Etienne, & Miller, 1997), which seem to reflect the consequences of a state of perpetual readiness to confront danger.

The Nature of Fear and Panic: True Alarms, False Alarms, and Learned (Conditioned) Anxiety

Only in the mid-1980s did researchers begin to collect information on the nature of panic. The accumulating evidence points to a complex biopsychosocial process. This process involves the interaction of an ancient alarm system, crucial for survival, with inappropriate and maladaptive learning and subsequent cognitive and affective complications. First, it is important to consider the alarm system most commonly known as fear.

There is general agreement that fear occurs when people are directly threatened with a dangerous, perhaps life-threatening, event. An impending attack from wild animals is something few people experience today, but our ancestors knew this threat well in millennia past. This history may account for our somewhat greater susceptibility to becoming alarmed in the presence of snakes and mountain lions (Cook, Hodes, & Lang, 1986; Ohman et al., in press; Seligman, 1971). Relevant threats today include speeding vehicles, guns, drowning, or seeing the safety of our children threatened. Under these conditions, the emotion of fear represents a true alarm that mobilizes us physically and cognitively for quick action and sometimes superhuman efforts. Most typically, running away or escaping is the behavioral manifestation of fear. Occasionally, directed action to counter the threat is apparent, such as attacking a predator or single-handedly lifting an automobile so that a child trapped underneath can escape. These reactions represent Cannon’s (1929) emergency reaction characterized by the compelling action tendencies of fight or flight. Sometimes these actions are counterproductive, as in the case of a drowning victim vainly struggling when the rational response would be to lie still and attempt to float. The ancient response of freezing (tonic immobility) may be called forth if other action tendencies, such as escape or aggression, are ineffective or not available and one is under direct attack by a predator (e.g., Gallup, 1974; Suarez & Gallup, 1979). Most theorists would agree that these basic responses are primitive alarm reactions observed far down the phylogenetic scale. As such, they have profound evolutionary significance.

In 1988, I described the phenomenon of false alarms (Barlow, 1988). That is, spontaneous or uncued panic seems phenomenologically nearly identical in all respects to fear, except for the ability of the individual to specify an antecedent (Carter & Barlow, 1995; Forsyth & Elfert, 1996). The very definition of panic, specifying as it does sudden feelings of marked apprehension and impending doom that are associated with a wide range of distressing physical sensations, would certainly qualify as a definition for fear in other contexts. How common are false alarms, and why do they occur?

False alarms or panic attacks seem to be far more prevalent in the general population than was assumed previously. For example, our own data ( Rapee et al., 1988) and data from epidemiological surveys (e.g., Wittchen & Essau, 1991) suggest that between 10% and 14% of the population had experienced an unexpected, uncued panic attack during the past year. Typically, attacks were less intense and less frequent in these “nonclinical panicers” than in patients with anxiety disorders. Panic attacks also occurred during sleep in nonclinical panicers and aggregated more strongly in the families of these individuals than in families of participants who had not experienced panic (Craske, 1999; Norton, Dorward, & Cox, 1986). Researchers have made progress in the search for the causes of false alarms, particularly initial false alarms, during the past decade. Ongoing lines of investigation are targeting a complex web of preexisting biological and psychological vulnerabilities interacting with contemporaneous events (e.g., life stress) in the genesis of initial false alarms (panic; Bouton et al., in press).

The Structure of Anxiety, Mood, and Related Emotional Disorders and the Concept of Neurosis: Back to the Future?

Before discussing the origins of anxiety disorders and the role of anxiety and panic in this process, it is important to discuss the structure of anxiety, mood, and related disorders and the personality traits that may predispose individuals to the development of these disorders. The death of neurotic disorders in 1980, after almost a century of domination, resulted in a split-
ting of neurotic disorders into a number of major classes, such as anxiety, mood, and somatoform disorders, each containing its own list of more specific disorders. Yet, neuroticism lives on and continues to be a serious topic for study, mostly by personality and developmental psychologists interested in traits or temperaments as possible vulnerabilities for the development of anxiety and mood disorders. The major constructs in this study have been given different labels including neuroticism (Eysenck, 1967), trait anxiety (Gray, 1982), behavioral inhibition (Kagan, 1994), and negative affect (Tellegen, 1985), but I have presented evidence elsewhere that the concept and empirical overlap among these constructs seems to outweigh any differences (Barlow, in press).

Much evidence suggests the contribution of a unitary construct to these former neurotic disorders. This evidence includes high rates of comorbidity among these disorders (Brown et al., 1994) and the success of very similar treatments across this wide range of disorders, such as selective serotonergic reuptake inhibitors and very similar cognitive–behavioral strategies (e.g., exposure to emotionally salient cues and the prevention of avoidance; Barlow, in press). There is also evidence that treating one disorder in a comorbid spectrum often leads to the remission of the additional disorders (e.g., Brown, Antony, & Barlow, 1995). On the other hand, the key defining features of anxiety, mood, and related disorders may differ dramatically from each other. This diversity includes such features as perceptual derealization, intrusive thoughts, sensitivity to social evaluation, panic attacks, phobic avoidance of blood, flashbacks of trauma, psychomotor retardation, and cognitive rituals. Yet, all of these phenomena are subsumed under anxiety or mood disorders. This leads to a major conundrum. How can one reconcile the unitary nature of this construct, most often referred to as neuroticism or negative affectivity, with the variety of specific features that distinguish one disorder from another. To address these questions, my colleagues and I have explored the structure of anxiety and mood disorders.

Basically, a complex network of data supports a hierarchical model of anxiety and mood disorders with negative affect representing a higher order factor common to anxiety (and depression), whereas lower order factors may contribute uniqueness to specific disorders (Brown, Chorpita, & Barlow, 1998; Zinbarg & Barlow, 1996). Some of this work is an outgrowth of pioneering efforts by Tellegen (e.g., 1985) and Clark and Watson (e.g., 1991), who developed the tripartite model of anxiety and depression. The most recent iteration of the model of the structure of mood disorders from our center (Brown et al., 1998), based on structural equation modeling, is presented in Figure 2. These data suggest mood and anxiety disorders are closely related, with substantial contributions from the higher order factor of negative affect (neuroticism) to all disorders, as well as contributions to both depression and social phobia from a higher order factor of low positive affect. Thus, depression and anxiety, in this structural model, share negative affect, neurobiological processes (see below), and most likely, similar diatheses, making these two constructs more alike than different. Specific anxiety disorders may be differentiated by the cues that elicit anxious apprehension (the focus of anxiety). In this model, anxious arousal, to use the original term in the tripartite model, is identified as a separate panic factor that contributes differentially to the disorders in an expected fashion (Mineka, Watson, & Clark, 1998). Notice that generalized anxiety disorder and depression are particularly closely related, with a high zero-order correlation. Nevertheless, the best fitting model continues to treat generalized anxiety disorder and depression as separate disorders because of some differences in presenting characteristics.

What this structure suggests, pending further elaboration, is that any future system of nosology (e.g., DSM–V) describing emotional disorders may better represent these disorders in a dimensional framework in which overall severity of negative affect and low levels of positive affect are clearly articulated. In this context, key features of anxiety and mood disorders, such as intrusive thoughts, panic attacks, sensitivity to social evaluation, psychomotor retardation, and so forth, could be arrayed as dimensions emerging out of the higher order factor in a manner similar to a Minnesota Multiphasic Personality Inventory profile. It may be that this organization would lead to a more descriptive, and therefore more valid, approach to our nosology. With this structure in mind, it becomes possible to outline the origins of anxiety and related disorders.

The Origins of Anxiety and Related Emotional Disorders: Triple Vulnerabilities

The experience of the past decade has strengthened earlier speculations (Barlow, 1988) on an interacting set of three vulnerabilities or diatheses relevant to the development of anxiety, anxiety disorders, and related emotional disorders. Genetic contributions to the development of anxiety and negative affect constitute a generalized biological vulnerability. Evidence now suggests that specific early life experiences, under certain conditions, contribute to a psychological vulnerability, or diathesis, to experience anxiety and related negative affective states generally (a generalized psychological vulnerability). Although the unfortunate cooccurrence of generalized biological and psychological vulnerabilities may be sufficient to produce anxiety and related states, particularly generalized anxiety disorder and depression, yet a third set of vulnerabilities seems necessary to account for the development of at least some specific anxiety disorders. Thus, early learning experiences in some instances seem to focus anxiety on certain life circumstances. That is, these circumstances or events, such as social evaluation or the experience of certain somatic sensations, become imbued with a heightened sense of threat and danger. It is this specific psychological vulnerability that, when coordinated with generalized biological and psychologi-
Figure 2
Structural Relations of Anxiety Disorders and Depression


*p < .01.

cal vulnerabilities mentioned above, seems to contribute to the development of specific anxiety disorders such as social phobia or social anxiety disorder, obsessive-compulsive disorder, panic disorder, and specific phobias.

Generalized Biological Vulnerability: Genetic Contributions

Evidence suggests that the fundamental trait of being high strung, nervous, or emotional runs in families and has a genetic component. More formal studies of traits, such as anxiety, neuroticism, negative affect, or behavioral inhibition, also evidence a substantial genetic component (Clark, Watson, & Mineka, 1994). As noted earlier, the relationships among the closely related traits of neuroticism, negative affect, behavioral inhibition, and so forth have yet to be fully worked out, but it is likely that each represents variations on a theme underlying a biological vulnerability to develop emotional disorders generally. Genetic contributions to the expression of these generalized traits are most usually estimated to run in the range of 30% to 50% of the variance. More important, it has now been established that traits of neuroticism or negative affectivity are positively related to anxiety and anxiety disorders (Brown et al., 1998; Clark et al., 1994; Trull & Sher, 1994; Zinbarg & Barlow, 1996).

Of course, many of these early studies are correlational, but more satisfactory prospective designs detailing the relationship between neurotic temperaments and the later development of anxiety are now appearing. For example, Gershuny and Sher (1998) evaluated the extent to which personality dimensions of neuroticism (as well as extroversion and psychoticism) predicted global anxiety ratings in over 400 young adults. They found that an interaction of neuroticism and extroversion predicted both global anxiety and depression three years after initial assessment. They concluded that personality variables, in particular the combination of high neuroticism and low extroversion, constitute an important vulnerability for the later development of anxiety and its disorders (although the purpose of this study was not to predict the occurrence of specific anxiety disorders). Furthermore, Gershuny and Sher found a lack of specificity for predicting anxiety versus depression, in that the personality variables measured seemed to provide a common diathesis, a subject to which I return below.

Although some tantalizing evidence exists on more circumscribed genetic contributions to some disorders, particularly specific phobia (e.g., Fyer, Mannuzza, Chapman, Martin, & Klein, 1995), the strong consensus is that anxiety and related emotional disorders, such as depression, have a
common genetic basis, and that specific differences in these disorders are best accounted for by environmental factors (e.g., Andrews, Stewart, Allen, & Henderson, 1990; Kendler et al., 1995; Martin, Jardine, Andrews, & Heath, 1988). Furthermore, no reasonable evidence to date confirms the existence of a specific “anxious gene.” Instead, weak contributions from many genes in several different areas on a number of chromosomes (a polygenic model) seem to contribute to a generalized biological vulnerability to becoming anxious (e.g., Plomin et al., 1997).

The one deviation from the consensual conclusion regarding nonspecific genetic contributions to emotionality is the evidence for a differential, if overlapping, heritability for panic and perhaps related defensive reactions. That is, certain defensive reactions, such as responding to stressful situations with panic attacks, may have a separate genetic component, much as fainting and freezing in response to certain specific stimulus situations seem to evidence a strong heritable tendency (Craske, 1999; Kendler et al., 1995; Marks, 1986).

In the absence of concurrent psychological diatheses, discussed below, the individual with this nonspecific biological vulnerability would presumably not develop anxiety or other negative affective states later in life, but rather would manifest tendencies to emotionality or exaggerated responsiveness to stress that would be within normal limits. To activate the spectrum of anxiety and related negative affectivity, this normal personality trait must incubate in the fertile ground of early experience. This nonspecific genetic vulnerability could also influence the propensity to develop conditioned emotional responses when experiencing panic and anxiety, because it has been established that temperamental variables with known genetic contributions influence other forms of conditioning (Bouton et al., in press; Mineka & Zinbarg, 1996).

**Generalized Psychological Vulnerability: A Diminished Sense of Control**

The development of a sense of control in animals. As represented in Figure 1, I have suggested that a sense of unpredictability and uncontrollability is at the heart of anxiety. Individuals suffering from anxiety and related disorders process failures or perceived deficiencies as an indication of a chronic inability to cope with unpredictable, uncontrollable, negative events, and this sense of uncontrollability is associated with negatively valenced emotional responding. Functional or “normal” individuals, on the other hand, seem to manifest what has been described as an *illusion of control* in which response deficiencies are attributed to passing external causes or trivial and temporary internal states (Barlow, 1988, in press).

A fundamental question concerns the origins of this sense of uncontrollability. Although the study of etiology is fraught with difficulties, excellent analogues have in fact emanated from the laboratories of experimental psychology, where it seems researchers have been producing severe anxiety for over 50 years. In experiment after experiment, most of them now classic, investigators have produced behavior characterized by extreme agitation, restlessness, distractibility, hypersensitivity, increased autonomic responding, muscle tension, and interference with ongoing behavior. The names of the investigators associated with these experiments occupy a prominent place in every textbook of introductory psychology: Pavlov, Masserman, Liddell, and Gant. The phenomenon they produced was commonly termed *experimental neurosis*. Mineka and Kihlstrom (1978), in an important review, made a compelling case for the specification of one causal factor running through all paradigms subsumed under the name experimental neurosis. They suggested that the cause of “anxiety” in these animals is that “environmental events of vital importance to the organism become unpredictable, uncontrollable, or both” (Mineka & Kihlstrom, 1978, p. 257). These animal models of anxiety have been extended in an important way to primates. For example, Suomi and his colleagues have been studying anxiety in rhesus monkeys for years as a function of genetic vulnerability and early experience (e.g., Suomi, 1986, 1999).

Some fascinating research from Mineka, Insel, and their colleagues in the 1980s began to illustrate not only the seeming importance of negative life events in the production of anxiety in rhesus monkeys, but also their interaction with uncontrollability or unpredictability (e.g., Insel, Champoux, Scanlan, & Suomi, 1986; Mineka, Gunnar, & Champoux, 1986). For example, Mineka et al. (1986), in a sophisticated experiment, assigned infant monkeys to one of three groups: master, yoked, and standard reared. Monkeys in the master group had control over the delivery of food, drink, and other appetitive stimuli. Monkeys in the yoked group received equal amounts of these reinforcers but did not have control over their delivery. Monkeys in the standard reared group were treated according to standard laboratory procedures. Testing began when the monkeys were approximately seven months of age. Results showed that master monkeys engaged in significantly more exploring behavior and less clinging than did the yoked monkeys. Master monkeys also showed reduced fear of a toy robot compared with yoked monkeys. Finally, when separated from peers, master monkeys used coping strategies more effectively to reduce distress. These findings are significant in that they demonstrate the negative influence of experiences with uncontrollability in the early environment. In addition, whereas experimental neurosis paradigms suggest the importance of control over aversive stimuli, this study suggests that control over appetitive stimuli may be equally important.

Important extensions of this work have been reported by Sapolsky and colleagues (e.g., Sapolsky, 1992; Sapolsky, Alberts, & Altmann, 1997; Sapolsky & Ray, 1989) and by Coplan et al. (1996, 1998). These investigators also demon-
strated that the later manifestation of anxiety and stress seemed to be a function of early experiences with unpredictability and uncontrolability in primates, whether rearing occurred in a controlled environment or in the wild. Furthermore, both investigators characterized a neurobiological process associated with these emotional states that develops as a consequence of early experience with uncontrolability. This process involves increased corticotropin releasing factor (CRF) production combined with diminished sensitivity of the pituitary gland, increased production of stress hormones (particularly cortisol), reduced negative feedback sensitivity with lessened ability to regulate cortisol production, and ultimately, hippocampal degeneration. Thus, these animals are afflicted with chronically high levels of CRF secretion and, in many cases, high basal levels of cortisol. Ultimately, this neurobiological profile seems to result in autonomic inflexibility characterized by low vagal tone. This is the opposite psychophysiological profile of organisms that have developed resilience and physiological toughness as a function of early experience (Dienstbier, 1989).

Now there is additional evidence from the animal laboratories that early experience, particularly stressful experience, may effect relatively permanent alterations in brain function, particularly in CRF-containing neurons and receptors. Much of this work has emerged from the laboratories of Charles Nemeroff and his colleagues (Heim & Nemeroff, 1999; Ladd et al., 2000) and builds on the pioneering efforts of experimental psychologists such as Robert Ader (Ader & Groter, 1969), Victor Denenberg (e.g., 1964), and Neil Miller (1980). Nemeroff and his colleagues have demonstrated that early uncontrollable psychological stressors result in seemingly chronic alterations in hypothalamic pituitary adrenocortical (HPA) axis functioning. It is interesting that comparable physical stressors early in life, such as hemorrhage, do not produce this activation. As a mechanism, these investigators suggested that sensitivity of the hippocampus and frontal cortex to circulating glucocorticoids is attenuated by these experiences, thereby decreasing the efficacy of negative feedback inhibition over HPA axis activity. This, in turn, increases CRF and arginine vasopressin synthesis in the hypothalamic paraventricular nucleus and perhaps increases expression of CRF in the central nucleus of the amygdala (Ladd et al., 2000). What is important about these findings, again, is that a psychological variable, early unpredictable and uncontrollable experiences, but not early physical trauma, seems to result in an alteration of neurobiological function that may underlie chronic emotionality and perhaps neuroticism.

Taken together, this evidence indicates that, in animals at least, early stress—particularly uncontrollable and/or unpredictable life events—leads to increased HPA axis responding, negative emotionality (chronic anxious apprehension and/or depression), and alarm reactions. Instillation of a sense of mastery or control during development seems to protect against the likelihood of an anxious response. Other evidence indicates that monkeys receiving social support from a monkey peer group will have fewer anxiety reactions than will monkeys reared in isolation (Mineka, 1985a, 1985b). The development of coping responses that imply a sense of control (whether real or apparent) also buffers anxiety (Coplan et al., 1996; Heim & Nemeroff, 1999; Suomi, 1999). With this suggestive evidence in mind, it becomes possible to examine findings on the etiology of human anxious apprehension.

The development of a sense of control in humans. These findings with robust animal models of anxiety make it important to identify crucial early experiences in humans that may predispose the development of chronic anxiety (and depression). Building on important early psychological work delineating the concept of locus of control (Nowicki & Strickland, 1973; Rotter, 1954) and attachment theory (Bowlby, 1980), Chorpita and Barlow (1998) have recently reviewed evidence on the potential importance of early parenting styles to the development of a sense of control in children. Basically, a web of evidence has emerged supporting two propositions. First, parents who are more contingently responsive foster a sense of control. They may accomplish this by providing children with more opportunities to exercise control over their environment by influencing the parents’ behavior, particularly the provision of attention, food, and so forth early in life in a consistent and predictable manner. Second, parents who are less intrusive and protective and provide their children with more occasions to explore their world and develop new skills to cope with unexpected environmental occurrences enhance a healthy sense of control in their children. Similar data have appeared regarding the development of depression (Nolen-Hoeksema, Wolfson, Mumme, & Gusk, 1995), reflecting once again the similar and perhaps identical diatheses, both psychological and biological, for these two emotional states.

Recently, Chorpita, Brown, and Barlow (1998) attempted to evaluate this particular model of the development of anxiety through structural equation modeling. Building on previous evidence with depression (Nolen-Hoeksema, Girgus, & Seligman, 1992), Chorpita et al. used a cross-sectional design to evaluate a variety of models describing the development of anxiety in children presenting with anxiety disorders. The major hypothesis evaluated the notion that an overcontrolling family environment fostering a diminished sense of personal control should in fact produce a sense of uncontrollability, as reflected in a more external locus of control. This external locus of control should in turn contribute to increased negative affect and ultimately to clinical symptoms. We also evaluated the possibility, based on evidence from childhood depression studies, that attributional style would function as a mediator in the model. Compared with a number of alternative models, the model depicting a diminished sense of personal control (external locus of con-
control) as a mediator between a family environment fostering less autonomy and subsequent negative affect and clinical symptoms was the best fit for the data. The results are reflected in Figure 3. Thus, these findings once again suggest that a family environment characterized by limited opportunity for personal control is associated with the development of anxiety. This relationship is mediated by low perceived control in young children, which appears to be a more robust mediator than attributional style.

In summary, the evidence has begun to support a model of the development of anxiety (and depression) characterized by a sense of relative uncontrollability, as a mediator between negative life events and the emergence of anxiety and depression early in development. It is interesting that this mediational model in early childhood stands in contrast to a moderational model that seems operative in late childhood and adulthood (Chorpita et al., 1998; Cole & Turner, 1993; Hammen, Adrian, & Hiroto, 1988; Nolen-Hoeksema et al., 1992). These findings suggest an important developmental progression in the formation of this generalized psychological vulnerability. That is, the environment may help foster a (cognitive) template, with early experience contributing to the formation of a vulnerability (i.e., mediational model). Later in development, this vulnerability may begin to operate as an amplifier for stressful environmental events (i.e., moderational model). This development structure seems to be consistent across models of anxiety and depression.

Thus, genetic contributions to the development of anxiety seem to account for approximately 30% to 50% of the variance. However, neurobiological processes underlying anxious apprehension that may emerge from this biological (genetic) diathesis seem to be influenced substantially by early psychological processes, contributing to a generalized psychological vulnerability. This early experience with controllability and predictability, based in part but certainly not exclusively on interactions with caregivers, contributes to something of a psychological template, which at some point becomes relatively fixed and diathetic. Stated another way, this psychological dimension of a sense of control is possibly a mediator between stressful experience and anxiety, and over time this sense becomes a somewhat stable moderator of the expression of anxiety. (Chorpita & Barlow, 1998, p. 16)

A preliminary conceptual model outlining these operations is presented in Figure 4.

A synergism of generalized biological (genetic) and generalized psychological (early experience) vulnerabilities would be likely to lead to the clinical syndromes of generalized anxiety disorder and the depressive disorders triggered by a stressful life event as outlined in Figure 5. Notice that false alarms (panic attacks) may occur as a function of stressful life events, may be facilitated by high levels of baseline anxiety, and may emerge as a function of these synergistic generalized vulnerabilities. However, these false alarms would not in themselves be implicated in a clinical disorder. For that to occur, an additional layer of more specific psychological vulnerabilities must be considered.

Specific Psychological Vulnerabilities: Learning What Is Dangerous

I have also described a third set of psychological vulnerabilities that predisposes the individual to focus anxiety on some specific object or event (Barlow, 1988, in press; Bouton et al., in press). This particular psychological vulnerability, also a function of early learning experiences, becomes relevant for certain anxiety disorders where anxious apprehension is focused on potentially dangerous specific objects or events. In panic disorder (Ehlers, 1993; McNally & Eke, 1996), this would be somatic (interoceptive) sensations and other cues signaling the possible occurrence of the next panic attack. This vulnerability seems to arise when individuals learn early on from caregivers, through modeling or information transmission, that unexplained somatic sensations are dangerous and could signal possible illness or death. In specific phobias, this set of vulnerabilities contributes substantially to determining the particular object or situation that becomes the focus of fear (Antony & Barlow, in press). In social phobia, there is evidence that individuals have been differentially subjected to early experiences in which the potential danger of social evaluation was clearly communicated by parents or other important caregivers or friends (e.g., Barrett, Rupee,
Figure 4
Model of the Development of Vulnerability for Anxiety and Depression


Figure 5
Diatheses-Stress Model of the Development of Generalized Anxiety and Depression Specifying Synergistic Biological and Psychological Vulnerabilities


Figure 6
Triple Vulnerabilities in the Development of Certain Anxiety Disorders

Dadds, & Ryan, 1996; Bruch & Heimberg, 1994; Bruch, Heimberg, Berger, & Collins, 1987; Rapee, 1997). In obsessive–compulsive disorder, where obsessional thoughts, images, or urges themselves become the focus of anxiety, there is evidence that at least some of these individuals had previously learned to equate dangerous thoughts with dangerous actions (thought–action fusion; Steketee & Barlow, in press).

In summary, vicarious learning of potential threat emanating from objects or situations seems to serve as a specific psychological vulnerability for the development of individual anxiety disorders. Once again, these experiences in isolation would not be sufficient to produce a clinical disorder. For example, someone vicariously learning that physical sensations are potentially dangerous may well develop hypochondriacal tendencies as an adult or may differentially attend to illness-related behaviors in their children, but would be unlikely to develop a clinical disorder such as panic disorder or hypochondriasis in the absence of more generalized biological and psychological vulnerabilities. The synergism of these triple vulnerabilities is detailed in Figure 6.

To take one example, social phobia is often characterized by false alarms occurring after stressful events in social evaluative situations (or by true alarms occurring after traumatic, humiliating direct social experiences). The socially phobic individual then focuses anxiety on upcoming social and evaluative situations on the basis of having learned that these contexts are potentially threatening ones that may lead to undue anxiety and possibly a panic attack, resulting in social failure and ridicule. Alternatively, severe anxious apprehension, particularly associated with deficient social skills, may be sufficient to reach the threshold for social phobia in the absence of alarms, but chronic social anxiety would be unlikely to develop, even following a difficult social situation, in the absence of synergistic triple vulnerabilities. This arrangement is depicted in Figure 7.

Conclusions

I have broadly outlined a theory of the development of anxiety and related emotional disorders, as well as the structure of these disorders. This theory draws heavily on emotion theory and on scientific findings from the laboratories of experimental psychology, specifically cognitive science, neuroscience, developmental psychology, and learning theory. The applicability of the science of psychology to clinical disorders has become possible only in the past several decades, but seems essential to an understanding of the development, treatment,
and ultimately, prevention of anxiety and related disorders. The existence of the triple vulnerabilities consisting of generalized biological, generalized psychological, and specific psychological vulnerabilities is a hypothetical structure that requires further confirmation, although data supporting each vulnerability in isolation are increasingly robust. However, this effort is only a beginning, and the individual components recounted in this review, as well as the structure of their relationship to each other, must continue to be subject to the slow but inexorable process of science.

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