

# A Modern Learning Theory Perspective on the Etiology of Panic Disorder

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Several theories of the development of panic disorder (PD) with or without agoraphobia have emerged in the last 2 decades. Early theories that proposed a role for classical conditioning were criticized on several grounds. However, each criticism can be met and rejected when one considers current perspectives on conditioning and associative learning. The authors propose that PD develops because exposure to panic attacks causes the conditioning of anxiety (and sometimes panic) to exteroceptive and interoceptive cues. This process is reflected in a variety of cognitive and behavioral phenomena but fundamentally involves emotional learning that is best accounted for by conditioning principles. Anxiety, an anticipatory emotional state that functions to prepare the individual for the next panic, is different from panic, an emotional state designed to deal with a traumatic event that is already in progress. However, the presence of conditioned anxiety potentiates the next panic, which begins the individual's spiral into PD. Several biological and psychological factors create vulnerabilities by influencing the individual's susceptibility to conditioning. The relationship between the present view and other views, particularly those that emphasize the role of catastrophic misinterpretation of somatic sensations, is discussed.

Early learning theorists such as Pavlov (1927), Watson (J. B. Watson & Rayner, 1920), and later Mowrer (1947) and Solomon (e.g., Solomon, Kamin, & Wynne, 1953) were highly interested in the relevance of their work on conditioning and learning to understanding the genesis of what was then called neurotic behavior in humans. Other investigators, using a variety of experimental paradigms that induced so-called experimental neurosis in animals (e.g., Pavlov, Gantt, Liddell, and Masserman, to name a few; see Mineka & Kihlstrom, 1978), also assumed that their work would be directly relevant to human neurotic behavior. Unfortunately, enthusiasm for this work on the part of psychopathology research-

ers began to wane in the 1970s as criticisms of the applicability of this earlier work to human neuroses mounted (see Rachman, 1977, 1990, for reviews).

At the same time, a virtual revolution in the field of learning was occurring, focusing on the development of new paradigms and new theoretical developments about the nature of the associative learning process. However, most later learning theorists were not as interested as the founding fathers in the relevance of their findings for understanding psychopathology, and the two fields went their separate ways with little cross-fertilization of ideas. Over the past 15 years, a goal of some of our work has been to reinvigorate this cross-fertilization by demonstrating the relevance of newer perspectives on learning theory to understanding anxiety and the anxiety disorders (e.g., Barlow, 1988; Barlow, Chorpita, & Turovsky, 1996; Bouton, 1988, 1991b, 2000; Bouton & Nelson, 1998b; Bouton & Swartzentruber, 1991; Chorpita & Barlow, 1998; Mineka, 1985a, 1985b; Mineka & Zinbarg, 1991, 1995, 1996, 1998). The major goal of the present article is to spell out the relevance of some contemporary work on classical conditioning, and learning theory more broadly, to understanding the etiology and maintenance of anxiety disorders with an emphasis on one of the more common anxiety disorders: panic disorder (PD).

The study of anxiety disorders and their treatment expanded steadily in the 1970s and 1980s; the National Institute of Mental Health dubbed the 1980s the "decade of anxiety" (e.g., Rachman & Maser, 1988; Tuma & Maser, 1985). The efficacy of treatments for most of these disorders represents one of the great success stories of applied psychological science (e.g., Barlow & Lehmann, 1996). However, although our understanding of basic behavioral and cognitive processes underlying panic and anxiety likewise advanced significantly, the underlying development of theories

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focused on the etiology of panic disorder has not advanced appreciably since the 1980s. In our view, psychological theories of PD remain in an early developmental stage, as is the case with more biological theories, at least in part because they have not incorporated the latest developments in the basic behavioral, cognitive, and neural sciences or the integration of any of these fields. As noted, this is one purpose of this article. After briefly describing the disorder, as well as current theoretical perspectives on it, we proceed to an articulation of a new contemporary learning theory perspective on PD that does incorporate developments from these other fields.

PD is a clinical syndrome that provides a particularly appropriate context in which to examine the relevance of basic principles of conditioning and learning for the development and maintenance of psychopathology. In this anxiety disorder, the fundamental emotional constructs of anxiety, panic, and consequent phobic avoidance come together in an intricate relationship that can devastate the lives of those who develop it in severe form. Some patients are confined to their homes as virtual prisoners for years on end.

To meet criteria for PD, a person must experience recurrent unexpected panic attacks that occur without any obvious cues or triggers, such as encounters with a frightening object or experiencing a traumatic event. In other words, the panic attack seems to come out of the blue. A panic attack is an abrupt experience of intense fear or discomfort accompanied by a number of physical and mental symptoms, most usually heart palpitations, chest pain, sensations of shortness of breath, dizzy feelings, and thoughts of going crazy, losing control, or dying. Significantly, the attack must develop abruptly and reach a peak within 10 min (American Psychiatric Association, 1994).

The experience of unexpected panic attacks is not enough to meet criteria for PD, however. In addition, the individual must develop substantial anxiety or concern over the possibility of having another attack or about the implications of the attack or its consequences (such as the attack leading to a heart attack, to "going crazy," or to "losing control"). This is an important criterion, because we now know that numerous individuals experience "nonclinical panic attacks," in which a susceptible individual under stress may experience a sudden jolt of unexpected panic but fail to develop anxiety about a possible subsequent attack and its consequences, attributing it instead to benign events of the moment.

Many people with PD develop the complication of agoraphobia, which literally refers to fear of the marketplace. Agoraphobia, the most severe of all phobias, describes anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of an unexpected panic attack (or panic-like symptoms). Typically, agoraphobic fears occur in clusters of situations that include being outside of the home alone, being in a crowded church or shopping mall, or being on public transportation (buses, trains, or airplanes). Agoraphobic avoidance behavior is simply one of the learned consequences of having severe unexpected panic attacks. If you have an unexpected panic attack and are afraid you may have another one, it is not surprising that you want to be in a safe place or at least with a safe person who either can help or knows what you are experiencing in the event another attack occurs.

Not everyone develops agoraphobia, and in those who do, agoraphobic avoidance may develop along a continuum from mild to severe. Thus, PD may occur with or without agoraphobic avoidance. For those individuals who do not develop agoraphobic avoidance, it is characteristic to find other associated behavioral coping tendencies such as resorting to the use (and often the abuse) of drugs and/or alcohol to self-medicate anxiety and panic. Avoidance of behaviors or activities that might provoke somatic symptoms similar to those that occur during panic is also common. For example, patients may avoid exercising (which may produce breathlessness or trembling and perspiration), sexual relations (which may produce other similar physical symptoms), or frightening movies (which may produce emotional symptoms that are reminiscent of panic attacks). PD is fairly common; approximately 3.5% to 5.3% of the population meet the criteria for PD at some point during their lives (Kessler et al., 1994). Onset usually occurs in early adult life from the midteenage years to about 40 years, although it can occur in children as well (Barlow, in press).

### Current Theories of PD

Currently, there are at least three prominent psychological theories about the origins of PD. Two of them (cognitive theory and anxiety sensitivity theory) emphasize cognitive aspects of the disorder. An earlier conditioning theory was heavily criticized and has stimulated less research in recent years. We now briefly review these approaches and illustrate the criticisms that have been raised for each (see Thorn, Chosak, Baker, & Barlow, 1999, for a more detailed review).

#### *Cognitive Theories*

Cognitive theories, which are most closely associated with D. M. Clark (1986, 1988, 1996) and Beck (e.g., Beck & Emery, 1985), see an individual's "catastrophic misinterpretations" of somatic and other sensations as crucial to the development and maintenance of PD (see also Salkovskis, 1988). Specifically, an individual will experience panic when his or her focus on internal bodily sensations (whether produced by anxiety or not) leads to catastrophic thoughts about their imminent meaning (e.g., "I am going to have a heart attack"). Such catastrophic thoughts, which are anxiety-producing themselves, lead to further bodily sensations, which provide more fuel for more catastrophic thoughts, and thus a vicious cycle culminating in a panic attack. The internal focus on somatic and other sensations leads to chronic vigilance and increased sensitivity to otherwise normal physical sensations. Evidence in support of this theory includes the effects of direct manipulations of catastrophic cognitions in the laboratory. If such cognitions are hypothetically stimulated (as, e.g., by reading pairs of words consisting of various combinations of bodily sensations and catastrophes, such as palpitations-die or breathless-suffocate), the probability of panic increases (D. M. Clark et al., 1988). If such cognitions are reduced, the probability of panic in response to panic-provocation agents decreases (Clark, 1996). Further indirect evidence stems from the success of cognitive therapy in alleviating PD (e.g., D. M. Clark et al., 1994).

Problems for cognitive theory include the fact that panic attacks can occur in panic patients in the absence of detectable catastrophic cognitions. For example, patients may experience noctur-

nal panic attacks (usually during the transition from Stage 2 to Stage 3 sleep rather than during rapid eye movement sleep, when most dreaming occurs). Alternatively, they may sometimes have diurnal attacks without antecedent cognitions when the cognitions should have been readily detectable (e.g., Rachman, Lopatka, & Levitt, 1988; Zucker et al., 1989), even in studies using prospective self-monitoring of panic attacks (e.g., Kenardy, Fried, Kraemer, & Taylor, 1992; Kenardy & Taylor, 1999). The phenomenon of "nonfearful" panic, in which patients develop the disorder without having cognitions of danger or threat, also seems problematic for this theory (Barlow, Brown, & Craske, 1994; Kushner & Beitman, 1990). Proponents of the cognitive model might respond by suggesting that catastrophic misinterpretations in these cases may be very quick and below the threshold of awareness, even occurring during the transition between Stage 2 and Stage 3 sleep. However, without an independent measure of catastrophic misinterpretations (other than the panic attacks themselves), this sort of response begins to make the theory appear untestable (McNally, 1994, 1999).

It has also been claimed that cognitive models are somewhat vague in specifying or operationalizing terms such as "catastrophic misinterpretations" (Seligman, 1988; Teasdale, 1988). These terms, noted D. M. Clark (1996), "are expressed in everyday language rather than in the more precise technical terms that characterize many models in cognitive psychology (see Teasdale, 1988). . . . the advantage of such a model is the ease with which it suggests specific clinical procedures. The disadvantage is that it can be more difficult to test because it is not always clear how to operationalize key terms in a way that allows them to be precisely measured and manipulated" (p. 319). We suggest that the vagueness is not in the content of the cognitions, but rather how they are acquired, who acquires them, how they can be measured independently of panic itself, and under what conditions they become "catastrophic."

Two other problems with this approach are worth noting. First, as we discuss later, although catastrophic cognitions often may occur in panic patients, it is not necessarily clear that they play a causal role in creating panic attacks. Second, the cognitive model sees little need to distinguish between the emotional states of panic and anxiety, despite growing evidence to the contrary, described below.

### *Anxiety Sensitivity Theory*

Anxiety sensitivity (AS) theory posits the existence of a traitlike belief in some individuals, especially including patients with panic disorder. The essence of this belief is that anxiety and its associated symptoms, particularly somatic symptoms, may cause deleterious physical, psychological, or social consequences that extend beyond any immediate physical discomfort during an episode of anxiety or panic itself. Proponents of AS theory, such as Reiss (1991) and McNally (1994), differentiate this theory from other perspectives in several ways. First, they clearly see AS as an enduring traitlike tendency. Second, AS theorists argue that individuals with PD are often fully aware of the causes of their sensations (i.e., they do not misinterpret them) and yet are frightened by them because they still hold an inherent belief that the sensations are harmful to their body or mental state. (Cognitive

theorists might claim that it is the sensations and/or the immediate consequences of the sensations, e.g., fainting, heart attack, that are "misinterpreted.") Moreover, the two theories clearly emphasize different time perspectives regarding the consequences of the sensations, with cognitive theory emphasizing the idea of immediate impending disaster and AS theory emphasizing that harm or danger from the symptoms may accumulate over time.

The AS model has generated a widely used measure, the Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986) and much thoughtful research. Generally, AS has been found to be normally distributed in the population, suggesting that it is a dimensional construct, and it is seen as a vulnerability factor that increases the likelihood of developing an anxiety disorder, especially PD (Reiss, 1991). Yet questions remain about the cause of this trait as well as its precise role in the subsequent etiology of PD (as well as other anxiety disorders).

Three studies lend support to anxiety sensitivity as a vulnerability factor for panic attacks. In the first study, Schmidt, Lerew, and Jackson (1997) found that higher initial scores on the ASI (but not trait anxiety scores) in military recruits predicted more anxiety and depressive symptoms and a greater number of unexpected panic attacks after a very stressful course of basic military training. Although the investigators noted that the relationships were relatively weak in this sample of well-adjusted military recruits, accounting for a rather small percentage of the variance, this study helps to confirm AS as reflecting at least one possible vulnerability for later anxiety, panic attacks, and depressive symptoms, triggered by extreme stress. However, this study did not provide evidence of a unique relationship between AS and panic attacks (or PD), in that high AS scores also predicted later anxiety and depressive symptoms more generally. In a similar second study, Schmidt et al. (1999) replicated these findings and found that anxiety sensitivity was more specifically related to anxiety/panic symptoms compared with depressive symptoms, although the findings accounted for only 2% of the variance in predicting unexpected panic attacks. Finally, Hayward, Killen, Kraemer, and Taylor (2000), in a 4-year prospective study of high school adolescents, found that AS was a significant predictor of onset of panic attacks as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised (*DSM-III-R*; American Psychiatric Association, 1994) but not of major depression when changes in panic were measured while controlling for changes in depression. Although AS predicted changes in panic attacks but not major depression in this study, it was not the best predictor of panic attacks; instead, negative affectivity was the single biggest predictor of panic attacks (and major depression). (See also Ehlers, 1995.) Thus, questions remain both about the specificity of what AS predicts and about whether it is a better predictor of unexpected panic than negative affectivity (the Hayward et al. study suggests that it is not).

### *Conditioning Theories*

Conditioning theory has a long and distinguished tradition in helping to understand the etiology of anxiety disorders (e.g., Eysenck, 1979; Marks, 1969; Wolpe & Rowan, 1988), and it was one of the first types of theory applied to the cause of PD (e.g., Eysenck, 1960; Eysenck & Rachman, 1965). Generally, conditioning theories suggest that when stimuli, events, or situations (con-

ditioned stimuli [CSs]) are paired with a panic attack (and all of its associated physiological sensations), the learning that may occur can allow the CSs to trigger panic and anxiety when they are encountered again. This sort of theory has taken a number of different forms when applied to PD. Early conditioning theories focused on the role of conditioning in the onset of agoraphobia or situational panic attacks (i.e., conditioning to external or exteroceptive cues). However, perhaps the best known version of conditioning theory applied to PD originated in an important article by Goldstein and Chambless (1978) that described a process they termed "fear of fear." Citing Razran (1961), Goldstein and Chambless reintroduced the notion of *interoceptive conditioning*, in which low-level somatic sensations of anxiety or arousal effectively became CSs associated with higher levels of anxiety or arousal. Thus, they posited that early somatic components of the anxiety response can come to elicit significant bursts of anxiety or panic. (These were also expected to generalize to other stimuli.) Thus, the focus of conditioning theory changed from exteroceptive conditioning in explaining agoraphobia and situational panics to interoceptive conditioning in explaining the cause of more "spontaneous" or apparently uncued panic attacks.

Criticisms of conditioning theories are presented in more detail under Clarifying the Role of Classic Conditioning in PD. To summarize briefly, interoceptive conditioning has been criticized as being conceptually confusing because anxiety or panic seem to serve somewhat indiscriminately as CS, unconditioned stimulus (US), conditioned response (CR), and unconditioned response (UR; McNally, 1990, 1994; Reiss, 1987). According to Reiss (1987), for example, anxiety seems to become conditioned to itself, but what does that mean? In addition, conditioning theory seems to lead to an overprediction of panic, because a fear or panic response should theoretically occur every time the CS (e.g., a somatic sensation, such as a quickened heart rate) is encountered (e.g., D. M. Clark, 1988). A third criticism stemmed from the observation that the fear or panic response does not seem subject to extinction after numerous natural trials in which arousal and the somatic cues it generates are not followed by panic (Rachman, 1991; Seligman, 1988; Van den Hout, 1988). However, a major point of the present article is that all of these concerns fall away when one considers a more modern perspective on classical conditioning and its many effects on emotion and behavior.

### *Summary and Overview*

PD is a common anxiety disorder in which unexpected panic attacks lead to excessive anxiety about future attacks. The approaches sketched previously also contain a number of unmentioned common elements, such as vague allusions to biological vulnerabilities as well as fundamental cognitive or psychological vulnerabilities predating the development of the panic attacks, or PD, but these elements are seldom elaborated. Moreover, each approach tends to highlight one aspect or another of the process, such as interoceptive fear conditioning, catastrophic misinterpretations of physical sensations, or beliefs about the dangers of anxiety, as though they are mutually exclusive.

The present article provides an integrative theory of the etiology of PD that uses contemporary learning theory as its base. On the basis of information that is available in the psychometric, ethological, and neurobiological literatures, we distinguish between

two aversive motivational states: anxiety and panic. Further, on the basis of the conditioning literature, we expect that a major effect of early experience with panic is the conditioning of anxiety to cues that are associated with the episode. One result is that, in the presence of the interoceptive or exteroceptive cues associated with panic, anxiety now occurs. As is widely recognized, the classical conditioning of anxiety also makes it possible for new operant behaviors to be reinforced when they escape or reduce it (e.g., Mowrer, 1947).

Conditioning of anxiety can also have other major consequences that are emphasized here. As we show later, the presence of conditioned anxiety may serve to exacerbate or potentiate the next panic attack, beginning the vicious spiral into PD. A second factor that can exacerbate the next panic attack is that panic itself may come to be elicited by a more specific set of cues associated with panic. The conditioning of panic responses to some cues may occur in parallel with the conditioning of anxiety to other cues; conditioning is a multifaceted process in which a range of interacting stimuli can acquire the ability to control a constellation or system of different emotions, cognitions, and behaviors. These themes, coupled with a modern understanding of conditioning processes that will further modulate and influence the course of conditioning, constitute the core of our approach to the development of PD. Other biological and psychological processes that are thought to influence PD (including catastrophic thoughts, AS, and other processes that appear to make certain individuals vulnerable) may be seen as operating through their interaction with this core conditioning process.

## Introduction to a Modern Learning Theory Perspective on PD

### *Panic and Anxiety*

Any theory of PD must acknowledge the strong and growing network of evidence suggesting fundamental differences between the emotional phenomena of panic and anxiety. Panic attacks have been defined as a subjective sense of extreme fear or impending doom accompanied by a massive autonomic surge and strong flight-or-fight behavioral action tendencies (Barlow, Brown, & Craske, 1994; American Psychiatric Association, 1994). Anxiety has been defined as an apprehensive anticipation of future danger, often accompanied by somatic symptoms of tension or feelings of dysphoria. The focus of anticipated danger can be internal or external. Phenomenological as well as neurobiological evidence suggests that panic attacks are descriptively and functionally distinct events when compared with anxiety. Some of this evidence comes from detailed analyses of fear and anxiety in normal populations, in which the findings support these constructs as being partially overlapping and yet partially distinctive at a psychometric level. In early studies, fear emerged as a partially distinct primary (lower order) factor, but it also loaded on the higher order factor of negative affect (L. A. Clark & Watson, 1991; Tellegen, 1985; D. Watson & Clark, 1984). These lower and higher order factors not only seem separable but also relate in rather different ways to other anxiety disorders and depression. For example, more recent structural equation modeling and factor analyses of symptomatology exploring the dimensions of panic, anxiety, and depression in clinically anxious patients have also uncovered two different fac-

tors. One, which is characterized by a subjective sense of extreme fear or impending doom, strong autonomic arousal, and strong flight-or-fight behavioral action tendencies, seems best described as panic. The other is characterized by the kinds of apprehension and worry accompanied by tension that are best described as anxiety (T. A. Brown, Chorpita, & Barlow, 1998; Joiner et al., 1999; Mineka, Watson, & Clark, 1998; Zinbarg et al., 1994). Anxiety, a principal component of generalized anxiety disorder, is very closely related to depression. Spikes of strong autonomic arousal characteristic of panic, in contrast, are substantially restricted in patients experiencing more generalized anxiety (T. A. Brown et al., 1998; Borkovec, 1994; Hoehn-Saric, McLeod, & Zimmerli, 1989; Zinbarg et al., 1994). Also, these different emotional experiences may produce differential regional brain activity as measured by electroencephalography (Heller, Nitschke, Etienne, & Miller, 1997).

Ethological evidence concerning specific defensive reactions such as the flight-or-fight response points to their survival value and heritability as well as their distinctiveness (and partial separateness at the level of heritability; Kendler, Walters, et al., 1995) compared with more diffuse states analogous to generalized anxiety or depressed mood. Fanselow and Lester (1988), among others, noted the qualitative differences in animal defensive behavior that occur depending on the "imminence" or proximity of threat (see also D. C. Blanchard, 1997; R. J. Blanchard & D. C. Blanchard, 1987). In rodents, freezing may occur after a potential threat has been detected, whereas more active behaviors occur when a predator actually attacks. Ethologists have pointed to hierarchical arrangements between action tendencies of freezing and heightened vigilance, which may represent anxiety (see later discussion), and other more proximal action tendencies that may be associated with fear and panic (e.g., Gallup & Maser, 1977; Gray & McNaughton, 1996). That is, freezing (anxiety) may antedate and potentiate other behaviors that occur as a threatening predator approaches more closely.

There is also increasing evidence from neurobiology supporting the existence of at least two negative emotional states mediated by different brain circuits and potentially representing anxiety and panic (Charney, Grillon, & Bremner, 1998; Gray & McNaughton, 1996; Heller et al., 1997; Lang, Davis, & Öhman, 2000; White & Depue, 1999). A great deal of evidence suggests the role of the amygdala and related areas of the brain in fear and defensive behavior (e.g., Davis, 1992; Fanselow, 1994; Kapp, Whalen, Supple, & Pascoe, 1992; LeDoux, 1996; Rosen & Schulkin, 1998). Fanselow (1994) proposed two related but separable brain circuits that are implicated in different defensive emotional reactions. The first circuit, involving the central amygdala and the ventral periaqueductal gray, mediates freezing and opiate-mediated analgesia. (Other output from the amygdala mediates autonomic responses [see Kapp et al., 1992] and potentiated startle responses [see Davis, 1992]). These behaviors and autonomic responses correspond to anxiety in our approach. The second circuit identified by Fanselow, involving the dorsolateral periaqueductal gray and superior colliculus, mediates more active defensive behaviors, such as flight-or-fight and non-opiate-mediated analgesia. These behaviors are associated with what Fanselow called "circa-strike" defense, which has evolved to deal with actual predatory attack and corresponds to panic in our approach.

Other investigators, including Davis (e.g., Davis, Walker, & Yee, 1997; see also Rosen & Schulkin, 1998) and Gray and McNaughton (1996; McNaughton & Gray, in press) have also recently distinguished between two aversive motivational systems and circuits. Although there are differences in these various approaches, it is now common to distinguish between at least two negative emotional neural systems and the corresponding behavioral systems they control. Thus, many neuroscientists would now agree with psychopathologists that there are important distinctions to be made between emotional states that may correspond to anxiety and panic.

### *True Alarms, False Alarms, and Learned Alarms*

Barlow (1988; Barlow et al., 1996) proposed a conditioning theory of clinical anxiety disorders that accepts the distinction between panic and anxiety. This theory, which has come to be known as "alarm theory" (Carter & Barlow, 1995; Forsyth & Eifert, 1996), begins with the observation that the experience of unexpected panic attacks seems to be relatively common in the population at large (e.g., Norton, Cox, & Malan, 1992; Norton, Dorward, & Cox, 1986; Telch, Brouillard, Telch, Agras, & Taylor, 1989; Wittchen & Essau, 1991). Evidence suggests that these attacks seldom progress to PD and, therefore, are referred to as "nonclinical" attacks. Individuals experiencing nonclinical panic attacks show little or no concern over the possibility of experiencing additional attacks. Rather, they seem to dismiss the attacks, for the most part, as associated with some trivial and potentially controllable event. Other evidence suggests that panic attacks may be a nonspecific response to stress, similar to hypertension or headaches, that runs in families (Barlow et al., 1996).

Individuals with PD are clearly discriminable from nonclinical panickers in that they develop anxiety focused on the next potential panic attack. These individuals anticipate the next attack apprehensively, perceive the attacks as uncontrollable and unpredictable, and are extremely vigilant for somatic symptoms that might signal the beginning of the next attack. In this formulation, the crucial step in the development of PD is the conditioning of anxiety focused on the next panic attack, occurring most often in those with a preexisting vulnerability to make this association (see later discussion).

The model assumes that a panic attack (the flight-or-fight response) is the fundamental emotion of unconditioned fear occurring at the wrong time. When the danger is real, the responses are "true alarms." Thus, alarms are "false" if they occur when there is nothing to fear (no danger). Because there is nothing to fear, a false alarm often occurs to the great surprise of the individual experiencing one. It has been widely recognized that it is adaptive to learn to associate emotional responses very quickly with both discrete and contextual cues. When these alarms, true or false, are associated with, or conditioned to, external or internal cues, they become "learned alarms."

When the clinical disorder is a specific phobia, it seems clear that fear or anxiety is conditioned to an otherwise harmless object or situation. In contrast, in PD the cues eliciting fear or anxiety are often more diffuse (being away from a safe place or a safe person) or difficult to pinpoint. Thus, following Goldstein and Chambless (1978), Barlow proposed that false alarms could be conditioned to internal physiological stimuli reflecting the process of interocep-

tive conditioning (Razran, 1961). The occurrence of false alarms and subsequent learned alarms need not be pathological if the alarms are infrequent and anxiety focused on the possible occurrence of future alarms does not develop. It is the development of anxiety that fundamentally produces vigilance for somatic sensations, increased tension and arousal, a resulting increase in somatic cues, and a spiraling of anxiety and panic. Anxiety focused on a possible future panic attack is now part of the defining *DSM-IV* criteria for PD (American Psychiatric Association, 1994).

As noted earlier, the role of conditioning in PD has produced much controversy and confusion, which was not explicitly addressed by alarm theory. Therefore, we now consider some recent developments in our knowledge of conditioning and emotional learning for a fuller explication of this aspect of development of PD and other clinical anxiety disorders.

### Clarifying the Role of Classical Conditioning in PD

Although panic attacks do not inevitably lead to conditioning, we assume that a crucial element in the origin of PD is a conditioning episode (or episodes) involving early panic attacks (usually false alarms as opposed to true alarms reflecting confrontation with a traumatic event), often enabled or potentiated by biological factors and/or the presence of stress (e.g., Barlow, 1988; Barlow et al., 1996). As we review later, a large percentage of patients with PD do point to an initial panic attack at the beginning of the disorder (e.g., Craske, Miller, Rotunda, & Barlow, 1990; Öst & Hugdahl, 1983). Either the panic attack itself (e.g., Forsyth & Eifert, 1996, 1998) or the event that actually triggers it (if indeed there is an identifiable one) then becomes associated with initially neutral cues through the associative learning process known as classical conditioning. Those cues could include proximal or distal cues, such as specific social situations (e.g., eating in restaurants, going to church) or entering general shopping malls or sports arenas, and also interoceptive and exteroceptive stimuli that are more directly involved in panic, such as the bodily sensations arising from the increase in respiration that occurs with hyperventilation. Most likely, both types of cues are involved.

The consequences of this conditioning are spelled out in detail in the next sections. As a preliminary to this discussion, we note that classical conditioning has many characteristics and consequences that are not widely understood outside a relatively small community of specialists. Many psychologists now know that modern views of conditioning are "cognitive" in the sense that they use theoretical constructs like attention, surprise, information value, short-term memory, rehearsal, and so forth to explain even simple conditioning (e.g., Mackintosh, 1975; Pearce & Hall, 1980; Rescorla & Wagner, 1972; Wagner, 1976, 1981). We accept and embrace this view. However, we do not accept the idea that a modern view of conditioning implies that conditioning trials inevitably give rise to a kind of propositional, declarative knowledge that is the same as that created by verbal input (e.g., Lovibond, 1993). Conditioning theories themselves are agnostic on the issue. We suspect that, although conditioning and propositional systems may sometimes interact (e.g., Grings, Schell, & Carey, 1973), the extent to which they do will depend on the type of conditioning system, the specific conditioning procedure, and the brain systems they engage (Bechara et al., 1995; R. E. Clark & Squire, 1998; LeDoux, 1996).

LeDoux (1996) and Öhman, Flykt, and Lundqvist (2000) argued that aversive emotional learning can occur without any conscious representation of the learning. This means that implicit emotional memories can activate the fear system without the person necessarily having any conscious recollection or awareness of why they are aroused. A number of findings are consistent with this possibility, such as the fact that classically conditioned emotional responses are not always influenced by verbal instruction (e.g., Bridger & Mandel, 1964; Hamm & Vaitl, 1996) and that emotional conditioning does not appear to depend on conscious awareness (see LeDoux, 1996; Öhman et al., 2000; Öhman & Mineka, 2001). Data reported by Bechara et al. (1995) provide an especially compelling dissociation between emotional conditioning and verbal, declarative knowledge. When given a classical conditioning experience, a patient with a damaged amygdala did not acquire classical autonomic conditioning but was able to report what CSs predicted the US. Conversely, a patient with a damaged hippocampus acquired the autonomic responding but was unable to report what CSs predicted the US. Such findings encourage the view that conscious, declarative, or propositional knowledge about conditioning contingencies is not necessary or sufficient for emotional conditioning.

This is not to claim that cognitions are irrelevant in PD, however. We have already noted that PD may often involve catastrophic thoughts in which the patient believes that the somatic symptoms will lead to a heart attack, death, and so forth. Whether such cognitions have a truly causal role in creating panic attacks is not currently clear. However, the idea that they may sometimes play a causal role (albeit through a mechanism different from the one posited by cognitive theory) would not necessarily be inconsistent with a learning theory perspective on PD. Such thoughts may first arise during a panic attack either because they are an inherent component of a panic attack or because they are instrumental acts (i.e., operants) that have been reinforced in similar situations in the past. (We later review evidence that PD may be correlated with a childhood in which sick role behaviors were modeled and reinforced in the presence of panic symptoms by parents in the home; Ehlers, 1993). Once the thought occurs during a panic attack, it may become a verbal CS associated with the rest of the panic attack. Through a process of verbal conditioning, thought CSs could become capable of eliciting panic themselves; when the thoughts now occur, they might help cause panic, just as other CSs do. It is often productive to think of cognitions as responses or stimuli within the terms of learning theory (e.g., Baldwin & Baldwin, 1998). Thus, there may be nothing particularly unique about their role in PD.

As noted earlier, a variety of critiques of conditioning theories have been made in the past. We believe that many stem from the fact that modern issues and findings in conditioning and learning have not been communicated adequately to clinical scientists. One critique is that the conditioning approach lacks conceptual clarity when applied to PD (e.g., McNally, 1990, 1994, 1999; Reiss, 1987). For example, McNally argued that confusion exists about what constitutes the CS, US, CR, and UR, and that defining two arbitrary points on a continuum of arousal "blurs" the distinction between the CS and CR. He also argued that the distinction between the US and the UR is problematic. "Because certain bodily sensations are designated as CSs, by definition, they must have been established as such through association with a US.

What, then, is this US and what UR does it elicit?" (1994, p. 107). He concluded, "The interoceptive conditioning hypothesis... constitutes little more than a misleading metaphor for the mechanisms underlying panic" (1994, p. 108). In the next sections, we show that modern conditioning research has done much to blur the old distinctions between these different terms. Thus, we argue that this critique of conditioning theory is neither compelling nor valid.

A second criticism of conditioning theories is that they seem to "overpredict" panic (e.g., D. M. Clark, 1988). For example, while referring to early simplistic statements (e.g., Wolpe & Rowan, 1988), Clark argued that a conditioning theory should predict that every time a person experienced certain bodily sensations (CSs) that had been associated with panic, he or she should have a panic attack, and yet this is clearly not the case. We show that this argument loses force when one recognizes that the effects of CSs are routinely modulated by other stimuli in the background. A third criticism is that interoceptively conditioned responses should extinguish when the internal CS (such as a pounding heart) is not followed by panic, as might be the case when the patient runs up a flight of stairs (e.g., van den Hout, 1988). As we discuss in detail later, however, modern research on extinction, and particularly on what may be the inherent context specificity of extinction (Bouton, 1991a, 1993), obviates this criticism. Emotional responses extinguished in the context of athletic exertion would not be eliminated in other contexts.

In summary, learning theory sheds important light on the development of panic disorder, and earlier critiques of early conditioning theories of PD may be met by an analysis of the current research literature. We believe that the complex state of affairs surrounding the origins of PD is consistent with modern conceptualizations of classical conditioning. Several points seem especially salient as we consider the role of conditioning in the behavioral events surrounding the development of PD.

#### *Conditioning Allows the CS to Trigger Constellations of Behavior and Emotion That Are Not Necessarily the Same as the UR*

In textbook descriptions of Pavlov's original experiment, there is a focus on a single response, such as salivation. In fact, Pavlov's results were undoubtedly more interesting and complex than this. If one could stand back and look at what Pavlov's dogs were actually doing, one would find the bell eliciting not only drooling but other digestive reflexes (including gastric acid, pancreatic enzymes, and insulin secretion) as well as behavioral responses that are designed to help the animal to get ready for food (Powley, 1977; Woods & Strubbe, 1994). A similar complexity is true of defensive conditioning in animals. Thus, the CR has many components, including freezing and other natural defensive behaviors, changes in respiration, blood pressure, and heart rate, and the release of endogenous opiates that reduce pain (Bolles & Fanselow, 1980; Davis, 1992; Hollis, 1982). The general role of this constellation of behaviors is to prepare the organism to deal with an upcoming dangerous event (e.g., Hollis, 1982, 1997). So it may be with the conditioning involved with PD; conditioned anxiety is a complex set of responses, including ones corresponding to vigilance, that essentially help the person prepare for another panic attack.

Viewed this way, there is no reason to expect that the CR and the UR will necessarily be identical. One example of the difference between CR and UR is a common result seen in defensive conditioning in rats. Freezing is a common measure of conditioned anxiety (often referred to as conditioned "fear" in this literature, although here we maintain Barlow's distinction between anxiety and fear [panic]). Notably, freezing does not appear to be a component of the rat's unconditioned reaction to footshock. If the animal is shocked and then moved immediately to a different location, freezing is not observed; rather, freezing occurs only if the animal is returned to the place where the shock was encountered (Blanchard & Blanchard, 1969; Fanselow, 1980). It is a CR that may involve heightened vigilance (e.g., "risk assessment," D. C. Blanchard, R. J. Blanchard, & Rodgers, 1991), but it undoubtedly also functions to decrease attack or detection from predators (Hirsch & Bolles, 1980). The unconditioned reaction to shock is a very different burst of activity (Fanselow, 1994). Thus, even in basic aversive learning situations, there is often no identity relation between the UR and the CR.

Another classic example of different CRs and URs is some well-known work on drug conditioning that began in the 1970s (e.g., for reviews see Cunningham, 1998; Siegel, 1989). In this literature, there is a difference between the response one observes to the drug US and the response one observes to the CS that signals it. Specifically, the CR often appears to be "opposite" to the UR; it compensates for the upcoming drug effect, another example of a get-ready response. One widely studied example is conditioning with morphine injection as a US. Although the unconditioned effect of morphine itself is to reduce pain, the CR to cues associated with it may be hyperalgesia, an increase in sensitivity to pain (e.g., Siegel, 1975). This and other related drug-conditioning phenomena (e.g., Siegel, 1989) have helped elucidate the complex relationship between the CR and the UR, a complete review of which is outside the scope of this article (for further discussion, see Eikelboom & Stewart, 1982; Hollis, 1982; Ramsay & Woods, 1997).

#### *The CR Is Often Determined by the Nature of the CS*

In the 1970s, conditioning researchers also discovered that different CSs associated with the same US (and thus the same UR) can come to evoke very different CRs (e.g., Holland, 1977; Timberlake & Grant, 1975). For example, when presentation of a rat is used as a CS to signal food, the subject rat responds not merely with drooling but with social contact behaviors directed at the CS (Timberlake & Grant, 1975). Conditioning is now thought to engage whole *behavior systems*, or sets of behaviors that are functionally organized to deal with different USs (e.g., Domjan, 1994; Fanselow, 1994; Timberlake, 1994; Timberlake & Silva, 1995). Once a behavior system is engaged, different CSs provide "support" (Tolman, 1932) for particular behaviors in the same sense that a hallway makes it possible to walk and a swimming pool makes it possible to swim. A particularly interesting and potentially relevant example is the sexual conditioning system in Japanese quail (e.g., Domjan, 1994, 1997). In this research, a CS is presented to a male quail before a female US is presented and copulation ensues. The type of CR evoked by the CS depends on the CS's duration and qualitative nature. For example, when a 30-s presentation of a foam block with feathers signals the female, the

male begins to approach the CS; in contrast, when the foam block CS is presented for 20 min, the male instead paces back and forth when it is presented (Akins, Domjan, & Gutierrez, 1994). However, a CS can also come to elicit copulation as the CR (i.e., same as the UR), but only if it is a taxidermically prepared model that contains plumage and other features of the female quail (e.g., Domjan, Huber-McDonald, & Holloway, 1992).

Such research suggests that different CSs can support quite different CRs and that only certain cues may actually support a CR that resembles the UR. As mentioned earlier, studies of defensive conditioning in rats with footshock USs have tended to uncover CRs that mostly consist of freezing (e.g., Fanselow, 1989; Fanselow & Lester, 1988); here the freezing CR is very different from the activity-burst UR. Nevertheless, because the form of the CR in other systems depends on both the qualitative nature of the CS as well as its timing (see also Silva, Timberlake, & Koehler, 1996; Timberlake, Wahl, & King, 1982), we should remain open to the possibility that different types of CRs will develop with different types of CSs predicting the US at different delays. In a classic study of defensive conditioning in rabbits, VanDercar and Schneiderman (1967) signaled a shock US delivered near the eye with tone CSs of various durations. In this method, the shock US elicits a closure of the rabbit's nictitating membrane (which protects the eye) and also an increase in heart rate. Short CSs (e.g., less than 1 s) that ended with the US elicited the nictitating membrane response (i.e., a CR that resembled the UR) and caused a modest decrease in heart rate. In contrast, longer CSs (e.g., 6.75 s) supported no nictitating membrane response at all but elicited a strong decrease in heart rate. Thus, in some examples of aversive conditioning, qualitatively different CRs can emerge with cues associated with the US at different time intervals. One implication for PD is that the nature of the CR elicited by a CS (i.e., anxiety or panic) may depend on the CS's temporal proximity to the US.

The form of the CR in human fear conditioning also depends on the qualitative nature of the CS. For example, if interoceptive cues are "prepared" or "fear relevant" in the same way that evolutionarily based cues for phobias are (cf. Öhman & Mineka, 2001), then there is some evidence in humans that the CR may resemble the UR more so than is the case with unprepared or fear-irrelevant CSs. Cook, Hodes, and Lang (1986) showed that the CR using prepared CSs (slides of snakes) was heart rate acceleration rather than deceleration, as is more typically seen in human autonomic conditioning with fear-irrelevant or unprepared CSs (i.e., the CR is isodirectional to the UR in response to a US of shock). Dimberg (1987) also showed that with fear-relevant angry faces paired with shock, the CR was an accelerated heart rate response and an increase in activity in the corrugator muscle, which controls the eyebrow when frowning; neither of these responses occurred in individuals who received conditioning with fear-irrelevant or happy faces. Finally, Forsyth and Eifert (1998; see also Forsyth, Eifert, & Thompson, 1996) reported related results. One of their fear-relevant stimuli to which heart rate acceleration (rather than deceleration) was conditioned was a video clip of a heart beating arrhythmically, an exteroceptive representation of an interoceptive stimulus.

Given the variability in the form of the CR, it is easy to imagine that CSs associated with a panic attack will evoke responses that may often differ substantially from panic itself. However, it is also

conceivable, given what we know about many conditioning systems, that certain CSs and/or certain CS-US intervals may condition a CR that resembles the UR, a conditioned panic attack. Anxiety and panic reactions are functionally different; a functional perspective on conditioning actually causes us to anticipate that different conditions could support conditioning of different responses. Panic is an immediate response to an insult to the organism; although it may involve cognitions about impending doom, it must have temporal and other properties that help the organism deal with a terrifying event that is already in progress. Anxiety, in contrast, is functionally organized to help the organism prepare for a possible upcoming insult. It is more "forward looking" in this sense (Barlow, 1988, 1991). Given their different functional roles, it is not surprising that panic and anxiety are different. Our perspective thus accepts a qualitative distinction between the two, whereas other approaches to PD either do not make one or certainly do not focus on its importance (cf. Beck & Emery, 1985; D. M. Clark, 1996; McNally, 1994).

### *Interoceptive Conditioning*

An important component of the conditioning approach to PD is the idea that interoceptive conditioning is involved (Barlow, 1988; Goldstein & Chambless, 1978). The occurrence of a panic attack is itself a conditioning trial that allows the patient to associate internal bodily sensations that accompany the early onset of the attack with the rest of the attack; the result is that modest changes in heart rate and respiration become signals and can later elicit a full-blown attack. One relevant example is a classic Soviet dog experiment described by Razran (1961, p. 86). Distension of the intestine, an interoceptive CS, was paired with presentation of a mixture of 10% carbon dioxide administered directly to the trachea (the US). When these two events were paired, the intestinal distension (CS) quickly acquired the ability to elicit hypercapnic respiratory changes (CR) that were the same as the UR. The phenomenon might parallel what happens when and if internal sensations (such as intestinal contractions) are paired with hyperventilation, which often occurs during a panic attack; one might expect in the future that the intestinal contractions alone might become sufficient to trigger respiration changes and possibly panic. Interestingly, Razran (1961), in summarizing the Soviet literature, claimed that interoceptive conditioning is especially resistant to extinction, lending further plausibility to its likely role in the etiology of PD.

Little interoceptive conditioning research seems to have followed the methods used in the Soviet heyday described in Razran's (1961) classic monograph (see Dworkin, 1993). However, once again, the literature on classical conditioning with drug stimuli is relevant. Here, interoceptive events clearly do become associated. For example, Siegel (1988) showed that an injection of pentobarbital that signaled an injection of morphine caused a classical CR to pentobarbital: The rats were more tolerant to morphine when pentobarbital was present than when it was not. Evidently, they had learned to associate the morphine US with the pentobarbital CS, two interoceptive events. The reader might recognize this experiment as an example of "state-dependent learning," the well-known phenomenon in which learning is best when it is tested in the presence of the drug state (or mood state, see Eich, 1995) in which it originally occurred. To the extent that such states are interoceptive, state-dependent learning is an effect indi-

cating that interoceptive events can be associated with their consequences.

The idea that internal cues can be associated with interoceptive aversive events is also consistent with some research in humans. Human participants were exposed to three pairings of mental images with a US of 5.5% carbon dioxide (CO<sub>2</sub>)-enriched air (Stegen, De Bruyne, Rasschaert, Van de Woestijne, & Van den Bergh, 1999). The images were either fear relevant or fear irrelevant (being stuck in an elevator or sauna vs. reading a book or overlooking the sea). Participants exposed to the fear-relevant images (but not those exposed to the fear-irrelevant images) showed significant conditioning of both subjective symptoms of anxiety as well as altered respiratory behavior and cardiac/warmth symptoms similar to those produced by the US. That fear-relevant imagery can elicit such interoceptive and subjective CRs after only three conditioning trials has implications for our argument regarding the role of interoceptive conditioning in PD. The authors noted that "a little stress-induced hyperventilation in association with a phobia-relevant place or an image thereof may evoke the experience of similar symptoms and anxiety on next confrontations, even without apparent hyperventilation" (p. 150). Moreover, as noted earlier, the nature of the CR in animal conditioning can depend on the qualitative nature of the CS and the interstimulus interval (ISI). Thus, it is possible that a true panic CR might become conditioned with the right CS and the right ISI. Definitive tests of this idea must await future research.

A particularly interesting type of interoceptive conditioning is the case in which a low dose of a drug signals a higher dose of the same drug. Greeley, Lê, Poulos, and Cappell (1984) injected a small dose of ethanol in rats before administering a larger dose. Tolerance to the larger dose subsequently depended on the small dose preceding it, but only if the two injections had been paired. Pairings also enabled the small injection to initiate a stronger compensatory response. Thus, a small dose of ethanol acquired the ability to signal more of itself. Comparable results have been reported for morphine-morphine pairings (Cepeda-Benito & Short, 1997). Thus, animals can associate a strong interoceptive event with a weaker version of the same event. More recently, Kim, Siegel, and Patenall (1999) found evidence of a similar kind of learning occurring within single administrations of morphine. They found that rats given long exposures to morphine show a conditioned compensatory response to a short "probe" injection that deliberately mimicked the early-onset properties of the longer injection. Apparently, interoceptive cues corresponding to the onset of a long interoceptive stimulus can indeed become associated with the remainder of the stimulus. It is not difficult to imagine that early-onset properties of a panic attack can, therefore, come to signal the rest of the event as it continues to unfold in time.

Conditioning in which the onset of an event signals the rest of the event clearly blurs the traditional distinction between CS and US. Nonetheless, we believe this form of conditioning is probably very common. In an extended discussion of the relationship between learning and regulatory physiology, Dworkin (1993) reached a similar conclusion. Dworkin gave the type of conditioning in which early onset is associated with an event's later aspects a name, the *homoreflex*, and contrasted it with the better known arrangement in which CS and US are different, the *heteroreflex*. One example of a homoreflex is a baroreceptor that detects a small increase in blood pressure coming to predict a further increase in

blood pressure. Learning this sort of relationship presumably allows other parts of the system to respond and adapt to the blood pressure change more quickly. Because the "CS" and "US" are so similar, there are grounds for expecting this kind of learning to be robust: Similarity between signals and the things they signal can allow especially strong conditioning (e.g., Rescorla & Furrow, 1977; Rescorla & Gillan, 1980; Testa, 1975). Dworkin (1993) noted that if this is correct, then "homoreflexes should turn out to be even more common than heteroreflexes" (Dworkin, 1993, p. 79).

Interestingly, there is a sense in which the earliest conditioning experiments in Pavlov's own laboratory probably also involved the dog associating early and late aspects of a single event. Pavlov's students first noted that, after introducing sand into the dog's mouth, which caused salivation, the mere sight of sand itself soon came to cause anticipatory salivation (Domjan, 1998). The dog was associating the sight of sand with its later properties. This type of learning is undoubtedly common as organisms learn about events and objects in their world. Therefore, to understand this learning process better, Pavlov devised a method in which the signal and the signaled event were separated so that they could be manipulated independently. That is, the bell-food experiment we now know so well can be seen as a technique used to break down and analyze learning about dynamic individual events that naturally flow and change over time.

We suggest that this type of conditioning is fundamental to understanding PD. That is, the patient with PD has learned to associate weak and early panic symptoms with the remainder of the full-blown panic episode. Mere exposure to a US may inevitably allow cues that correspond to its early onset to become associated with its later aspects, allowing conditioning of anxiety and possibly panic itself. A panic attack can be seen as an opportunity to associate early "warning signs" with the full-blown emotional reaction. Furthermore, because early-onset cues are presumably similar to the US's later effects, they may be especially easy to condition (see prior discussion); theoretically, they might, therefore, overshadow learning about other perfectly valid predictors of the US, such as other predictive external cues. This scenario suggests that interoceptive conditioning may be a major contributor to the development of PD.

Of course, not all of the body's reactions during early panic onset are necessarily interoceptive. Shortness of breath, for example, may have exteroceptive as well as interoceptive aspects. It is easy to find evidence of related US-US conditioning with USs that have exteroceptive effects. Goddard (e.g., 1996, 1997; Goddard & Jenkins, 1988) reported a number of experiments in which food USs signaled the occurrence of additional USs (see Goddard, 1999, for a review and implications). When food USs are delivered close together in time, the first pellet comes to signal others to follow. Similar learning occurs with aversive stimuli. For example, a weak shock can become more aversive through pairings with a stronger shock (Crowell, 1974). In addition, exposure to long shocks can increase the aversiveness of shorter shocks, apparently because shock onset becomes associated with the later aspects of the long event (Anderson, Crowell, DePaul, & McEachin, 1997). Interestingly, US-US conditioning can be extinguished by presenting the predictive stimulus (e.g., shock-onset cues or the first pellet) on many trials alone (e.g., Anderson et al., 1997; Goddard, 1997). Clearly, with both interoceptive or exteroceptive stimuli,

nominal USs can signal other USs; one panic attack, or early aspects of a panic attack, can signal other panic attacks. It is not difficult to imagine this sort of learning contributing to the development and maintenance of PD.

*CSs Do Not Just Trigger Responses; They Also "Modulate" Other Responses Controlled by Other Events*

A case can thus be made for a role for interoceptive conditioning in PD as well as for the idea that the behaviors elicited by a CS will be multiple, complex, and not necessarily the same as the panic reaction itself. However, CSs have additional important means of influencing emotions and behavior; they also modulate other types of behavior. Historically, theorists (e.g., Mowrer, 1947, 1960) emphasized that aversive CSs that elicit anxiety can also modulate or influence the strength of ongoing operant or instrumental behaviors. According to two-process theory (e.g., Rescorla & Solomon, 1967), anxiety CSs should exaggerate avoidance behavior and weaken appetitively motivated behavior that occurs in their presence (see also Overmier & Lawry, 1979; Trapold & Overmier, 1972; see also Colwill, 1994). By this mechanism, conditioned anxiety might increase or potentiate instrumental acts that have been learned through negative reinforcement (e.g., escape or avoidance responses) to potentially keep the organism out of trouble. The tendency to carry "talismans" such as pill bottles, even if they are empty, and other safety signals or "safety behaviors" (Salkovskis, Clark, & Gelder, 1996) are presumably examples of avoidance or escape behaviors that have been reinforced by anxiety reduction or safety. The idea that anxiety CSs can modulate these behaviors means that heightened anxiety may exaggerate them, even if they appear "irrational" (i.e., an empty pill bottle has no objective effect on anxiety). As with all avoidance responses, they may serve to prevent extinction of the CR (which would include preventing disconfirmation of catastrophic thoughts).

Interestingly, modulation effects of CSs on instrumental behaviors can sometimes be specific. That is, CSs sometimes seem to arouse expectancies of the specific US with which they are associated and, therefore, mainly modulate instrumental behaviors that are connected with the same US (e.g., Colwill & Motzkin, 1994; Colwill & Rescorla, 1988; Delamater, 1996; Kruse, Overmier, Konz, & Rokke, 1983). In principle, then, a CS may arouse anxiety about a particular US (e.g., fainting and falling to the floor), and thereby selectively increase seemingly bizarre or idiosyncratic behaviors that have been reinforced for avoiding that particular US (e.g., clutching door handles, walls). Other behaviors connected with other USs (e.g., taking a spouse or trusted companion along for fear of panicking while driving) might not be affected.

Another important modulating effect of CSs is to exaggerate or potentiate the strength of URs or CRs that are elicited in their presence by other stimuli. This point has been emphasized by Wagner, Brandon, and their associates (e.g., Wagner & Brandon, 1989). Following Konorski (1967), they emphasized the fact that CSs enter into associations with both emotive and sensory aspects of the USs with which they are paired. The emotive CR (generated by the emotive association) functions to augment other responses, such as an eyeblink CR elicited by a second CS (Bombace, Brandon, & Wagner, 1991; Brandon, Betts, & Wagner, 1994; Brandon & Wagner, 1991) or an eyeblink or startle reflex evoked by other stimuli (Brandon, Bombace, Falls, & Wagner, 1991;

McNish, Betts, Brandon, & Wagner, 1997). The latter effect is consistent with the well-known fact that anxiety CSs also potentiate startle responses elicited by sudden bursts of noise (e.g., J. S. Brown, Kalish, & Farber, 1951; see Davis, 1992, for a review). In the presence of a CS controlling anxiety, we may become more reactive to sudden stimuli that evoke startle responses.

These modulating effects of emotions and emotional CSs have been emphasized in discussions of human emotion (e.g., Lang, 1994, 1995; Lang, Bradley, & Cuthbert, 1990) and anxiety disorders (Cook, Hawk, Davis, & Stevenson, 1991; Grillon, Ameli, Goddard, Woods, & Davis, 1994; Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Morgan, Grillon, Southwick, Davis, & Charney, 1995). They may also be especially important to an understanding of PD. Through conditioning, anxiety cues may augment and exacerbate minor panic reactions that are triggered by other stimuli. This may be a key difference between patients who suffer from PD and other individuals who may occasionally experience nonclinical panic episodes without anxiety. Conditioned anxiety may lower the threshold of (or exaggerate) subsequent panic reactions. The modulating effects of anxiety CSs could thus cause, at a level below conscious awareness, the kind of exaggerated panic that cognitive theorists would assume requires catastrophic misinterpretations (e.g., D. M. Clark, 1986, 1988). A "floater," or floating object observed in the visual field, may mean nothing to a normal individual. However, to a person sensitized by anxiety, it could elicit another panic attack. In other words, classical conditioning may conceivably allow CSs to potentiate panic either through the modulating effect described here or through a more direct, traditional, eliciting effect described earlier in the section on interoceptive conditioning. Thus, by virtue of the modulating function, we can accept and retain the distinction between panic and anxiety but still find the state of anxiety exacerbating panic attacks.

*The Effects of CSs Are Also Further Modulated by Other Stimuli*

We have just emphasized how CRs and URs can be modulated by the presence of another stimulus; the CR to one CS can be potentiated by the emotional effect controlled by another. The general idea that the CR evoked by a CS is quite commonly modulated by the effects of other stimuli has received a great deal of attention in the conditioning literature (e.g., Swartzentruber, 1995). It introduces another layer to a conditioning theory of PD. Because responding is always viewed as the product of a CS as well as other modulating cues in the background, the CR cannot be assumed to be evoked automatically by a CS. This explains why a conditioning theory of PD does not "overpredict" panic in the presence of interoceptive (or exteroceptive) cues associated with panic attack. The conditioning experience creates a potential for a CS to evoke a CR, but the actual strength of the response always further depends on other stimuli in the situation.

Learning theory now recognizes several types of CR modulation. One is the potentiation-style effect described previously, in which the emotional properties of a CS can energize CRs, URs, or instrumental actions that are controlled by other stimuli. An even simpler modulation effect is summation: The strength of the CR observed in any situation is determined by the summed value of all the CSs that are currently present. The idea is captured by the

Rescorla-Wagner model (Rescorla & Wagner, 1972), which gives excitatory CSs (those that predict USs) positive values and inhibitory CSs (those that, in general, predict no US) negative values. When put together, the strength of the response is determined by the summed value of all the CSs that are present. Thus, when two excitatory CSs are put together, the response is larger than when either is presented alone (e.g., Hendersen, 1975; Reberg, 1972; Van Houten, O'Leary, & Weiss, 1970; S. J. Weiss & Emurian, 1970). Importantly, when an excitatory CS and an inhibitory CS (e.g., a safety signal) are put together, there will be less responding than to the excitator alone (e.g., Rescorla & Holland, 1977).<sup>1</sup>

Another implication of the Rescorla-Wagner model's summation mechanism is worth mentioning. According to the model, learning is an adjustment that occurs when there is a discrepancy between the outcome predicted on a conditioning trial (e.g., US or no US) and the actual outcome that occurs. The outcome predicted is determined by the sum of all stimuli present on the trial, as just discussed. This simple idea has several straightforward but remarkable implications. For example, when there is no US, and extinction would ordinarily occur, the presence of an inhibitor along with a to-be-extinguished excitator will subtract from and may cancel the excitator's prediction of a US, eliminating the discrepancy between prediction and actual outcome and thus leaving the excitator unextinguished. The inhibitor is said to "protect" the excitator from extinction (Chorazyna, 1962; Soltysik, Wolfe, Nicholas, Wilson, & Garcia-Sanchez, 1983). To the extent that agoraphobic "safety" behaviors such as carrying pill bottles also operate by canceling an excitatory CS's prediction of danger, combining the pill bottle with a trip to the shopping mall (an anxiety-evoking CS) may similarly protect the shopping mall CS from extinction (e.g., Soltysik, 1960). The converse of protection from extinction is also possible: During extinction, the addition of extra excitatory CSs that predict the US (instead of predicting no US, as an inhibitor does) would sum to yield an overprediction of the US, increasing the discrepancy between prediction and actual outcome and thus facilitating any associative loss to all the CSs resulting from extinction (Rescorla, 2000; Wagner, 1969). Therefore, extinguishing multiple excitatory CSs together should be more effective than extinguishing any one in isolation. The implication is that, to facilitate extinction of the shopping mall, it would be best to combine that CS with other CSs (e.g., elevators, a fast heart rate, shortness of breath) during exposure. Clinically, this is often used as an approach during cognitive-behavioral therapy for agoraphobia, although a different rationale is usually given (e.g., Barlow & Craske, 2000). A complete explication of the Rescorla-Wagner model is beyond the scope of this article. However, our discussion illustrates the extent to which all cues present at any time are important in determining anxiety and learning.

A related, and equally important, modulating effect is provided by *contextual stimuli* that are present but even further in the background when the CS is presented. In the conditioning laboratory, contextual cues are often operationally defined as the room or apparatus in which CSs and USs are presented; however, they can include a variety of other cues, including drug states, mood states, cues correlated with the passage of time, and the memory of recent events (e.g., Bouton & Nelson, 1998b; Bouton & Swartzentruber, 1991). Although such cues are indeed in the background, they can have potent effects on the CR that are relevant to any disorder in

which classical conditioning plays a role (e.g., see Bouton & Nelson, 1998b).

Bouton and colleagues showed that contextual stimuli are especially important in determining performance after extinction (e.g., Bouton, 1991a) or other situations in which learning in a second phase replaces or interferes with something learned first (Bouton, 1993). For example, anxiety evoked by a CS that has been through extinction is "renewed" if the context is changed after extinction (e.g., Bouton & King, 1983; Bouton & Ricker, 1994). This effect and others related to it have important implications for understanding relapse or return of fear (e.g., Bouton, 1988, 1991b; Bouton & Swartzentruber, 1991; see Mineka, Mystkowski, Hladek, & Rodriguez, 1999, for a preliminary example in humans). Somewhat surprisingly, in contrast to extinction, anxiety itself often generalizes almost perfectly between contexts: If anxiety is conditioned to a CS (by pairing it with shock) in one context and then the CS is tested in a second context, conditioned anxiety there is just as strong (e.g., Bouton & King, 1983; Hall & Honey, 1989; Lovibond, Preston, & Mackintosh, 1984). Thus, if a panic attack on a crowded bus conditioned anxiety to the feeling of dizziness, dizziness should elicit anxiety quite well in other contexts, such as the home, an airplane, or a ski lift. However, because extinction does not generalize as well between contexts, if anxiety were extinguished to dizziness in the context of the home, then dizziness would stop eliciting anxiety at home but could still evoke anxiety in other contexts (on the ski lift, the airplane, or the bus). The generalization of anxiety and the lack of generalization of extinction would contribute to the persistence of the disorder.

Interestingly, the psychological mechanism through which contexts control performance is different from the other modulating mechanisms described earlier. Instead of working through its direct association with the US, a context often modulates performance to the CS by signaling or retrieving the CS's own current connection with the US. It is as though the context disambiguates the CS (i.e., gives it its current meaning) in a manner analogous to the way in which contexts determine the meanings of words (e.g., Bouton, 1988, 1994b). This view has a number of implications for the persistence and treatment of anxiety disorders (e.g., Bouton, 1991b; Bouton & Nelson, 1998b; Bouton & Swartzentruber, 1991). For present purposes, what we view as the inherent context specificity of extinction performance is another reason why a conditioning model does not overpredict the occurrence of panic attacks: Anxiety elicited by an interoceptive CS may extinguish in some contexts without eliminating its impact in others.

The disambiguating effect of context is theoretically linked to a final form of modulation known as *occasion setting* (e.g., Holland, 1992; Schmajuk & Holland, 1998; Swartzentruber, 1995). Occasion setters are discrete stimuli (such as tones or lights) that can turn on or turn off responding to other CSs through some mechanism besides their direct association with the US and thus without necessarily evoking behavior on their own. Although their mechanism of action is currently a matter of debate, they are clearly

<sup>1</sup> It is worth noting that summation might not occur in all Pavlovian methods or response systems (e.g., Bouton, 1984; Bouton & King, 1986; Rescorla & Coldwell, 1995). One factor (among others) that appears to facilitate summation is similarity between the separate CSs and the compound (Pearce, Aydin, & Redhead, 1997).

connected with the theoretical issues concerning contextual control (e.g., Bouton & Swartzentruber, 1986; see also Bouton & Nelson, 1998a). Because neither contexts nor occasion setters operate through their direct associations with the US, simple extinction of an occasion setter (or a context) that “turns on” responding to a CS may not influence its ability to modulate responding to the CS (Bouton & Swartzentruber, 1986; Holland, 1989; Rescorla, 1985). Thus, we may find that the reaction of a patient with PD to his or her own racing heart (a CS) is especially problematic during visits to a shopping mall (a possible context or occasion setter). Exposure to the shopping mall alone may not weaken its ability to modulate the response to the heart racing. What is needed is extinction of the CS and the context together (e.g., Rescorla, 1986). This final example should make clear why so-called modulatory mechanisms are relevant to our understanding of PD. This may also be why many cognitive-behavioral therapists find it useful to encourage their patients to bring on frightening bodily sensations (such as by hyperventilating) while engaging in exteroceptive exposure to their agoraphobic situations (Barlow & Craske, 2000).

### *Some Pertinent Clinical Evidence*

*Evidence that anxiety potentiates panic.* From the perspective we are taking here, anxiety often potentiates panic rather than panic attacks truly coming out of the blue, as was originally thought to occur in most cases (Klein, 1981; Sheehan, 1983). As Basoglu, Marks, and Sengün (1992) argued, the problem with most prior studies suggesting that panic attacks come out of the blue is that they were based on retrospective recall. They noted that patients may not recall episodes of anxiety that preceded their panic episodes. Thus, Basoglu et al. (1992) conducted a prospective study of panic and anxiety in 39 patients who had PD with agoraphobia. Each patient recorded in a diary using an event-sampling technique the duration and intensity of episodes of panic and anxiety over three 24-hr periods, including their anxiety levels before panic episodes. Episodes of anxiety and panic were also classified as “situational/expected/predictable” versus “spontaneous/unexpected/unpredictable” based on whether the episode was expected and/or clearly linked to a situation that usually triggered such episodes (p. 58). Several results are of primary interest for our purposes. First, of 117 panic episodes recorded, 80% were situational/expected/predictable, and only 20% were spontaneous/unexpected/unpredictable. Moreover, of the 32 patients who reported at least one panic, 69% reported that their panics surged from an already heightened plateau of anxiety. Only 13% of the 32 who panicked had not reported a preceding period of anxiety. Another 18% reported anxiety preceding some panics but not others. In other words, more than 66% reported that anxiety had always preceded their panics on these recorded days, and 87% reported that this happened some or all of the time. Moreover, longer and more intense prepanic baseline anxiety was correlated with more intense panic (including number of episode symptoms). These results are consistent with our view that anxiety may often precede and potentiate the intensity of a panic attack.

Two other somewhat different prospective studies using computer-assisted self-monitoring techniques both reported related findings. Kenardy et al. (1992) followed 20 female panic patients for a 1-week period in a study of the psychological precursors of

panic attacks (not differentiating between predicted and unpredicted attacks). Patients answered a variety of questions every hour and whenever they believed they were having a panic attack. Anxiety in the hours preceding panic attacks (based on the question “How anxious do you feel?”) was higher than in control hours (preceding no panic), although not significantly so. However, the participants’ estimates of “the likelihood of panic this hour” (a more cognitive but conceptually related concept to anxiety) were significantly elevated in the hour preceding panic attacks relative to control hours. The authors deemed these elevated estimates of the likelihood of panic to support Barlow’s (1988) position that “an underlying apprehension is a precursor to panic” and that such expectancies “can be thought of as developing from a conditioned fear of panic attacks” (Kenardy et al., 1992, p. 672).

Another related study (Kenardy & Taylor, 1999) had a somewhat different goal of determining the accuracy of predictions with predicted panic attacks (i.e., the sensitivity and specificity of the predictions) and whether psychological precursors (such as anxiety and perception of physical symptoms) were associated with panic attack prediction versus panic attack occurrence. In this study, 10 female panic patients monitored their panic attacks for 7 days, making predictions every hour about whether they would have a panic attack in that hour as well as their sense of threat or danger, their level of anxiety, number of physical symptoms of panic, and so on at the time of the ratings. Unpredicted panic attacks were only preceded by reports of elevated physical symptoms. Predictions that a panic attack would occur (whether or not it occurred) were associated with both physical symptoms and an elevated sense of threat or danger and anxiety. Thus, elevated physical symptoms and anxiety (only the former for unpredicted attacks) commonly preceded panic attacks, although they also occurred frequently at other times when no panic attacks occurred. (The only related finding reported in the Kenardy et al., 1992, study was that some panic symptoms—about one on average—frequently occurred in hours not associated with panic attacks.) Together, these results are consistent with our learning theory perspective that posits anxiety or physical symptoms as CSs—or potentiating factors—for panic.

Other evidence that anxiety precipitates panic comes from laboratory research on panic provocation, in which it has long been recognized that the single best predictor of panic in response to a variety of panic provocation agents is the baseline level of anxiety (e.g., Barlow, 1988; Margraf, Ehlers, & Roth, 1986). For example, Liebowitz et al. (1984) reported that patients who experienced panic attacks during lactate infusions in the laboratory experienced heightened anxiety before the infusion compared with the patients who did not panic. In another study (Liebowitz et al., 1985), heart rate averaged 83.98 beats per minute (bpm) during baseline for patients who went on to panic as opposed to 75.30 bpm during baseline for patients who did not go on to panic. Heart rate in control participants was 62.79 bpm. In fact, baseline differences in levels of anxiety between patients and controls before panic provocation have been reported in almost all studies dating back to the 1940s (e.g., Cohen & White, 1947, 1950). Breggin (1964) suggested current baseline anxiety as one of four principal factors accounting for the production of panic attacks in panic provocation experiments, thus anticipating our contemporary learning theory account by more than 35 years.

Interestingly, although anxiety seems to play a role, the specific somatic responses capable of provoking panic may differ markedly from patient to patient. This has never been better illustrated than in the data reported long ago by Lindemann and Finesinger (1938), in which individual patients responded with panic to infusions of either adrenaline or acetylcholine but not both. These substances produce very different, and almost opposing, sets of somatic sensations and have very different underlying neurobiological mechanisms of action. That individuals are specifically sensitive to dissimilar provocation procedures, a finding that characterizes the panic provocation literature (e.g., Barlow, 1988; van den Hout, 1988), suggests that individuals have learned a specific association between panic and certain discrete somatic sensations possibly associated with an earlier major alarm reaction.

*Evidence that PD starts with a panic attack conditioning episode.* Most patients report that PD usually starts with an initial panic attack followed by one or more attacks within a matter of weeks or months. It is generally over the course of these initial attacks that anxious apprehension about the possible occurrence of further attacks begins to develop. During this early stage, agoraphobic avoidance of situations that provide a possible setting for the attack may also begin to develop. For example, as noted earlier, Öst and Hugdahl (1983) gave detailed questionnaires to 80 people with PD and found that approximately 91% could recall the initial episode of panic (or vicarious experience of panic) after which the disorder began to develop; only 10% could not recall a conditioning event. Of these 91% with a conditioning mode of onset (as Öst & Hugdahl referred to it), more than 50% said that, after the first panic attack, the initial development of agoraphobia was rapid (i.e., fully developed agoraphobia within 2 weeks), and only 14% described a slow onset. Other investigators reported similar findings (Craske et al., 1990; Merckelbach, de Ruiter, Van den Hout, & Hoekstra, 1989; Thyer & Himle, 1985; Uhde et al., 1985).

Although Öst and Hugdahl (1983) acknowledged that the US (i.e., the specific trigger) for the first panic attack could be identified in only a minority of cases, they shared our opinion, as well as that of Forsyth and Eifert (1996), that identifying a specific US is not essential in determining that conditioning plays a crucial role here. They noted that the attack itself was generally terrifying, with thoughts of losing control, fainting, or dying as core symptoms, and that this is sufficient to allow conditioning to occur. It is perhaps worth noting here that critics of this view, such as Menzies and Clarke (1995), have claimed that a US must be identified to ascribe a role to conditioning, but this argument is based on an unnecessarily restrictive view of conditioning. As argued elsewhere (e.g., Barlow, 1988; Carter & Barlow, 1995; see also Forsyth & Eifert, 1996), all that is needed for conditioning to occur is that either a true alarm or a false alarm reaction (activation of the flight-or-fight response) occurs in the presence of some potential interoceptive or exteroceptive CS.

The percentage of panic patients who claim to recall an initial panic attack conditioning episode might actually be considered impressive in light of evidence suggesting that emotional conditioning can occur without declarative memory of the conditioning experience. We have already described evidence suggesting that patients without an intact hippocampus can show emotional conditioning even though they cannot report the conditioning contingency (Bechara et al., 1995). Research by Öhman and colleagues has shown that the exteroceptive conditioning sometimes involved

in the origins of phobic fears may occur outside of conscious awareness if fear-relevant stimuli are involved (e.g., Öhman, 1996, 1997; Öhman, et al., 2000). In addition, it is worth noting that interoceptive conditioning has historically been thought to occur unconsciously and in the absence of an overt specifiable US because the US is internal (e.g., Razran, 1961). Together, these considerations suggest that accurate self-report data depending on conscious awareness may provide an inherently conservative estimate of the extent to which conditioning processes may be involved in the etiology of anxiety disorders. We should also note, however, that although the extant self-report data are consistent with a conditioning account of PD, there is a clear need for more objective data on the involvement of early conditioning trials.

### *Factors That May Affect the Potency of Panic Attacks and Hence the Strength of Conditioning*

Several factors may further affect the potency of panic attacks and thus the likelihood that they will lead to PD through classical conditioning. These factors, which we now review, include whether the attacks are perceived as controllable and predictable, whether they occur in the presence or absence of safety cues, and whether separate experience with panic attacks has increased their emotional impact through some sensitization process.

Full-blown panic attacks are themselves experienced by people with PD as unpredictable and uncontrollable aversive (even terrifying) events. They are perceived as uncontrollable in the sense that there is nothing that can be done to abort an ongoing attack. However, they are also sometimes perceived as unpredictable in the sense that they seem to come from out of the blue, even if they may actually be triggered by unconscious interoceptive cues. First, consider the controllability dimension. The animal conditioning literature indicates that uncontrollable shock conditions anxiety to neutral CSs more powerfully than does the same amount of controllable shock (e.g., Mineka, Cook, & Miller, 1984; Mowrer & Viek, 1948). Indeed, Mineka et al. (1984) found that levels of anxiety conditioned with inescapable shock were twice as high as levels of anxiety conditioned with the exact same amount of escapable shock. In fact, there is evidence that initial panic attacks occurring in difficult-to-escape situations (e.g., driving on a highway, flying, being in a formal meeting) condition more anxiety than panics that occur in more escapable locations, such as being home alone or with a significant other (Barlow, 1988; Craske et al., 1990). Moreover, prior experiences with uncontrollable aversive events can later potentiate the conditioning of defensive reactions. Given this, and that initial panic attacks often occur during periods of uncontrollable stressors, we would expect them to be especially powerful sources of conditioning (e.g., see Maier, 1990).<sup>2</sup>

Sanderson, Rapee, and Barlow (1989) demonstrated that a sense of control may be important in influencing the occurrence of a panic attack itself. Using a 5% CO<sub>2</sub> panic provocation procedure, Sanderson et al. divided patients with PD into two groups. Both

<sup>2</sup> As discussed extensively elsewhere (e.g., Mineka et al., 1984; Mineka & Hendersen, 1985), the mechanisms through which controllability operates may functionally be mediated by the added predictability over offset of a US that controllability affords (namely, when the US will end). However, for our purposes, the precise mechanisms through which controllability exerts its effects are not important and are not detailed here.

groups were told to inhale the CO<sub>2</sub>; they were also told that if the sensations created by it were sufficiently bothersome, if and when a red light came on, they could turn a dial to reduce the rate of infusion of the CO<sub>2</sub> if they felt they had to. The two groups differed only in whether the red light actually came on during the CO<sub>2</sub> inhalation, affording one group the perception of control. Although no one in the perceived control group attempted to turn the dial, the dial was actually inoperative (it did not affect levels of CO<sub>2</sub>). Thus, the two groups experienced equal amounts of CO<sub>2</sub>. Nevertheless, there were substantial group differences in physiological reactivity to the CO<sub>2</sub>; the perceived control group showed lower levels of physiological responding to the CO<sub>2</sub> than the no perceived control group. Moreover, 8 of 10 patients in the no perceived control group reported experiencing a panic attack compared with only 2 of 10 in the perceived control group.

Turning to unpredictability, there is evidence in the animal literature that unpredictable aversive events are perceived as more stressful than predictable aversive events (and that when given a choice, humans and animals generally prefer predictable to unpredictable aversive events; cf. Mineka & Hendersen, 1985). There is also evidence that unpredicted panics lead to more anxiety in a clinical population. On the basis of hypotheses developed from the animal conditioning literature, Craske, Glover, and Decola (1995) hypothesized that patients with PD would experience greater levels of anxiety on days that happened to follow an unpredicted panic than on days after a predicted panic. Although there were no differences between the group who only experienced predicted panic attacks and the group who only experienced unpredicted attacks, among the group who experienced a combination of the two this hypothesis was upheld. That is, patients with PD who experienced a mixture of the two kinds of attacks showed higher levels of anxiety and worry on days after an unpredicted attack than on days after a predicted attack. The authors also noted that these findings might be related to findings from the animal literature on experimental neurosis suggesting that having a history of predictability may exacerbate the effects of lack of predictability (Mineka & Kihlstrom, 1978; see also Mineka & Zinbarg, 1996). This is because the prediction was only upheld among those who had some history of predicted attacks intermixed with unpredicted attacks.

Another factor affecting the potency of a panic attack may be the anxiety-inhibiting presence of having a safe person present. Clinical observations have long suggested that patients with PD show a far greater range of activity and are less prone to panic when a safe person (often a spouse but sometimes a trusted companion of another sort) is with them than when they are alone. This phenomenon has been studied and documented in a laboratory study. Patients with PD showed fewer panic symptoms (distress symptoms, catastrophic cognitions, and physiological arousal) in response to CO<sub>2</sub> if a safe person was with them than in the absence of a safe person (Carter, Hollon, Carson, & Shelton, 1995).

The potency of panic attacks might also change as a function of previous experience with panic. Such experience might increase the intensity of later panics by engaging sensitization processes, including the neurobiological process recently described by Rosen and Schulkin (1998). Rosen and Schulkin argued that animal laboratory experiments on sensitization (in which exposure to

uncontrollable stressors increases the organism's reactions to later stressors) serve as a model for similar observations in humans, showing that either distal or proximal exposure to uncontrollable stressors sensitizes them to the effects of subsequent stress, possibly including panic itself. They emphasized nonassociative (unlearned) neurobiological processes that might occur in the amygdala as underlying these effects. We would note that associative processes might also be involved. For example, as noted earlier, through repeated exposure to the stressor, the organism might learn to associate onset of the event with the rest of the event (e.g., Anderson et al., 1997). Event onset (including panic attack onset) could thus acquire a stronger and stronger emotional impact. Thus, either nonassociative or associative mechanisms could allow early panic attacks or other stressors to make later attacks more intense. Thus, in turn, sensitization to panic attacks could increase the strength of conditioning that results when a panic attack is subsequently associated with new CSs.

Sensitization of panic attacks might also influence the strength of anxiety reactions that have been conditioned previously. For example, inflation effects, first discovered by Rescorla (1974) and later replicated (at least through clinical case studies) in humans by Davey, de Jong, and Tallis (1993), are said to occur when a mild fear that is first conditioned to some cue using a mild unconditioned stressor later grows in magnitude when the animal or person is exposed noncontingently to a more powerful unconditioned stressor (not paired with the CS). Thus, a rat first experiencing a tone paired with a mild shock shows a weak conditioned fear response, but if the rat is later exposed to a noncontingent strong shock on its own, the rat's level of fear of the tone is increased. By analogy, if a person experienced several mild panic attacks that were preceded by an upset or growling stomach, some conditioned excitatory strength might accrue to the stomach cues. However, this excitatory strength might later be inflated through the experience of other more severe panic attacks that were not accompanied by the same stomach cues. Bouton (1984) showed that such inflation effects are not context specific; that is, the inflation events need not occur in the same context in which the original conditioning took place, or where fear is tested, for inflation to occur. In addition, Hendersen (1985) also showed that inflation effects are often larger when the strong stressors are experienced a long time after the initial conditioning experience.

### Summary

PD begins in individuals with certain psychological and biological vulnerabilities (to be discussed next) when early panic attacks occur and condition anxiety, a functional, forward-looking constellation of responses that prepares the person for the next panic attack. Several psychological factors that influence the perceived intensity of panic (e.g., its perceived controllability or predictability) may influence the potency of the US and thus the degree of conditioning. Panic may be associated with the setting or environment in which it occurs, and with interoceptive and/or exteroceptive correlates of early stages of panic itself. Anxiety can have a number of consequences. We have emphasized the possibility that it can potentiate or exaggerate the effects of other triggering events (other CSs, USs, or perhaps endogenous events) that may stimulate the next panic. Importantly, these potentiating effects are further

modulated by other CSs and contextual cues that may be present in the background. It is plausible to suppose that conditioned anxiety is an essential process that allows early panics to spiral into PD. The idea is further consistent with clinical evidence suggesting that anxiety often precedes panic attacks and that anxiety seems to contribute to the evocation of panic in the laboratory. It is also consistent with evidence suggesting that PD often begins with panic experiences that can provide potent conditioning trials.

We have tended to emphasize the conditioning of anxiety CRs over panic CRs. This emphasis is consistent with the conditioning literature in animals such as rats, in which defensive CRs (e.g., freezing and endogenous analgesia) are not the same as the UR to footshock (activity bursting and pain). However, we believe it is likely that panic itself can also become a CR when certain fear-relevant interoceptive or exteroceptive cues are associated with panic attacks. From a functional perspective, panic reactions, unlike anxiety reactions, are designed to deal with an aversive US that is already in progress. Therefore, cues that are especially proximal in time to panic, such as the interoceptive correlates of panic onset, may be more likely than other kinds of cues to evoke this kind of CR. Support for this idea is largely indirect at this point, coming from a few animal and human conditioning experiments in which the CR is the same as the UR with certain CSs or certain interstimulus intervals (e.g., Cook et al., 1986; Dimberg, 1987; Domjan et al., 1992; Forsyth & Eifffert, 1996, 1998; Stegen et al., 1999; VanDercar & Schneiderman, 1967). Nonetheless, the idea that panic itself can be a CR is also an implication of what we know about conditioning in other behavior systems (e.g., Domjan, 1994, 1997). Further research is necessary before it can be determined what kinds of conditions allow panic itself to be a CR.

Importantly, conditioning processes and reactions like those we are describing here may often occur without conscious awareness, perhaps reflecting the operation of neurobiological emotional systems that are dissociable from declarative knowledge systems (see Bechara et al., 1995; R. E. Clark & Squire, 1998; see also LeDoux, 1996; Öhman, 1996, 1997; Öhman et al., 2000). As noted earlier, evidence suggests that emotional conditioning may be independent of declarative memory and conscious awareness. This aspect of emotional conditioning may obviate the well-known problem that cognitive perspectives have in explaining why panics can occur in the absence of catastrophic thoughts or ideas (e.g., Kenardy et al., 1992; Rachman et al., 1988). We believe that conditioning processes may go a considerable distance in explaining the major features of PD.

### Vulnerabilities for the Development of PD

As noted earlier, not everyone who experiences occasional stress-related false alarms goes on to develop PD. Indeed, a majority do not. What makes some people who experience panic more vulnerable to developing PD than others? We have already noted that certain psychological concomitants of early panic attacks, such as their perceived controllability and predictability, can influence their perceived intensity and hence their ability to initiate conditioning. Moreover, multiple genetic, temperamental, and experiential factors have some empirical support as contributing to vulnerability to PD, and we now review what we consider to be three of the most prominent sets of factors. Two of these vulnerability factors (one biological and one psychological) are rather

nonspecific and may cause vulnerability to many different anxiety, mood, and related disorders. One additional set of psychosocial (experiential) factors is more specific for PD. Each may have an impact by influencing the conditioning process, described previously, that we view as central to the development of PD.

### *Nonspecific Biological (Genetic) Factors*

There is clear evidence of the heritability of the trait variously referred to as "trait anxiety," "neuroticism," or "negative affect" (e.g., Eysenck, 1967; Gray & McNaughton, 1996; McGuffin & Reich, 1984; Plomin, DeFries, McClearn, & Rutter, 1997). It is unlikely that a single gene will be identified that relates to this heritability, but behavior genetic methods are at least beginning to identify the role of genetic contributions to anxiety and mood disorders. Nonetheless, although there is clear evidence for the heritability of each of these disorders, it should be emphasized that it is only modest in magnitude. For example, Kendler, Neale, Kessler, Heath, and Eaves, (1992), in a large female twin study, estimated that 35% to 39% of the variance in liability to agoraphobia and PD was due to genetic factors.

There is also evidence that the genetic vulnerability factors for PD and specific phobias (among other related disorders) may overlap (Kendler, Walters, et al., 1995). The possible genetic overlap between panic and phobias discussed by Kendler, Kessler, et al. (1995) is interesting in light of our learning theory perspective on the etiology of PD. Classical conditioning has long been implicated in the etiology of many specific phobias (e.g., Mineka, 1985a, 1985b; Mineka & Zinbarg, 1996; Öst & Hugdahl, 1981; J. B. Watson & Rayner, 1920), and we are making a parallel argument for PD here. In both specific phobias and PD, anxiety is conditioned to either exteroceptive cues or interoceptive cues, and conditioning of the flight-or-fight response may also occur. There is a long history of documenting the contribution of genetic and temperamental variables such as neuroticism or trait anxiety to classically conditioned aversive emotional responses (e.g., Brush, 1985; Levey & Martin, 1981; Pavlov, 1927), and this may be how the partially overlapping genetic diatheses between phobias and panic disorder may operate. Alternatively, another possible explanation for this partially shared genetic vulnerability may be for the frequency or intensity of experiencing panic attacks themselves, which sets the stage for conditioning of anxiety and/or panic.

Some evidence also suggests that genetic contributions to panic and generalized anxiety may differ, at least to some degree (Barlow, 1988; Kendler, Walters, et al., 1995). Elsewhere (Barlow, 1988) we have articulated how separate but perhaps overlapping biological vulnerabilities to anxiety and panic may increase the synergy between anxiety and panic (in which the presence of anxiety increases the probability of the occurrence of panic), long noted by ethologists (Maser & Gallup, 1974) and now emphasized here.

Thus, although having a genetically based vulnerability does not cause either panic or anxiety directly, it may well create the appropriate conditions for the occurrence of anxiety or panic or both in people undergoing stress. (Similarly, the tendency to react to stress with specific psychophysiological responses other than panic, e.g., headaches or irritable bowel syndrome, also seems to run in families and may have a somewhat heritable component; Barlow, 1991.) These overlapping genetic vulnerabilities could

conceivably influence the onset of PD in one or more of three different ways. First, as already noted, they might influence the potency of panic attacks, making some people more prone to experiencing especially terrifying panic episodes. Second, they might influence the salience of fear-relevant CSs. For example, patients with PD are known to differentially attend to bodily sensations that occur when aroused (e.g., Ehlers & Breuer, 1992, 1996; see Craske, 1999, for a review). This heightened awareness of, or attention to, somatic sensations of arousal could increase their salience and, in turn, increase the probability of developing conditioned anxiety to subsequent panic attacks (see Mackintosh, 1974, for a review of the effects of CS salience on conditioning). Finally, as already noted, genetic vulnerabilities might influence the conditionability of panic and anxiety just as genetic and temperamental variables are known to influence other forms of conditioning (see Mineka & Zinbarg, 1991, 1995, for reviews).

With regard to temperamental or personality variables influencing conditioning, it is interesting to speculate that observed sex differences in neuroticism and trait anxiety (cf. Feingold, 1994, for a meta-analysis) could at least partially mediate the corresponding sex differences in PD (approximately 2:1 female:male) and agoraphobia (4:1 for severe agoraphobia). For example, in a meta-analysis, the average effect size ( $d$ ) for sex differences in trait anxiety across 28 studies was  $-.30$  (Feingold, 1994). Trait anxiety (or neuroticism) is the major personality variable known to be a risk factor for both anxiety and mood disorders (L. A. Clark, Watson, & Mineka, 1994), including PD (Hayward et al., 2000). Furthermore, as discussed earlier, trait anxiety has been consistently shown to increase the conditionability of aversive emotional reactions (e.g., Levey & Martin, 1981; Spence & Spence, 1966; Zinbarg & Mohlman, 1998). If higher trait anxiety in females were to lead to greater vulnerability to emotional conditioning, then PD would be more likely to develop in females even if females and males have the same probability of having initial panic attacks, as a number of studies indicate (e.g., King, Gullone, Tonge, & Ollendick, 1993; Telch et al., 1989).

### *Nonspecific Psychological Factors*

The genetic and temperamental vulnerabilities just discussed do not operate in isolation, but must combine with psychological vulnerabilities emanating from early experiences to create a diathesis for the development of an anxiety disorder. Two of these early experiential factors seem to be nonspecific, serving as vulnerabilities for most anxiety and mood disorders; another seems to be more specific to PD.

*Prior experience with control and mastery.* There is reason to believe that people who have grown up with a sense of mastery or control over their environments (including their emotional lives) may be less likely to develop anxiety (and subsequently PD) when and if they have an unexpected panic attack than people who have grown up with a relatively impoverished sense of control and mastery over their environment. Developmental psychologists have long argued that an infant's experience with control over important aspects of his or her environment promotes exploration of novel events and less fearful reactions to strange or arousing stimuli. Infants and young children can gain such a sense of mastery if they have parents who respond to their needs, requests, and initiatives in a contingent way; this is in contrast to the

impoverished sense of mastery (or helplessness) that occurs in infants and young children with unresponsive parents who respond to their child in a relatively noncontingent manner. Chorpita, Brown, and Barlow (1998) investigated this general idea in a retrospective study. They operationalized the degree of experience with control or mastery that school-age children had received by using a measure of parenting style that assessed the degree to which the parent discourages autonomy and shows high protection of the child. Previous work had shown that this parenting style may influence the child's locus of control (i.e., high overprotectiveness is associated with external locus of control in the child; Schneewind, 1995). This parenting style is also associated with anxious and depressive symptoms in the child (e.g., Parker, 1983). In a cross-sectional study, Chorpita et al. found that parental overprotectiveness predicted external locus of control in the children (replicating Schneewind, 1995) and that the locus of control variable mediated the effects of parental overprotectiveness on clinical symptoms of anxiety and depression.

Unfortunately, these ideas regarding the role of mastery in reducing susceptibility to panic and anxiety are difficult to study experimentally in human infants and children because it is unethical to manipulate directly the controllability of a child's environment for significant periods of time. However, experimental evidence generally supports this idea in a study conducted in infant monkeys that were reared in controllable versus uncontrollable environments for the first year of life (Mineka, Gunnar, & Champoux, 1986). In the controllable environments, the master monkeys had levers to press and chains to pull to deliver themselves food, water, and treats. In the uncontrollable environments, the yoked monkeys received access to the same food, water, and treats, but these were delivered uncontrollably whenever a master monkey earned a reinforcer. When tested in several frightening and novel situations between 7 and 11 months of age, the master monkeys reared with control adapted more quickly in several different fear-provoking situations compared with the yoked monkeys reared without control. Thus, early experience with control and mastery over positive reinforcers appears to affect the level of fear that novel and frightening events evoke, paralleling what is thought to occur in early human development. By decreasing the intensity of reactions to frightening events or by increasing the rate of habituation to them, having a sense of control or mastery may thereby decrease the conditioning of panic or anxiety.

One thing that makes this example especially noteworthy is that the sense of mastery generalized across domains (in this case, from appetitive to aversive). Related findings have also been found in several other animal studies in the learned helplessness tradition. For example, Joffe, Rawson, and Mulick (1973) reported that rats raised in environments in which they had control over access to food, water, and visual stimulation later showed less emotionality and more exploratory behavior in a novel situation (known to evoke some anxiety) than did rats reared in yoked-uncontrollable environments. Hannum, Rosellini, and Seligman (1976) also showed that immunization effects (at least within an aversive domain) could be demonstrated over a substantial time frame. They found that immunization (or mastery) experiences with controllable shock given to young weanling rats had a protective effect when rats were later exposed as adults to inescapable shocks. Finally, J. Williams and Maier (1977) found immunization effects even when different kinds of aversive stimuli were used in the

immunization (mastery) and helplessness induction phases (e.g., experiencing escaping from cold water immunized rats against the effects of subsequent exposure to uncontrollable footshocks). In combination, these studies suggest that learning a sense of mastery or control in one or more areas of life (but not necessarily related to control over aversive stimuli or emotions) could generalize to situations in which aversive stimuli or emotions are involved, such as coping with a few unexpected panic attacks.

Thus far, we have emphasized the ways in which an enhanced sense of mastery and control may immunize against later anxiety and possibly depression relative to some normative level of controllability. Conversely, high levels of prior experience with uncontrollable stressors may also enhance vulnerability to anxiety and depression relative to some normative baseline of experience with stress. Relevant to this latter line of research, stressful life events have been found to play two somewhat distinctive roles in the etiology of PD. First, stressful life events such as early parental death, separation, or divorce have been found in many, but not all, studies to enhance vulnerability to development of some of these disorders, most notably PD and agoraphobia (e.g., Kendler et al., 1992; Tweed, Schoenback, George, & Blazer, 1989). Second, for PD (and major depression), higher than normal levels of stressful life events have been found to precede and possibly precipitate the onset of the disorder in vulnerable individuals (e.g., see reviews by Monroe & Simons, 1991, for depression; Craske, 1999, for anxiety disorders).

Neurobiological mechanisms might also be involved in these effects. One possible mechanism is the one proposed by Rosen and Schulkin (1998), who argued that both distal (e.g., early childhood) and proximate (e.g., past few months) stressful life events, both physical and psychological, may serve to sensitize fear circuits in the brain (primarily the amygdala), making them "hyperexcitable" or easier to trigger for a long time. Such hyperexcitability might also occur simply as a function of the experience of panic attacks themselves, which are often perceived as terrifying life-threatening events. In addition, building on the pioneering efforts of Ader and Denenberg, Nemeroff et al. (e.g., Heim & Nemeroff, 1999; Ladd et al., 2000) noted permanent effects on brain function of early stressful experiences (separation) in rat pups. Specifically, early stressful experiences exert a significant impact on the developing hypothalamic-pituitary-adrenal (HPA) axis, causing an increase in the organism's response to psychologically stressful events as adults (e.g., exposure to a novel environment, restraint) but not physical stress (e.g., hemorrhage). This very specific heightened responsiveness to psychological stress in adulthood seems to be a function of hyperreactive HPA axis responding to these stressors as indexed by markedly elevated corticosterone and adrenocorticotrophic hormone. Thus, early experience with uncontrollable stress may create a nonspecific diathesis for later life events perceived as unpredictable and/or uncontrollable.

*Prior experience with unpredictability.* Lack of control over one's environment often implies lack of predictability as well (i.e., if one cannot control an event, one often does not know when it will occur or terminate). As noted earlier, a good deal of research shows that the predictability versus unpredictability of uncontrollable events (possibly including panic attacks, cf. Craske et al., 1995) has a large impact on the amount of stress generated (e.g., Overmier, 1985; Seligman & Binik, 1977; J. Weiss, 1971; see

Mineka & Hendersen, 1985, for a review). Unfortunately, there is very little in the way of longitudinal research during early development on the effects of being raised in a highly unpredictable versus predictable environment. However, one important study in monkeys investigated this issue. Coplan et al. (1996) found that infant monkeys whose mothers experienced unpredictable foraging conditions (food sometimes scarce and sometimes abundant) showed higher levels of corticotropin-releasing factor (one of the major stress hormones) in cerebrospinal fluid as adults than did infants whose mothers had either a predictable overabundance of food or chronically (i.e., predictably) scarce food.

In summary, these findings regarding the effects of early experience with uncontrollable or unpredictable events, in conjunction with a larger web of related findings from developmental psychology, may have considerable relevance for understanding an individual's vulnerability to PD (Barlow, 1988; Barlow et al., 1996; Chorpita & Barlow, 1998; Mineka, 1985a; Mineka & Kelly, 1989; Mineka & Zinbarg, 1991, 1995, 1996). The mechanisms for these effects may be consistent with a traditional learned helplessness account (e.g., Maier & Seligman, 1976; Peterson, Maier, & Seligman, 1993). Specifically, learning that one does not have control over important life events at one point in time can produce associative and motivational deficits that result in failure to learn control at future points at which control is indeed possible. Alternatively or additionally, a nonassociative neurobiological sensitization mechanism may also operate (e.g., Heim & Nemeroff, 1999; Rosen & Schulkin, 1998). Once again, this vulnerability is viewed as nonspecific to PD and most likely undergirds the development of all or most anxiety and mood disorders as well as related disorders.

### *Specific Psychological Factors: Vicarious and Instrumental Learning*

We have discussed both nonspecific biological and nonspecific psychological vulnerabilities for anxiety and mood disorders. In addition, there also seem to be some specific early vulnerability factors that may predispose only some people who experience a panic attack to develop PD as opposed to other anxiety disorders or no disorder. One rather specific set of psychological factors not yet reviewed concerns early learning experiences regarding the potential dangers of unexplained bodily sensations and how to respond to them based on observations of one's parents' behavior (see Levy, 1998, for a review). In an early study of these influences in the realm of medical illness, Turkat (1982) studied 27 diabetics whose parents had not been chronically ill while they were growing up. Two thirds of these individuals reported that their parents had engaged in sick role behavior (such as not going to work, canceling activities, or receiving special attention) when temporarily ill. Of the individuals with diabetes whose parents had shown sick role behavior when ill, 66% reported illness-related avoidance as adults themselves. Another 33% reported that their parents had not engaged in sick role behavior when they were ill while they were growing up; only 22% of these people with diabetes reported illness-related avoidance themselves. Thus, diabetics whose parents showed sick role behavior appeared much more likely to demonstrate similar illness behavior themselves as well as work and responsibility avoidance, leading Turkat to conclude that "parental reactions to illness may be transmitted to

their offspring as well" (1982, p. 522). In addition, the individuals with diabetes whose parents had engaged in sick role behavior made more visits to their doctors and had more hospital admissions and more days ill than the other group, even though there was no evidence that they were more seriously ill based on physiological measures.

In another large-scale study, Whitehead, Winget, Fedoravicius, Wooley, and Blackwell (1982) found that adults were more likely to miss school or work as a result of illness and to seek medical help if their parents had reinforced them (e.g., with toys or special food) when they were ill as children. Moreover, in a later study of women, Whitehead, Bush, Heller, and Costa (1986) showed some correlational specificity to such relationships. For example, if the women had been encouraged to be cautious as children when they had colds, they were more likely to seek help for gynecological problems. However, if they had been reinforced for sick role behavior for menstrual symptoms while growing up, they were more likely to miss school or work and seek medical attention for menstrual symptoms as adults.

Turning to PD, Ehlers (1993) suggested that any learning experience encouraging sick role behavior and/or negative evaluations of somatic symptoms associated with panic attacks may create a potential specific vulnerability factor for PD. In a retrospective study, Ehlers (1993) assessed 121 panic patients (including 24 in remission for at least 6 months), 86 infrequent panickers, 38 patients with other anxiety disorders (mostly specific phobias), and 61 normal controls for learning experiences when they were children and adolescents with respect to somatic symptoms. All individuals were asked about parental encouragement of sick role behavior when they were experiencing panic symptoms (as well as their frequency of occurrence), observation of parental sick role behavior and of frequency of parental panic symptoms, parental encouragement of sick role behavior when sick with colds, number of chronically ill family members (where chronic illness was defined as six months in duration or longer), and frequency of uncontrolled behavior of household members (because of rage or being drunk). Ehlers reported that the frequency of uncontrolled behavior was assessed because of the clinical observation that patients with PD who report fear of loss of control often have parents who abuse substances.

No differences were found between patients with PD and infrequent panickers on most variables, and the patterns of correlations between the groups were identical. All three anxiety groups reported greater frequency of uncontrolled behavior in their parents compared with controls. In addition, patients with PD and infrequent panickers reported having observed parents experiencing panic symptoms more frequently than anxiety disorder or normal controls; all three anxious groups also reported more panic symptoms in themselves while growing up than controls. The four groups had comparable parental encouragement of sick role behavior during the experience of panic-like symptoms (e.g., special attention and instructions to take special care of themselves and to avoid strenuous activities or social engagements). However, because of the differences in frequency with which actual symptoms were experienced across the four groups, there was more parental reinforcement of panic symptoms in the participants in the three anxiety groups relative to controls and more parental engagement in sick role behavior when the parents had panic symptoms in the two panic groups relative to the other groups. In contrast, there

were no differences between anxiety disorder groups and controls in reported parental encouragement of sick role behavior in the event of colds. Moreover, among the two panic groups combined, there were some modest but significant correlations between a combined index of this encouragement of sick role behavior and responses on two widely used measures of fear of bodily sensations: the Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire (Chambless, Caputo, Bright, & Gallagher, 1984; Ehlers, Margraf, & Chambless, 1992). Overall, the results suggest that both clinical and nonclinical panickers had a history of sick role encouragement when experiencing panic symptoms (but not cold symptoms); controls reported significantly fewer symptoms in themselves and their parents, although when such symptoms occurred sick role behavior was also reinforced.

Ehlers (1993) also found that patients with PD and infrequent panickers reported a higher number of chronic illnesses in their households while growing up compared with those with other anxiety disorders or controls. She noted, "Observing physical suffering can also contribute to the evaluation that somatic symptoms are dangerous and that special care is needed" (p. 276). Whether this learning should be interpreted as an instance of vicarious classical conditioning (cf. Mineka & Cook, 1993), in which the child associates his or her own distress at watching the parent's distress with symptoms they are showing, or instrumental learning, in which the child observes the parent's reinforcement for doing certain things in response to certain symptoms, awaits further analysis (although these two possibilities are not mutually exclusive). In the former, illness cues might become associated with negative affect through evaluation of somatic symptoms as dangerous. In the latter, family members might have reinforced attributions about being sick and sick role behavior more directly.

Finally, there is some evidence that prior experience causes individuals to focus their anxiety on specific constellations of responses within a panic attack, such as respiratory symptoms (e.g., breathlessness), vestibular symptoms (e.g., dizziness), cardiovascular symptoms (e.g., increased heart rate), or symptoms of dissociation (e.g., depersonalization). Reports of a preexisting and presumably learned sensitivity to suffocation cues differentially predicts panic attacks to respiratory challenges such as breathing through a straw (e.g., Taylor & Rachman, 1994) or breathing into a paper bag (McNally & Eke, 1996). In addition, Craske (1999) reviewed some evidence that early experience with specific chronic illness in family members (e.g., chronic obstructive pulmonary disease) may lead to enhanced sensitivity to specific constellations of sensations such as respiratory symptoms. Also, Barrett, Rapee, Dadds, and Ryan (1996) observed parents of socially anxious children unwittingly reinforcing specific avoidant behavior associated with hypothetically threatening social situations, and this behavior increased after family discussions of ambiguously threatening social situations. Barrett et al. also found that parents of children with specific phobias reinforced their children for avoidance of hypothetically physically threatening situations. These results suggest that parents convey specific fear information to children including, perhaps, information about specific somatic sensations.

Of course, many of the studies we have discussed in this section have major methodological limitations in that they are retrospective in nature, and recall of early learning experiences may be colored by the participant's current emotional tendencies and

symptomatology. Moreover, given the genetic vulnerabilities contributing to PD, one must consider the possible role of genetic factors in some of the associations described here. Nevertheless, they do suggest that early learning factors (including vicarious ones) may contribute to a specific vulnerability for PD by sensitizing individuals to the potential danger of somatic sensations. Thus, when a stress-related panic attack occurs in someone with such specific vulnerabilities, certain somatic sensations may be especially salient for that person, leading to especially robust conditioning of anxiety and/or panic to those cues.

### Summary

Vulnerability factors for PD seem to include a variety of general and specific factors; that is, some vulnerability factors may predispose to other anxiety and related disorders, and some may be rather specific for PD. Genetic evidence on the specificity issue is somewhat inconsistent, but Kendler, Walters et al.'s large twin study (e.g., 1995) suggests that there may be some shared vulnerability between PD and specific phobias, which would be consistent with the theory proposed here. This is because the shared vulnerability could either be for experiencing especially intense or frequent panic-fear episodes, which set the stage for conditioning of specific phobias or for the onset of PD, or because of enhanced conditionability to exteroceptive or interoceptive cues. In addition, early experience with uncontrollable and unpredictable events is likely to serve as a psychosocial vulnerability factor for many anxiety disorders (Barlow, 1988; Barlow et al., 1996; Chorhita & Barlow, 1998; Mineka, 1985a, 1985b; Mineka & Zinbarg, 1995, 1996). Finally, vicarious learning of anxiety focused on certain bodily sensations and/or reinforcement of illness behavior while growing up may serve as a more specific vulnerability factor for PD but not other anxiety disorders (Ehlers, 1993).

### Relationships Between a Learning Theory Perspective and Other Accounts of PD

A contemporary learning theory perspective appears to be consistent with much that is known about PD. It is also broadly consistent with what we view as the positive aspects of the other approaches and theories reviewed at the beginning of this article. For example, the data supporting the role of AS in the development of PD fit with the notion of a specific psychological vulnerability based, perhaps, on vicarious learning encouraging sick role behavior or negative evaluation of somatic symptoms such as those occurring during panic attacks. In our approach, individuals who go on to develop PD would learn AS or, more specifically, that somatic symptoms are potentially dangerous. In support of this idea, a reanalysis of data from the Barlow laboratory (Zinbarg, Brown, Barlow, & Rapee, in press) suggests that the physical harm factor of the ASI (anxiety focused on somatic sensations), in contrast to other factors derived from this scale, accounts for almost all of the variance in predicting whether panic attacks will occur in patients with PD who are provoked with CO<sub>2</sub> inhalations. In addition, Hayward et al. (2000) also found that the physical harm factor of the ASI was the only significant predictor from the ASI of naturally occurring panic attacks, when controlling for depression, in their 4-year prospective study of adolescents. However, as noted earlier, high scores on the ASI do not invariably

predict the development of panic attacks (and in the Hayward et al., 2000, study, high negative affectivity was a substantially better predictor). Moreover, no study has yet shown them to predict onset of full-blown PD in an unselected population. Thus, in our view AS plays an important role in the development of PD but at the level of only one of our three hypothetical vulnerabilities.

We also believe that an approach based on contemporary learning theory is consistent with data that seem to support cognitive theories emphasizing a role for catastrophic misinterpretation (e.g., Beck & Emery, 1985; D. M. Clark, 1986, 1988, 1996). As we noted earlier, catastrophic misinterpretations may indeed accompany many panic attacks. This may be because such thoughts are a natural part of the constellation of responses involved in panic or because they might have been encouraged and reinforced in a manner analogous to the sick role behaviors and negative evaluations identified by Ehlers (1993) during earlier experience of panic-like symptoms during childhood and adolescence. If they actually play a causal role in generating or exacerbating panic, they may do so because they serve as CSs that have been associated with panic. Through classical conditioning, they may come to elicit anxiety and panic when they occur again. Although a causal role for catastrophic cognition is thus not outside the scope of a learning theory analysis, we are less convinced than other theorists that catastrophic thoughts are necessary to generate panic attacks. Whether they are sufficient remains to be determined. It is worth noting that the modal observation during panic attacks or extreme fear during confrontation with a phobic situation (as opposed to the period of anxiety preceding the confrontation) is an absence, or substantial diminishment, of cognitive activity such as catastrophic cognitions or other conscious appraisals of danger (Craske, 1999; Last, O'Brien, & Barlow, 1985; S. L. Williams, Kinney, Harap, & Liebmann, 1997).

D. M. Clark (e.g., 1996) and others (Beck & Emery, 1985; Salkovskis, 1988) have, of course, emphasized the role of catastrophic cognitions in causing panic attacks as well as several threads of evidence that seem to justify their importance. However, few of the threads truly force one to accept a causal role. For example, D. M. Clark (e.g., 1996) reviewed evidence from a variety of studies supporting the idea that panic patients are more likely to choose negative interpretations of ambiguous internal events than are normals and other anxiety-disordered controls. Although such results are consistent with cognitive theory, he acknowledged that they do not show that catastrophic cognitions play a causal role in creating panic but rather may be epiphenomenal. For example, these cognitions may be one manifestation of a preexisting psychological vulnerability that facilitates the conditioning of anxiety to CSs signaling subsequent panic attacks. D. M. Clark (1996) also cited a study by Ehlers, Margraf, Roth, Taylor, and Birbaumer (1988) in which panic patients were given false auditory feedback indicating a sudden increase in heart rate to determine whether activating patients' catastrophic cognitions would increase their anxiety more than that in normal controls. Panic patients did show greater increases in heart rate, blood pressure, skin conductance, and self-reported anxiety than normals. However, there is no need to invoke catastrophic misinterpretations to explain these findings, even though they may well occur. That is, one can easily construe the false heart rate feedback as an exteroceptive CS similar to a conditioned interoceptive CS (increased heart rate); conditioned anxiety may merely generalize

to it. Moreover, one would expect signs of an elevated heart rate to be an effective stimulus for anxiety in patients with PD, but not in normal controls who do not have the same conditioning history.

Cognitive theorists (e.g., D. M. Clark, 1996) have also cited a study from Clark's laboratory (D. M. Clark, Salkovskis, & Anastasiades, 1990) in which panic patients, recovered panic patients, and normal controls read pairs of words that involved combinations of bodily sensations and catastrophes (e.g., palpitations-dying, breathless-suffocate, numbness-stroke) and were asked to rate their anxiety and occurrence of any *DSM-III* panic symptoms. The results indicated that 83% of the panic patients (but none of the recovered controls or normal controls) had a *DSM*-defined panic attack while reading the cards with these pairs of words. Although these results were seen as evidence that catastrophic misinterpretations were sufficient to provoke panic attacks, a role for catastrophic misinterpretations per se was not directly established. For example, the word pairs might alternatively evoke thoughts and images that have been associated with panic and thus have become CSs capable of evoking panic.

A learning theory perspective accepts the role of other cognitive factors. It is undoubtedly true that certain kinds of cognitive processes other than catastrophic cognitions can also influence the perceived intensity of panic and thus influence its impact as a US on the development of conditioning. The learning literature has long emphasized predictability and controllability, which may be mediated by cognitions that modulate the perceived intensity of aversive events. Two experiments that have been interpreted to suggest the role of catastrophic cognitions may merely emphasize the importance of the perception of predictability and controllability. Panic patients were given virtually no explanation of what to expect before inhaling 5% CO<sub>2</sub> (Rapee, Mattick, & Murrell, 1986) or infusing sodium lactate (D. M. Clark et al., 1990), or they were given detailed information about what sensations to expect and that these sensations were due to the experimental agent. In both studies, the patients given the detailed explanations were significantly less likely to report panicking than those not given much explanation of what to expect. As discussed earlier, predictable aversive events are generally perceived as less stressful than are unpredictable aversive events. One way of making an event predictable is by providing extensive information about it ahead of time, as was done in these experiments (see Leventhal, 1982; Leventhal, Brown, Shacham, & Engquist, 1979; Mineka & Henderson, 1985). Thus, panic patients, like normal controls, find predictable stressors to be far less stressful (and, therefore, less likely to provoke panic) than they find unpredictable stressors. The effect is cognitively mediated, but prior researchers have not found it necessary to invoke catastrophic misinterpretations to explain it. The Sanderson et al. (1989) study, already discussed, is also consistent with this point: The effects of perceived control (rather than predictability) over the rate of CO<sub>2</sub> infusion underscore the importance of a sense of control in reducing vulnerability to anxiety. Controllability and predictability are cognitive constructs that are relatively easy to operationalize and are connected with a long tradition of experimental research (e.g., Mineka & Henderson, 1985; Minor, Dress, & Overmier, 1991; Peterson et al., 1993; Seligman, Maier, & Solomon, 1971).

We should also acknowledge that, as mentioned earlier, classical conditioning itself may sometimes give rise to cognitive processes that may permit input from other cognitive sources. Al-

though we have emphasized the idea that conditioning processes can be engaged without consciousness or awareness, many forms of human classical conditioning may involve the acquisition of explicit expectancies of the US. In such cases, it might be possible to influence conditioned responding with verbal information or cognition. Consistent with this idea, Lovibond (e.g., 1993) argued that verbal information about the nature of the US can be sufficient to cause changes in conditioned electrodermal responses elicited by conditioned stimuli (e.g., see Grings et al., 1973). We believe that this sort of verbal influence on conditioning is probably not universal and depends on the type of conditioning and the brain system involved. There is a need for more research on the interaction between verbal input and conditioning processes. Nonetheless, at this point we should expect some overlap between conditioning and these overtly "cognitive" processes (see also Öhman & Mineka, 2001).

A modern view of conditioning may also suggest reinterpretation of other evidence sometimes cited in favor of the catastrophic misinterpretation view. In an important early study suggesting the role of cognitive factors in determining panic reactions, D. M. Clark and Hemsley (1982) had normal participants hyperventilate. There was variability in their responses to this event. Participants who recalled experiencing the sensation during sex or while they were high on a pleasant drug rated the sensations as positive; those who recalled an unpleasant experience (e.g., fainting) rated the sensations as negative. To us, this result implies a clear role for the participant's associative learning history, the subject matter of conditioning. Memory retrieval is part of what the associative learning process represented by conditioning is all about (e.g., Bouton, 1994a). Like classical conditioning itself, the Clark and Hemsley result looks to us like another interesting example of associative learning.

Finally, there has also been an emphasis on the idea that the success of any treatment will depend on cognitive changes having occurred during the course of therapy (D. M. Clark, 1996, p. 322). In a treatment study, D. M. Clark et al. (1994) compared the effects of cognitive therapy for panic with the effects of applied relaxation treatment and imipramine. Collapsing across the three groups, misinterpretation of bodily sensations at the end of treatment was a significant predictor of a composite measure of panic/anxiety at follow-up even when partialing out the level of panic-anxiety at the end of treatment. Moreover, among those patients who were panic free at the end of treatment, misinterpretations of bodily sensations at the end point predicted subsequent relapse. On this point, we note that catastrophic cognitions seem to be part of a "context" or constellation of cues that have been associated with panic or are even part of the response itself, and may signal or mark residual anxiety conditioned specifically to panic attacks. If they are not extinguished, PD could well return. In addition, several treatment studies have shown that extensive exteroceptive and interoceptive exposure therapy may be equally effective as cognitive therapy in reducing panic disorder, in both the short term and long term (Margraf & Schneider, 1995; Telch, 1995). A contemporary learning theory perspective may uniquely accommodate these different forms and mechanisms of therapy.

In summary, many findings that seem uniquely interpretable from the perspective of cognitive theory (e.g., Beck & Emery, 1985; D. M. Clark, 1986; 1988, 1996) are not incompatible with contemporary learning theory. The evidence favoring the idea that

catastrophic cognitions cause panic is weak. A learning theory perspective has advantages, moreover, in that it can account for panic attacks that occur apparently without identifiable catastrophic misinterpretations, including nocturnal panic (e.g., Craske, 1999; Kenardy & Taylor, 1999; Rachman et al., 1988). This perspective also recognizes the distinction between anxiety and panic, which seem central to current psychometric (e.g., T. A. Brown et al., 1998) and neurobiological work (e.g., Fanselow, 1994; Gray & McNaughton, 1996). In addition, it allows prediction of return of fear and anxiety based on a thorough analysis of context and conditioning (e.g., Bouton, 1991b) and a more explicit analysis of factors modulating the acquisition of fear, panic, and PD based on well-established paradigms in the laboratories of experimental psychology.

### Implications and Conclusion

We are in a good position at this point to summarize our argument and mention some of its major implications. First, in keeping with earlier approaches to PD, our perspective emphasizes a fundamental role for early conditioning episodes in the etiology of the disorder. This idea can be seen as a strength of a learning perspective, because it constitutes a testable explanation of PD etiology. Prospective data on early panic attacks and their associative and psychological consequences are needed. We would expect, for example, that after an initial panic attack, people—especially those with one or more of the general or specific vulnerabilities discussed earlier—would show more anxiety to cues associated with the first attack. Such results could theoretically be obtained from prospective diary monitoring studies in vulnerable adolescents or young adults (similar to those reported by Basoglu et al., 1992; Kenardy et al., 1992; Kenardy & Taylor, 1999, although with additional measures). However, we also emphasize the fact that current learning theory does not regard conditioning as an inevitable consequence of CS-US pairings. Instead, the extent to which conditioning develops depends on many additional factors, including the person's previous experience with the CS and the US and with the "informativeness" of the various CSs present on the conditioning trial and on other modulating factors in the background, and so on. As we have emphasized throughout this article, laboratory research on conditioning and learning has progressed considerably since the 1960s, and it suggests a surprisingly nuanced perspective on the associative learning involved in panic and other anxiety disorders (see also Mineka, 1985a; Mineka & Zinbarg, 1996).

A second important aspect of our approach is that anxiety and panic are seen as separable aspects of PD. Anxiety is not merely a weak version of panic, and panic is not merely a strong form of anxiety. We see each state, and the constellation of behaviors and physiological responses connected with each, as serving different functions. Anxiety prepares the system for an anticipated trauma, whereas panic deals with one that is already in progress. Anxiety and panic are thus different. This perspective is consistent with data addressed early in this article suggesting that anxiety and panic seem at least in good part phenomenologically, psychometrically, ethologically, and neurobiologically distinct.

Anxiety and panic do interact, however, and our approach assumes that their interaction is central to the development of PD. We propose that anxiety potentiates panic, and the development

and presence of conditioned anxiety, therefore, serve to exacerbate subsequent panic attacks. A third crucial feature of our perspective, then, is the idea that the conditioned anxiety that comes to be elicited by interoceptive and exteroceptive cues associated with panic serves to augment future panic reactions. Anxiety thus becomes a precursor of panic. The approach fits conditioning research, which suggests that anxiety is perhaps the major response learned in aversive conditioning situations, and that anxiety can function to exacerbate CRs and URs elicited while in that state (e.g., Lang, 1994, 1995; Lang et al., 1990; Wagner & Brandon, 1989). It is also consistent with available data that suggest that panic attacks are very often preceded by anxiety in patients with PD (e.g., Barlow, 1988; Basoglu et al., 1992; Kenardy & Taylor, 1999). We expect that prospective data sets would show that, once conditioned anxiety develops as a consequence of the first panic attack, it would potentiate and exacerbate subsequent panics and thus begin the spiral into PD.

It should also be noted that the conditioned elicitation of anxiety does not rely on conscious processing (e.g., LeDoux, 1996; Öhman et al., 2000). Therefore, we predict that panic can be potentiated in the absence of conscious thought or reflection, as is more consistent with functioning in largely subcortical emotional networks connected to defensive motivational systems (Barlow, *in press*; Lang, 1995).

Although we believe that the conditioning of anxiety is a major consequence of the conditioning made possible by panic attacks, we also suspect that panic itself may become conditioned directly to certain kinds of cues. That is, although anxiety is a prevalent CR, panic itself, instead of anxiety, may also emerge as a CR to some of the available CSs. As we reviewed earlier, laboratory research suggests that the nature of the CR depends on a number of factors, including the qualitative nature of the CS and its temporal proximity to the US. We predict that proximal, fear-relevant cues, which might include early somatic aspects of panic itself, are especially likely to have the ability to elicit panic CRs. However, this issue needs more research; we need a more complete understanding of the kinds of cues or circumstances that allow a CS associated with an aversive US to control a CR that resembles the UR. We also predict that those CSs that do elicit panic should do so more strongly when they are presented after the evocation of anxiety. That is, anxiety should potentiate panic whether it is a CR or UR.

A fourth implication of our analysis concerns treatment. Like other conditioning perspectives, we expect that treatments that involve extinction or counterconditioning exposure to the interoceptive and exteroceptive CSs influencing the disorder are the most likely to yield success. However, we explicitly accept many different kinds of events and cues—interoceptive, exteroceptive, verbal, and cognitive—as potential CSs involved in the disorder. Therefore, we predict that approaches that entail extinction or counterconditioning exposure to all of these kinds of events will be most successful, particularly if they are conducted in a way that recognizes the crucial role of context in controlling extinction and other retroactive interference effects (e.g., Bouton, 1991b; Bouton & Nelson, 1998b; Bouton & Swartzentruber, 1991). Moreover, we also predict that treatments designed in part to extinguish the anxiety-reducing properties of safety behaviors (such as carrying a pill bottle or an umbrella) will be very useful (for preliminary evidence see Salkovskis et al., 1996). In our view, this is because

such safety behaviors serve to protect fear of various exteroceptive cues (and potentially interoceptive cues as well) from extinction. If therapists endeavor to expose the anxiety-providing cues without allowing safety behaviors, fear of those cues should extinguish more fully.

In the last analysis, a good theory is a useful tool to guide future scientific exploration of a given topic. Unfortunately, early learning theory approaches to the etiology of panic and other anxiety disorders were overly simplistic, leading to some of the confusion regarding the usefulness of these approaches (e.g., McNally, 1990, 1994). However, the underlying science has developed rapidly over the decades and has been enriched by increasingly important developments in the biological and cognitive bases of learning reviewed here. In our view, a modern learning theory approach will provide the soundest base for future theoretical and empirical developments in the study of PD. Thus, we look forward to precise experimental tests of the various components of our approach, some of which have been suggested here. It is this kind of activity that will ultimately best advance our understanding.

We also believe that contemporary learning theory, perhaps integrated with related research on neurobiology, will continue to provide an essential framework for studying the development and maintenance of other anxiety and emotional disorders. Many of the processes described here in the context of PD are equally applicable to other anxiety and emotional disorders, although each has distinctive features (Barlow, 1988, in press; T. A. Brown et al., 1998; Mineka, 1985a; Mineka & Zinbarg, 1995, 1996, 1998). Although we have touched on evidence supporting the existence of both biological and psychological vulnerabilities, it is the etiological process that occurs in the context of these vulnerabilities on which we have focused most intently (i.e., what happens during and after the first panic attack). Finally, efforts at prevention, one ultimate goal of the study of psychopathology, will benefit from a greater understanding not only of etiological processes but also of the development of various vulnerabilities. Thus, we have attempted to point out how modern learning theory conceptualizes psychosocial vulnerabilities that, when combined with biological vulnerabilities, set the stage for the development of PD. In so doing, we have attempted to reflect the complexity of modern learning theory and of the psychopathology of PD as well as the enormous task, both theoretical and empirical, that remains before us before we fully understand the genesis of PD.

## References

- Akins, C. K., Domjan, M., & Gutierrez, G. (1994). Topography of sexually conditioned behavior in male Japanese quail (*Coturnix japonica*) depends on the CS-US interval. *Journal of Experimental Psychology: Animal Behavior Processes*, *20*, 199–209.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Anderson, D. C., Crowell, C. R., DePaul, M., & McEachin, J. (1997). Intensification of punishment effects through exposure to prolonged, fixed-duration shocks: The role of shock cues as a stimulus for fear. *Animal Learning & Behavior*, *25*, 68–83.
- Baldwin, J. D., & Baldwin, J. I. (1998). *Behavior principles in everyday life* (3rd ed.). Englewood Cliffs, NJ: Prentice Hall.
- Barlow, D. H. (1988). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. New York: Guilford Press.
- Barlow, D. H. (1991). The nature of anxiety: Anxiety, depression, and emotional disorders. In R. M. Rapee & D. H. Barlow (Eds.), *Chronic anxiety: Generalized anxiety disorder and mixed anxiety-depression* (pp. 1–28). New York: Guilford Press.
- Barlow, D. H. (in press). *Anxiety and its disorders: The nature and treatment of anxiety and panic* (2nd ed.). New York: Guilford Press.
- Barlow, D. H., Brown, T. A., & Craske, M. G. (1994). Definitions of panic attacks and panic disorder in the *DSM-IV*: Implications for research. *Journal of Abnormal Psychology*, *103*, 553–564.
- Barlow, D. H., Chorpita, B. F., & Turovsky, J. (1996). Fear, panic, anxiety, and disorders of emotion. In D. A. Hope (Ed.), *Perspectives on anxiety, panic, and fear* (The 43rd Annual Nebraska Symposium on Motivation) (pp. 251–328). Lincoln: Nebraska University Press.
- Barlow, D. H., & Craske, M. G. (2000). *Mastery of your anxiety and panic: Client workbook for anxiety and panic (MAP-3)*. San Antonio, TX: Graywind Publications.
- Barlow, D. H., & Lehman, C. L. (1996). Advances in the psychosocial treatment of anxiety disorders: Implications for national health care. *Archives of General Psychiatry*, *53*, 727–735.
- Barrett, P. M., Rapee, R. M., Dadds, M. M., & Ryan, S. M. (1996). Family enhancement of cognitive style in anxious and aggressive children. *Journal of Abnormal Child Psychology*, *24*, 187–203.
- Basoglu, M., Marks, I., & Sengün, S. (1992). A prospective study of panic and anxiety in agoraphobia with panic disorder. *British Journal of Psychiatry*, *160*, 57–64.
- Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, *269*, 1115–1118.
- Beck, A. T., & Emery, T. (1985). *Anxiety disorders and phobias*. New York: Basic Books.
- Blanchard, D. C. (1997). Stimulus, environmental, and pharmacological control of defensive behaviors. In M. E. Bouton & M. S. Fanselow (Eds.), *Learning, motivation, and cognition: The functional behaviorism of Robert C. Bolles* (pp. 283–303). Washington, DC: American Psychological Association.
- Blanchard, D. C., Blanchard, R. J., & Rodgers, R. J. (1991). Risk assessment and animal models of anxiety. In B. Olivier, J. Mos, & J. L. Slangen (Eds.), *Animal models in psychopharmacology* (pp. 117–134). Basel, Switzerland: Birkhäuser.
- Blanchard, R. J., & Blanchard, D. C. (1969). Crouching as an index of fear. *Journal of Comparative & Physiological Psychology*, *67*, 370–375.
- Blanchard, R. J., & Blanchard, D. C. (1987). An ethoexperimental approach to the study of fear. *The Psychological Record*, *37*, 305–316.
- Bolles, R. C., & Fanselow, M. S. (1980). A perceptual-defensive-recuperative model of fear and pain. *Behavioral & Brain Sciences*, *3*, 291–323.
- Bombace, J. C., Brandon, S. E., & Wagner, A. R. (1991). Modulation of a conditioned eyeblink response by a putative emotive stimulus conditioned with hindleg shock. *Journal of Experimental Psychology: Animal Behavior Processes*, *17*, 323–333.
- Borkovec, T. D. (1994). The nature, functions, and origins of worry. In G. Davey & F. Tallis (Eds.), *Worrying: Perspectives on theory, assessment, and treatment* (pp. 5–35). Sussex, England: Wiley.
- Bouton, M. E. (1984). Differential control by context in the inflation and reinstatement paradigms. *Journal of Experimental Psychology: Animal Behavior Processes*, *10*, 56–74.
- Bouton, M. E. (1988). Context and ambiguity in the extinction of emotional learning: Implications for exposure therapy. *Behaviour Research & Therapy*, *26*, 137–149.
- Bouton, M. E. (1991a). Context and retrieval in extinction and in other examples of interference in simple associative learning. In L. Dachowski & C. F. Flaherty (Eds.), *Current topics in animal learning: Brain, emotion, and cognition* (pp. 25–53). Hillsdale, NJ: Erlbaum.
- Bouton, M. E. (1991b). A contextual analysis of fear extinction. In P. R.

- Martin (Ed.), *Handbook of behavior therapy and psychological science: An integrative approach* (pp. 435–453). New York: Pergamon Press.
- Bouton, M. E. (1993). Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychological Bulletin*, *114*, 80–99.
- Bouton, M. E. (1994a). Conditioning, remembering, and forgetting. *Journal of Experimental Psychology: Animal Behavior Processes*, *20*, 219–231.
- Bouton, M. E. (1994b). Context, ambiguity, and classical conditioning. *Current Directions in Psychological Science*, *3*, 49–53.
- Bouton, M. E. (2000). A learning theory perspective on lapse, relapse, and the maintenance of behavior change. *Health Psychology*, *19* (Suppl.), 57–63.
- Bouton, M. E., & King, D. A. (1983). Contextual control of the extinction of conditioned fear: Tests for the associative value of the context. *Journal of Experimental Psychology: Animal Behavior Processes*, *9*, 248–265.
- Bouton, M. E., & King, D. A. (1986). Effect of context on performance to conditioned stimuli with mixed histories of reinforcement and nonreinforcement. *Journal of Experimental Psychology: Animal Behavior Processes*, *12*, 4–15.
- Bouton, M. E., & Nelson, J. B. (1998a). Mechanisms of feature-positive and feature-negative discrimination learning in an appetitive conditioning paradigm. In N. A. Schmajuk & P. C. Holland (Eds.), *Occasion setting: Associative learning and cognition in animals* (pp. 69–112). Washington, DC: American Psychological Association.
- Bouton, M. E., & Nelson, J. B. (1998b). The role of context in classical conditioning: Some implications for cognitive behavior therapy. In W. T. O'Donohue (Ed.), *Learning and behavior therapy* (pp. 59–84). Boston: Allyn & Bacon.
- Bouton, M. E., & Ricker, S. T. (1994). Renewal of extinguished responding in a second context. *Animal Learning & Behavior*, *22*, 317–324.
- Bouton, M. E., & Swartzentruber, D. (1986). Analysis of the associative and occasion-setting properties of contexts participating in a Pavlovian discrimination. *Journal of Experimental Psychology: Animal Behavior Processes*, *12*, 333–350.
- Bouton, M. E., & Swartzentruber, D. (1991). Sources of relapse after extinction in Pavlovian and instrumental learning. *Clinical Psychology Review*, *11*, 123–140.
- Brandon, S. E., Betts, S. L., & Wagner, A. R. (1994). Discriminated lateralized eyeblink conditioning in the rabbit: An experimental context for separating specific and general associative influences. *Journal of Experimental Psychology: Animal Behavior Processes*, *20*, 292–307.
- Brandon, S. E., Bombace, J. C., Falls, W. A., & Wagner, A. R. (1991). Modulation of unconditioned defensive reflexes by a putative emotive Pavlovian conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes*, *17*, 312–322.
- Brandon, S. E., & Wagner, A. R. (1991). Modulation of a discrete Pavlovian conditioned reflex by a putative emotive Pavlovian conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes*, *17*, 299–311.
- Breggin, P. R. (1964). The psychophysiology of anxiety with a review of the literature concerning adrenaline. *Journal of Nervous and Mental Disease*, *139*, 558–568.
- Bridger, W. H., & Mandel, I. J. (1964). A comparison of GSR fear responses produced by threat and electric shock. *Journal of Psychiatric Research*, *2*, 31–40.
- Brown, J. S., Kalish, H. I., & Farber, I. E. (1951). Conditioned fear as revealed by magnitude of startle response to an auditory stimulus. *Journal of Experimental Psychology*, *41*, 317–327.
- Brown, T. A., Chorpita, B. F., & Barlow, D. H. (1998). Structural relationships among dimensions of the *DSM-IV* anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology*, *107*, 179–192.
- Brush, F. R. (1985). Genetic determinants of avoidance learning: Mediation by emotionality? In F. R. Brush & J. B. Overmier (Eds.), *Affect, conditioning, and cognition: Essays on the determinants of behavior* (pp. 27–42). Hillsdale, NJ: Erlbaum.
- Carter, M. M., & Barlow, D. H. (1995). Learned alarms: The origins of panic. In W. O'Donohue & L. Krasner (Eds.), *Theories of behavior therapy: Exploring behavior change* (pp. 209–228). New York: Guilford Press.
- Carter, M. M., Hollon, S., Carson, R., & Shelton, R. (1995). Effects of a safe person on induced distress following a biological challenge in panic disorder with agoraphobia. *Journal of Abnormal Psychology*, *104*, 156–163.
- Cepeda-Benito, A., & Short, P. (1997). Morphine's interoceptive stimuli as cues for the development of associative morphine tolerance in the rat. *Psychobiology*, *25*, 236–240.
- Chambless, D., Caputo, G., Bright, P., & Gallagher, R. (1984). Assessment of fear of fear in agoraphobics: The Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire. *Journal of Consulting and Clinical Psychology*, *52*, 1090–1097.
- Charney, D. S., Grillon, C., Bremner, J. D. (1998). The neurobiological basis of anxiety and fear: Circuits, mechanisms, and neurochemical interaction, part 1. *The Neuroscientist*, *4*, 35–44.
- Chorzyna, H. (1962). Some properties of conditioned inhibition. *Acta Biologica Experimentalis*, *22*, 5–13.
- Chorpita, B. F., & Barlow, D. H. (1998). The development of anxiety: The role of control in the early environment. *Psychological Bulletin*, *124*, 3–21.
- Chorpita, B. F., Brown, T., & Barlow, D. (1998). Perceived control as a mediator of family environment in etiological models of childhood anxiety. *Behavior Therapy*, *29*, 457–476.
- Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy*, *24*, 461–470.
- Clark, D. M. (1988). A cognitive model of panic attacks. In S. Rachman & J. D. Maser (Eds.), *Panic: Psychological perspectives* (pp. 71–89). Hillsdale, NJ: Erlbaum.
- Clark, D. M. (1996). Panic disorder: From theory to therapy. In P. M. Salkovskis (Ed.), *Frontiers of cognitive therapy* (pp. 318–344). New York: Guilford Press.
- Clark, D. M., & Hemsley, D. (1982). The effects of hyperventilation: Individual variability and its relation to personality. *Journal of Behavior Therapy and Experimental Psychiatry*, *13*, 41–47.
- Clark, D. M., Salkovskis, P., & Anastasiades, P. (1990, November). Cognitive mediation of lactate induced panic. In R. Rapee (Chair), *Experimental investigations of panic disorder. Symposium of the Association for Advancement of Behavior Therapy*, San Francisco, CA.
- Clark, D. M., Salkovskis, P. M., Gelder, M. G., Koehler, C., Martin, M., Anastasiades, P., Hackman, A., Middleton, H., & Jevons, A. (1988). Tests of a cognitive theory of panic. In I. Hand & H. U. Wittchen (Eds.), *Panic and phobias II*. New York: Springer-Verlag.
- Clark, D. M., Salkovskis, P. M., Hackmann, A., Middleton, H., Anastasiades, P., & Gelder, M. (1994). A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. *British Journal of Psychiatry*, *164*, 759–769.
- Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. Special issue: Diagnoses, dimensions, and *DSM-IV*: The science of classification. *Journal of Abnormal Psychology*, *100*, 316–336.
- Clark, L. A., Watson, D., & Mineka, S. (1994). Temperament and personality in mood and anxiety disorders. *Journal of Abnormal Psychology*, *103*, 103–116.
- Clark, R. E., & Squire, L. R. (1998). Classical conditioning and brain systems: The role of awareness. *Science*, *280*, 77–81.
- Cohen, M. E., & White, P. D. (1947). Studies of breathing, pulmonary ventilation, and subjective awareness of shortness of breath (dyspnea) in

- neurocirculatory asthenia, effort syndrome, anxiety neurosis. *Journal of Clinical Investigation*, 26, 520.
- Cohen, M. E., & White, P. D. (1950). Life situations, emotions, and neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome). In H. G. Wolff (Ed.), *Life stress and bodily disease* (Nervous and Mental Disease, Research Publication No. 29). Baltimore, MD: Williams & Wilkins.
- Colwill, R. M. (1994). Associative representations of instrumental contingencies. In D. L. Medin (Ed.), *The psychology of learning and motivation: Advances in research and theory*. (Vol. 31, pp. 1–72). San Diego, CA: Academic Press.
- Colwill, R. M., & Motzkin, D. K. (1994). Encoding of the unconditioned stimulus in Pavlovian conditioning. *Animal Learning & Behavior*, 22, 384–394.
- Colwill, R. M., & Rescorla, R. A. (1988). Associations between the discriminative stimulus and the reinforcer in instrumental learning. *Journal of Experimental Psychology: Animal Behavior Processes*, 14, 155–164.
- Cook, E. W., Hawk, L. W., Davis, T. L., & Stevenson, V. E. (1991). Affective individual differences and startle reflex modulation. *Journal of Abnormal Psychology*, 100, 5–13.
- Cook, E. W., Hodes, R. L., & Lang, P. J. (1986). Preparedness and phobia: Effects of stimulus content on human visceral conditioning. *Journal of Abnormal Psychology*, 95, 195–207.
- Coplan, J. D., Andrews, M. W., Rosenblum, L. A., Owens, M. J., Friedman, S., Gorman, J. M., & Nemeroff, C. B. (1996). Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: Implications for the pathophysiology of mood and anxiety disorders. *Proceedings of the National Academy of Sciences*, 93, 1619–1623.
- Craske, M. G. (1999). *Anxiety disorders: Psychological approaches to theory and treatment*. Boulder, CO: Westview Press.
- Craske, M. G., Glover, D., & DeCola, J. (1995). Predicted versus unpredicted panic attacks: Acute versus general distress. *Journal of Abnormal Psychology*, 104, 214–223.
- Craske, M. G., Miller, P. P., Rotunda, R., & Barlow, D. H. (1990). A descriptive report of features of initial unexpected panic attacks in minimal and extensive avoiders. *Behaviour Research & Therapy*, 28, 395–400.
- Crowell, C. R. (1974). Conditioned-aversive aspects of electric shock. *Learning and Motivation*, 5, 209–220.
- Cunningham, C. L. (1998). Drug conditioning and drug-seeking behavior. In W. T. O'Donohue (Ed.), *Learning and behavior therapy* (pp. 518–544). Boston: Allyn & Bacon.
- Davey, G., de Jong, P., & Tallis, F. (1993). UCS inflation in the etiology of a variety of anxiety disorders: Some case histories. *Behaviour Research and Therapy*, 31, 495–498.
- Davis, M. (1992). The role of the amygdala in conditioned fear. In J. P. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction* (pp. 255–305). New York: Wiley-Liss.
- Davis, M., Walker, D. L., & Yee, Y. (1997). Amygdala and bed nucleus of the stria terminalis: Differential roles in fear and anxiety measured with the acoustic startle reflex. In L. Squire & D. Schacter (Eds.), *Biological and psychological perspectives on memory and memory disorders*. Washington, DC: American Psychiatric Association.
- Delamater, A. R. (1996). Effects of several extinction treatments upon the integrity of Pavlovian stimulus-outcome associations. *Animal Learning & Behavior*, 24, 437–449.
- Dimberg, U. (1987). Facial reactions, autonomic activity, and experienced emotion: A three-component model of emotional conditioning. *Biological Psychology*, 24, 105–122.
- Domjan, M. (1994). Formulation of a behavior system for sexual conditioning. *Psychonomic Bulletin & Review*, 1, 421–428.
- Domjan, M. (1997). Behavior systems and the demise of equipotentiality: Historical antecedents and evidence from sexual conditioning. In M. E. Bouton & M. S. Fanselow (Eds.), *Learning, motivation, and cognition: The functional behaviorism of Robert C. Bolles* (pp. 31–51). Washington, DC: American Psychological Association.
- Domjan, M. (1998). *The principles of learning and behavior* (4th ed.). Pacific Grove, CA: Brooks/Cole.
- Domjan, M., Huber-McDonald, M., & Holloway, K. S. (1992). Conditioning copulatory behavior to an artificial object: Efficacy of stimulus fading. *Animal Learning & Behavior*, 20, 350–362.
- Dworkin, B. R. (1993). *Learning and physiological regulation*. Chicago: University of Chicago Press.
- Ehlers, A. (1993). Somatic symptoms and panic attacks: A retrospective study of learning experiences. *Behaviour Research and Therapy*, 31, 269–278.
- Ehlers, A. (1995). A 1-year prospective study of panic attacks: Clinical course and factors associated with maintenance. *Journal of Abnormal Psychology*, 104, 164–172.
- Ehlers, A., & Breuer, P. (1992). Increased cardiac awareness in panic disorder. *Journal of Abnormal Psychology*, 101, 371–382.
- Ehlers, A., & Breuer, P. (1996). How good are patients with panic disorder at perceiving their heartbeats? *Biological Psychology*, 42, 165–182.
- Ehlers, A., Margraf, J., & Chambless, D. (1992). *Fragebögen zu körperbezogenen Ängsten, Kognitionen und Vermeidung*. Weinheim: Beltz.
- Ehlers, A., Margraf, J., Roth, W. T., Taylor, C. B., & Birbaumer, N. (1988). Anxiety induced by false heart rate feedback in patients with panic disorder. *Behaviour Research and Therapy*, 26, 1–11.
- Eich, E. (1995). Searching for mood dependent memory. *Psychological Science*, 6, 67–75.
- Eikelboom, R., & Stewart, J. (1982). Conditioning of drug-induced physiological responses. *Psychological Review*, 89, 507–528.
- Eysenck, H. J. (Ed.). (1960). *Behavior therapy and the neuroses*. Oxford, England: Pergamon Press.
- Eysenck, H. J. (1967). *The biological basis of personality*. Springfield, IL: Charles C Thomas.
- Eysenck, H. J. (1979). The conditioning model of neurosis. *Behavioral and Brain Sciences*, 2, 155–199.
- Eysenck, H. J., & Rachman, S. (1965). *The causes and cures of neurosis*. London: Routledge & Kegan Paul.
- Fanselow, M. S. (1980). Conditional and unconditional components of postshock freezing. *Pavlovian Journal of Biological Science*, 15, 177–182.
- Fanselow, M. S. (1989). The adaptive function of conditioned defensive behavior: An ecological approach to Pavlovian stimulus-substitution theory. In R. J. Blanchard, P. F. Brain, D. C. Blanchard, & S. Parmigiani (Eds.), *Ethoexperimental approaches to the study of behavior* (pp. 151–166). Dordrecht, the Netherlands: Kluwer Academic.
- Fanselow, M. S. (1994). Neural organization of the defensive behavior system responsible for fear. *Psychonomic Bulletin & Review*, 1, 429–438.
- Fanselow, M. S., & Lester, L. S. (1988). A functional behavioristic approach to aversively motivated behavior: Predatory imminence as a determinant of the topography of defensive behavior. In R. C. Bolles & M. D. Beecher (Eds.), *Evolution and learning* (pp. 185–212). Hillsdale, NJ: Erlbaum.
- Feingold, A. (1994). Gender differences in personality: A meta-analysis. *Psychological Bulletin*, 116, 429–456.
- Forsyth, J. P., & Eifert, G. H. (1996). Systemic alarms in fear conditioning I: A reappraisal of what is being conditioned. *Behavior Therapy*, 27, 441–462.
- Forsyth, J. P., & Eifert, G. H. (1998). Response intensity in content-specific fear conditioning comparing 20% versus 13% CO<sub>2</sub>-sub-2-enriched air as unconditioned stimuli. *Journal of Abnormal Psychology*, 107, 291–304.
- Forsyth, J. P., Eifert, G. H., & Thompson, R. N. (1996). Systemic alarms

- in fear conditioning: II. An experimental methodology using 20% carbon dioxide inhalation as an unconditioned stimulus. *Behavior Therapy*, *27*, 391–415.
- Gallup, G. G., Jr., & Maser, J. D. (1977). Tonic immobility: Evolutionary underpinnings of human catalepsy and catatonia. In J. D. Maser & M. E. P. Seligman (Eds.), *Psychopathology: Experimental models* (pp. 334–357). San Francisco: Freeman.
- Goddard, M. J. (1996). Effect of US signal value on blocking of a CS-US association. *Journal of Experimental Psychology: Animal Behavior Processes*, *22*, 258–264.
- Goddard, M. J. (1997). Spontaneous recovery in US extinction. *Learning & Motivation*, *28*, 118–128.
- Goddard, M. J. (1999). The role of US signal value in contingency, drug conditioning, and learned helplessness. *Psychonomic Bulletin & Review*, *6*, 412–423.
- Goddard, M. J., & Jenkins, H. M. (1988). Blocking of a CS-US association by a US-US association. *Journal of Experimental Psychology: Animal Behavior Processes*, *14*, 177–186.
- Goldstein, A. J., & Chambless, D. L. (1978). A reanalysis of agoraphobia. *Behavior Therapy*, *9*, 47–59.
- Gray, J. A., & McNaughton, N. (1996). The neuropsychology of anxiety: Reprise. In D. A. Hope (Ed.), *Perspectives on anxiety, panic, and fear* (The 43rd Annual Nebraska Symposium on Motivation) (pp. 61–134). Lincoln: Nebraska University Press.
- Greeley, J., Lê, D. A., Poulos, C. X., & Cappell, H. (1984). Alcohol is an effective cue in the conditional control of tolerance to alcohol. *Psychopharmacology*, *83*, 159–162.
- Grillon, C., Ameli, R., Goddard, A., Woods, S. W., & Davis, M. (1994). Baseline and fear-potentiated startle in panic disorder patients. *Biological Psychiatry*, *35*, 431–439.
- Grillon, C., Ameli, R., Woods, S. W., Merikangas, K., & Davis, M. (1991). Fear-potentiated startle in humans: Effects of anticipatory anxiety on the acoustic blink reflex. *Psychophysiology*, *28*, 588–595.
- Grings, W. W., Schell, A. M., & Carey, C. A. (1973). Verbal control of an autonomic response in a cue reversal situation. *Journal of Experimental Psychology*, *99*, 215–221.
- Hall, G., & Honey, R. C. (1989). Contextual effects in conditioning, latent inhibition, and habituation: Associative and retrieval functions of contextual cues. *Journal of Experimental Psychology: Animal Behavior Processes*, *15*, 232–241.
- Hamm, A. O., & Vaitl, D. (1996). Affective learning: Awareness and aversion. *Psychophysiology*, *33*, 698–710.
- Hannum, R., Rosellini, R., & Seligman, M. (1976). Retention of learned helplessness and immunization in the rat from weaning to adulthood. *Developmental Psychology*, *12*, 449–454.
- Hayward, C., Killen, J. D., Kraemer, H. C., & Taylor, C. B. (2000). Predictors of panic attacks in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *39*, 207–214.
- Heim, C., & Nemeroff, C. B. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry*, *46*, 1509–1522.
- Heller, W., Nitschke, J. B., Etienne, M. A., & Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology*, *106*, 376–385.
- Henderson, R. W. (1975). Compounds of conditioned fear stimuli. *Learning & Motivation*, *6*, 28–42.
- Henderson, R. W. (1985). Fearful memories: The motivational significance of forgetting. In F. R. Brush & J. B. Overmier (Eds.), *Affect, conditioning and cognition: Essays on the determinants of behavior* (pp. 43–52). Hillsdale, NJ: Erlbaum.
- Hirsch, S. M., & Bolles, R. C. (1980). On the ability of prey to recognize predators. *Zeitschrift fuer Tierpsychologie*, *54*, 71–84.
- Hoehn-Saric, R., McLeod, D. R., & Zimmerli, W. D. (1989). Somatic manifestations in women with generalized anxiety disorder: Psychological responses to psychological stress. *Archives of General Psychiatry*, *46*, 1113–1119.
- Holland, P. C. (1977). Conditioned stimulus as a determinant of the form of the Pavlovian conditioned response. *Journal of Experimental Psychology: Animal Behavior Processes*, *3*, 77–104.
- Holland, P. C. (1989). Feature extinction enhances transfer of occasion setting. *Animal Learning & Behavior*, *17*, 269–279.
- Holland, P. C. (1992). Occasion setting in Pavlovian conditioning. In G. Bower (Ed.), *The psychology of learning and motivation* (Vol. 28, pp. 69–125). Orlando, FL: Academic Press.
- Hollis, K. L. (1982). Pavlovian conditioning of signal-centered action patterns and autonomic behavior: A biological analysis of function. *Advances in the Study of Behavior*, *12*, 131–142.
- Hollis, K. L. (1997). Contemporary research on Pavlovian conditioning: A “new” functional analysis. *American Psychologist*, *52*, 956–965.
- Joffe, J., Rawson, R., & Mulick, J. (1973). Control of their environment reduces emotionality in rats. *Science*, *180*, 1383–1384.
- Joiner, T. E., Jr., Steer, R. A., Beck, A. T., Schmidt, N. B., Rudd, M. D., & Catanzaro, S. J. (1999). Physiological hyperarousal: Construct validity of a central aspect of the tripartite model of depression and anxiety. *Journal of Abnormal Psychology*, *108*, 290–298.
- Kapp, B. S., Whalen, P. J., Supple, W. F., Jr., & Pascoe, J. P. (1992). Amygdaloid contributions to conditioned arousal and sensory information processing. In J. P. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction* (pp. 229–254). New York: Wiley.
- Kenardy, J., Fried, L., Kraemer, H. C., & Taylor, C. B. (1992). Psychological precursors of panic attacks. *British Journal of Psychiatry*, *160*, 668–673.
- Kenardy, J., & Taylor, C. B. (1999). Expected versus unexpected panic attacks: A naturalistic prospective study. *Journal of Anxiety Disorders*, *13*, 435–445.
- Kendler, K. S., Kessler, R. C., Walters, E. D., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *American Journal of Psychiatry*, *152*, 833–842.
- Kendler, K. S., Neale, M., Kessler, R., Heath, A., & Eaves, L. (1992). The genetic epidemiology of phobias in women: The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Archives of General Psychiatry*, *49*, 273–281.
- Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry*, *52*, 374–382.
- Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, H.-U., & Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Archives of General Psychiatry*, *51*, 8–19.
- Kim, J. A., Siegel, S., & Patenall, V. R. A. (1999). Drug-onset cues as signals: Intra-administration associations and tolerance. *Journal of Experimental Psychology: Animal Behavior Processes*, *25*, 491–504.
- King, N. J., Gullone, E., Tonge, B. J., & Ollendick, T. H. (1993). Self-reports of panic attacks and manifest anxiety in adolescents. *Behaviour Research and Therapy*, *31*, 111–116.
- Klein, D. F. (1981). Anxiety reconceptualized. In D. F. Klein & J. Rabkin (Eds.), *Anxiety: New research and changing concepts* (pp. 235–264). New York: Raven Press.
- Konorski, J. (1967). *Integrative activity of the brain*. Chicago: University of Chicago Press.
- Kruse, J. M., Overmier, J. B., Konz, W. A., & Rokke, E. (1983). Pavlovian conditioned stimulus effects upon instrumental choice behavior are reinforcer specific. *Learning and Motivation*, *14*, 165–181.

- Kushner, M. G., & Beitman, B. D. (1990). Panic attacks without fear: An overview. *Behaviour Research and Therapy*, 28, 469–479.
- Ladd, C. O., Huot, R. L., Thirivikraman, K. V., Nemeroff, C. B., Meaney, M. J., & Plotsky, P. M. (2000). Long-term behavioral and neuroendocrine adaptations to adverse early experience. In E. A. Mayer & C. B. Saper (Eds.), *Progress in brain research: The biological basis for mind body interactions* (Vol. 122, pp. 81–103). Amsterdam: Elsevier.
- Lang, P. J. (1994). The varieties of emotional experience: A meditation on James-Lange theory. *Psychological Review*, 101, 211–221.
- Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *American Psychologist*, 50, 372–385.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, 97, 377–395.
- Lang, P. J., Davis, M., & Öhman, A. (2000). Fear and anxiety: Animal models and human cognitive psychophysiology. *Journal of Affective Disorders*, 61, 137–159.
- Last, C. G., O'Brien, G. T., & Barlow, D. H. (1985). The relationship between cognitions and anxiety. *Behavior Modification*, 9, 235–241.
- LeDoux, J. E. (1996). *The emotional brain: The mysterious underpinnings of emotional life*. New York: Simon & Schuster.
- Leventhal, H. (1982). The integration of emotion and cognition: A view from the perceptual-motor theory of emotion. In M. Clark & S. Fiske (Eds.), *Affect and Cognition: The 17th Annual Carnegie Symposium on Cognition*. Hillsdale, NJ: Erlbaum.
- Leventhal, H., Brown, D., Shacham, S., & Engquist, G. (1979). Effects of preparatory information about sensations, threat of pain, and attention on cold pressor distress. *Journal of Personality and Social Psychology*, 37, 688–714.
- Levey, A., & Martin, I. (1981). Personality and conditioning. In H. Eysenck (Ed.), *A model for personality* (pp. 123–168). Berlin: Springer-Verlag.
- Levy, E. (1998). *Learning experiences and vulnerability to panic disorder: Possible origins of high anxiety sensitivity and acquisition of catastrophic misinterpretation of sensations*. Unpublished doctoral dissertation, Northwestern University.
- Liebowitz, M. R., Fyer, A. J., Gorman, J. M., Dillon, D., Appleby, I. L., Levy, G., Anderson, S., Levitt, M., Palij, M., Davies, S. O., & Klein, D. F. (1984). Lactate provocation of panic. *Archives of General Psychiatry*, 41, 764–770.
- Liebowitz, M. R., Gorman, J. M., Fyer, A. J., Levitt, M., Dillon, D., Levy, G., Appleby, I. L., Anderson, S., Palij, M., Davies, S. O., & Klein, D. F. (1985). Lactate provocation of panic attacks: II. Biochemical and physiological findings. *Archives of General Psychiatry*, 42, 709–719.
- Lindemann, E., & Finesinger, J. E. (1938). The effect of adrenaline and mecholyl in states of anxiety in psychoneurotic patients. *American Journal of Psychiatry*, 95, 353–370.
- Lovibond, P. F. (1993). Conditioning and cognitive-behaviour therapy. *Behaviour Change*, 10, 119–130.
- Lovibond, P. F., Preston, G. C., & Mackintosh, N. J. (1984). Context specificity of conditioning, extinction, and latent inhibition. *Journal of Experimental Psychology: Animal Behavior Processes*, 10, 360–375.
- Mackintosh, N. J. (1974). *The psychology of animal learning*. San Diego, CA: Academic Press.
- Mackintosh, N. J. (1975). A theory of attention: Variations in the associability of stimuli with reinforcement. *Psychological Review*, 82, 276–298.
- Maier, S. F. (1990). Role of fear in mediating shuttle escape learning deficit produced by inescapable shock. *Journal of Experimental Psychology: Animal Behavior Processes*, 16, 137–149.
- Maier, S. F., & Seligman, M. E. P. (1976). Learned helplessness: Theory and evidence. *Journal of Experimental Psychology: General*, 105, 3–46.
- Margraf, J., Ehlers, A., & Roth, W. T. (1986). Sodium lactate infusions and panic attacks: A review and critique. *Psychosomatic Medicine*, 48, 23–51.
- Margraf, J., & Schneider, S. (1995, July). *Psychological treatment of panic: What works in the long run?* Paper presented at the World Congress of Behavioural and Cognitive Therapies, Copenhagen, Denmark.
- Marks, I. (1969). *Fears and phobias*. London: Heineman Medical Books.
- Maser, J. D., & Gallup, G. G. (1974). Tonic immobility in the chicken: Catalepsy potentiation by uncontrollable shock and alleviation by imipramine. *Psychosomatic Medicine*, 36, 199–205.
- McGuffin, P., & Reich, T. (1984). Psychopathology and genetics. In H. Adams & P. Sutker (Eds.), *Comprehensive handbook of psychopathology*. New York: Plenum.
- McNally, R. J. (1990). Psychological approaches to panic disorder: A review. *Psychological Bulletin*, 108, 403–419.
- McNally, R. J. (1994). *Panic disorder: A critical analysis*. New York: Guilford Press.
- McNally, R. J. (1999). Theoretical approaches to the fear of anxiety. In S. Taylor (Ed.), *Anxiety sensitivity: Theory, research, and treatment of the fear of anxiety*. Hillsdale, NJ: Erlbaum.
- McNally, R. J., & Eke, M. (1996). Anxiety sensitivity, suffocation fear, and breath-holding duration as predictors of response to carbon dioxide challenge. *Journal of Abnormal Psychology*, 105, 146–149.
- McNaughton, N., & Gray, J. A. (in press). Anxiolytic action on the behavioural inhibition system implies multiple types of arousal contribute to anxiety. *Journal of Affective Disorders*.
- McNish, K. A., Betts, S. L., Brandon, S. E., & Wagner, A. R. (1997). Divergence of conditioned eyeblink and conditioned fear in backward Pavlovian training. *Animal Learning & Behavior*, 25, 43–52.
- Menzies, R., & Clarke, J. (1995). The etiology of phobias: A nonassociative account. *Clinical Psychology Review*, 15, 23–48.
- Merckelbach, H., de Ruiter, C., van den Hout, M., & Hoekstra, R. (1989). Conditioning experiences and phobias. *Behaviour Research and Therapy*, 27, 657–662.
- Mineka, S. (1985a). Animal models of anxiety-based disorders: Their usefulness and limitations. In A. H. Tuma & J. Maser (Eds.), *Anxiety and the anxiety disorders* (pp. 199–244). Hillsdale, NJ: Erlbaum.
- Mineka, S. (1985b). The frightful complexity of the origins of fears. In F. R. Brush & J. B. Overmier (Eds.), *Affect, conditioning, and cognition: Essays on the determinants of behavior* (pp. 55–73). Hillsdale, NJ: Erlbaum.
- Mineka, S., & Cook, M. (1993). Mechanisms underlying observational conditioning of fear in monkeys. *Journal of Experimental Psychology: General*, 122, 23–38.
- Mineka, S., Cook, M., & Miller, S. (1984). Fear conditioned with escapable and inescapable shock: Effects of a feedback stimulus. *Journal of Experimental Psychology: Animal Behavior Processes*, 10, 307–323.
- Mineka, S., Gunnar, M., & Champoux, M. (1986). Control and early socioemotional development: Infant rhesus monkeys reared in controllable versus uncontrollable environments. *Child Development*, 57, 1241–1256.
- Mineka, S., & Hendersen, R. (1985). Controllability and predictability in acquired motivation. *Annual Review of Psychology*, 36, 495–530.
- Mineka, S., & Kelly, K. (1989). The relationship between anxiety, lack of control, and loss of control. In A. Steptoe (Ed.), *Stress, personal control and health* (pp. 163–191). New York: Wiley.
- Mineka, S., & Kihlstrom, J. F. (1978). Unpredictable and uncontrollable events: A new perspective on experimental neurosis. *Journal of Abnormal Psychology*, 87, 256–271.
- Mineka, S., Mystkowski, J., Hladek, D., & Rodriguez, B. (1999). The effects of context on return of fear following successful exposure treatment for spider phobia. *Journal of Consulting and Clinical Psychology*, 67, 599–604.
- Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Psychology*, 49, 377–412.
- Mineka, S., & Zinbarg, R. (1991). Animal models of psychopathology. In

- C. E. Walker (Ed.), *Clinical psychology: Historical and research foundations* (pp. 51–86). New York: Plenum.
- Mineka, S., & Zinbarg, R. (1995). Conditioning and ethological models of social phobia. In R. Heimberg, M. Liebowitz, D. Hope, & F. Schneier (Eds.), *Social phobia: Diagnosis, assessment and treatment* (pp. 1134–1162). New York: Guilford Press.
- Mineka, S., & Zinbarg, R. (1996). Conditioning and ethological models of anxiety disorders: Stress-in-dynamic-context anxiety models. In D. A. Hope (Ed.), *Perspectives on anxiety, panic, and fear. Nebraska Symposium on Motivation* (Vol. 43, pp. 135–210). Lincoln: Nebraska University Press.
- Mineka, S., & Zinbarg, R. (1998). Experimental approaches to understanding the mood and anxiety disorders. In J. Adair (Ed.), *Advances in psychological research, volume 2* (pp. 429–454). Hove, England: Psychology Press.
- Minor, T., Dess, N., & Overmier, J. B. (1991). Inverting the traditional view of “learned helplessness.” In R. Denny (Ed.), *Fear, avoidance, and phobias* (pp. 87–133). Hillsdale, NJ: Erlbaum.
- Monroe, S. M., & Simons, A. E. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*, *110*, 406–425.
- Morgan, C. A., Grillon, C., Southwick, S. M., Davis, M., & Charney, D. (1995). Fear-potentiated startle in posttraumatic stress disorder. *Biological Psychiatry*, *36*, 378–385.
- Mowrer, O. H. (1947). On the dual nature of learning—A re-interpretation of “conditioning” and “problem-solving.” *Harvard Educational Review*, *17*, 102–148.
- Mowrer, O. H. (1960). *Learning theory and behavior*. New York: Wiley.
- Mowrer, O. H., & Vieck, P. (1948). An experimental analogue of fear from a sense of helplessness. *Journal of Abnormal Social Psychology*, *83*, 193–200.
- Norton, G. R., Cox, B. J., & Malan, J. (1992). Nonclinical panickers: A critical review. *Clinical Psychology Review*, *12*, 121–139.
- Norton, G. R., Dorward, J., & Cox, B. J. (1986). Factors associated with panic attack in non-clinical subjects. *Behavior Therapy*, *17*, 239–252.
- Öhman, A. (1996). Preferential pre-attentive processing of threat in anxiety: Preparedness and attentional biases. In R. Rapee (Ed.), *Current controversies in the anxiety disorders* (pp. 253–290). New York: Guilford Press.
- Öhman, A. (1997). Unconscious pre-attentive mechanisms in the activation of phobic fear. In G. C. L. Davey (Ed.), *Phobias: A handbook of theory, research, and treatment* (pp. 349–374). Chichester: Wiley.
- Öhman, A., Flykt, A., & Lundqvist, D. (2000). Unconscious emotion: Evolutionary perspectives, psychophysiological data, and neuropsychological mechanisms. In R. Lane & L. Nadel (Eds.), *The Cognitive neuroscience of emotion* (pp. 296–327). New York: Oxford University Press.
- Öhman, A., & Mineka, S. (2001). Revisiting preparedness: Toward an evolved module of fear learning. *Psychological Review*. Manuscript submitted for publication.
- Öst, L.-G., & Hugdahl, K. (1981). Acquisition of phobias and anxiety response patterns in clinical patients. *Behaviour Research and Therapy*, *19*, 439–447.
- Öst, L.-G., & Hugdahl, K. (1983). Acquisition of agoraphobia, mode of onset, and anxiety response patterns. *Behaviour Research and Therapy*, *19*, 439–447.
- Overmier, J. B. (1985). Toward a reanalysis of the causal structure of the learned helplessness syndrome. In F. R. Brush & J. B. Overmier (Eds.), *Affect, conditioning, and cognition: Essays on the determinants of behavior* (pp. 211–227). Hillsdale, NJ: Erlbaum.
- Overmier, J. B., & Lawry, J. A. (1979). Pavlovian conditioning and the mediation of behavior. In G. H. Bower (Ed.), *The psychology of learning and motivation* (Vol. 13, pp. 1–55). New York: Academic Press.
- Parker, G. (1983). *Parental overprotection: A risk factor in psychosocial development*. New York: Grune & Stratton.
- Pavlov, I. P. (1927). *Conditioned reflexes*. London: Oxford University Press.
- Pearce, J. M., Aydin, A., & Redhead, E. S. (1997). Configural analysis of summation in autoshaping. *Journal of Experimental Psychology: Animal Behavior Processes*, *23*, 84–94.
- Pearce, J. M., & Hall, G. (1980). A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological Review*, *87*, 532–552.
- Peterson, C., Maier, S. F., & Seligman, M. E. P. (1993). *Learned helplessness: A theory for the age of personal control*. New York: Oxford University Press.
- Plomin, R., DeFries, J., McClearn, G., & Rutter, M. (1997). *Behavioral genetics, third edition*. New York: Freeman.
- Powley, T. L. (1977). The ventromedial hypothalamic syndrome, satiety, and a cephalic phase hypothesis. *Psychological Review*, *84*, 89–126.
- Rachman, S. (1977). The conditioning theory of fear-acquisition: A critical examination. *Behaviour Research and Therapy*, *15*, 375–387.
- Rachman, S. (1990). *Fear and courage*. New York: Freeman.
- Rachman, S. (1991). Neo-conditioning and the classical theory of fear acquisition. *Clinical Psychological Review*, *11*, 155–173.
- Rachman, S., Lopatka, C., & Levitt, K. (1988). Experimental Analyses of panic: II. Panic patients. *Behaviour Research and Therapy*, *26*, 33–40.
- Rachman, S. J., & Maser, J. (1988). *Panic and cognition*. Hillsdale, NJ: Erlbaum.
- Ramsay, D. S., & Woods, S. C. (1997). Biological consequences of drug administration: Implications for acute and chronic tolerance. *Psychological Review*, *104*, 170–193.
- Rapee, R., Mattick, R., & Murrell, E. (1986). Cognitive mediation in the affective component of spontaneous panic attacks. *Journal of Behavior Therapy and Experimental Psychiatry*, *17*, 245–253.
- Razran, G. (1961). The observable unconscious and the inferable conscious in current Soviet psychophysiology: Interoceptive conditioning, semantic conditioning, and the orienting reflex. *Psychological Review*, *68*, 81–147.
- Reberg, D. (1972). Compound tests for excitation in early acquisition and after prolonged extinction of conditioned suppression. *Learning & Motivation*, *3*, 246–258.
- Reiss, S. (1987). Theoretical perspectives on the fear of anxiety. *Clinical Psychology Review*, *7*, 585–596.
- Reiss, S. (1991). Expectancy model of fear, anxiety, and panic. *Clinical Psychology Review*, *11*, 141–153.
- Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. *Behaviour Research and Therapy*, *24*, 1–8.
- Rescorla, R. A. (1974). Effect of inflation of the unconditioned stimulus value following conditioning. *Journal of Comparative and Physiological Psychology*, *86*, 101–106.
- Rescorla, R. A. (1985). Conditioned inhibition and facilitation. In R. R. Miller & N. E. Spear (Eds.), *Information processing in animals: Conditioned inhibition* (pp. 299–326). Hillsdale, NJ: Erlbaum.
- Rescorla, R. A. (1986). Extinction of facilitation. *Journal of Experimental Psychology: Animal Behavior Processes*, *12*, 16–24.
- Rescorla, R. A. (2000). Extinction can be enhanced by a concurrent excitor. *Journal of Experimental Psychology: Animal Behavior Processes*, *25*, 251–260.
- Rescorla, R. A., & Coldwell, S. E. (1995). Summation in autoshaping. *Animal Learning & Behavior*, *23*, 314–326.
- Rescorla, R. A., & Furrow, D. R. (1977). Stimulus similarity as a determinant of Pavlovian conditioning. *Journal of Experimental Psychology: Animal Behavior Processes*, *3*, 203–215.
- Rescorla, R. A., & Gillan, D. J. (1980). An analysis of the facilitative effect

- of similarity on second-order conditioning. *Journal of Experimental Psychology: Animal Behavior Processes*, 6, 339–351.
- Rescorla, R. A., & Holland, P. C. (1977). Associations in Pavlovian conditioned inhibition. *Learning & Motivation*, 8, 429–447.
- Rescorla, R. A., & Solomon, R. L. (1967). Two-process learning theory: Relationships between Pavlovian conditioning and instrumental learning. *Psychological Review*, 74, 151–182.
- Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy (Eds.), *Classical conditioning: II. Current research and theory* (pp. 64–99). New York: Appleton-Century-Crofts.
- Rosen, J. B., & Schulkin, J. (1998). From normal fear to pathological anxiety. *Psychological Review*, 105, 325–350.
- Salkovskis, P. M. (1988). Phenomenology, assessment, and the cognitive model of panic. In S. M. J. D. Rachman (Ed.), *Panic: Psychological perspectives* (pp. 111–136). Hillsdale, NJ: Erlbaum.
- Salkovskis, P. M., Clark, D. M., & Gelder, M. G. (1996). Cognition-behaviour links in the persistence of panic. *Behaviour Research & Therapy*, 34, 453–458.
- Sanderson, W., Rapee, R., & Barlow, D. (1989). The influence of an illusion of control on panic attacks induced via inhalation of 5.5% carbon dioxide-enriched air. *Archives of General Psychiatry*, 46, 157–162.
- Schmajuk, N. A., & Holland, P. C. (Eds.). (1998). *Occasion setting: Associative learning and cognition in animals*. Washington, DC: American Psychological Association.
- Schmidt, N. B., Lerew, D. R., & Jackson, R. J. (1997). The role of anxiety sensitivity in the pathogenesis of panic: Projective evaluation of spontaneous panic attacks during acute stress. *Journal of Abnormal Psychology*, 106, 355–364.
- Schmidt, N. B., Lerew, D. R., Jackson, R. J. (1999). Prospective evaluation of anxiety sensitivity in the pathogenesis of panic: Replication and extension. *Journal of Abnormal Psychology*, 108, 532–537.
- Schneewind, K. (1995). Impact of family processes on control beliefs. In A. Bandura (Ed.), *Self-efficacy in changing societies* (pp. 114–148). New York: Cambridge Press.
- Seligman, M. E. P. (1988). Competing theories of panic. In S. Rachman & J. D. Maser (Eds.), *Panic: Psychological perspectives* (pp. 321–329). Hillsdale, NJ: Erlbaum.
- Seligman, M. E. P., & Binik, Y. (1977). The safety signal hypothesis. In H. Davis & H. M. B. Hurwitz (Eds.), *Operant-Pavlovian interactions* (pp. 165–188). Hillsdale, NJ: Erlbaum.
- Seligman, M. E. P., Maier, S., & Solomon, R. (1971). Unpredictable and uncontrollable aversive events. In F. Brush (Ed.), *Aversive conditioning and learning* (pp. 347–400). New York: Academic Press.
- Sheehan, D. (1983). *The anxiety disease*. New York: Bantam Books.
- Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative and Physiological Psychology*, 89, 498–506.
- Siegel, S. (1988). State dependent learning and morphine tolerance. *Behavioral Neuroscience*, 102, 228–232.
- Siegel, S. (1989). Pharmacological conditioning and drug effects. In A. J. Goudie & M. W. Emmett-Oglesby (Eds.), *Psychoactive drugs: Tolerance and sensitization* (pp. 115–180). Clifton, NJ: Humana Press.
- Silva, F. J., Timberlake, W., & Koehler, T. L. (1996). A behavior systems approach to bidirectional excitatory serial conditioning. *Learning and Motivation*, 27, 130–150.
- Solomon, R. L., Kamin, L. J., & Wynne, L. C. (1953). Traumatic avoidance learning: The outcomes of several extinction procedures with dogs. *Journal of Abnormal and Social Psychology*, 48, 291–302.
- Soltysik, S. S. (1960). Studies on avoidance conditioning: III. Alimentary conditioned reflex model of the avoidance reflex. *Acta Biologica Experimentalis*, 20, 183–191.
- Soltysik, S. S., Wolfe, G. E., Nicholas, T., Wilson, W. J., & Garcia-Sanchez, L. (1983). Blocking of inhibitory conditioning within a serial conditioned stimulus-conditioned inhibitor compound: Maintenance of acquired behavior without an unconditioned stimulus. *Learning & Motivation*, 14, 1–29.
- Spence, J. T., & Spence, K. (1966). The motivational components of manifest anxiety: Drive and drive stimuli. In C. Spielberger (Ed.), *Anxiety and behavior* (pp. 291–326). New York: Academic Press.
- Stegen, K., De Bruyne, K., Rasschaert, W., Van de Woestijne, K., & Van den Bergh, O. (1999). Fear-relevant images as conditioned stimuli for somatic complaints, respiratory behavior, and reduced end-tidal pCO<sub>2</sub>. *Journal of Abnormal Psychology*, 108, 143–152.
- Swartzentruber, D. (1995). Modulatory mechanisms in Pavlovian conditioning. *Animal Learning & Behavior*, 23, 123–143.
- Taylor, S., & Rachman, S. (1994). Klein's suffocation theory of panic. *Archives of General Psychiatry*, 51, 505–506.
- Teasdale, J. (1988). Cognitive models and treatments for panic. A critical evaluation. In S. Rachman & J. D. Maser (Eds.), *Panic: Psychological perspectives* (pp. 189–203). Hillsdale, NJ: Erlbaum.
- Telch, M. J. (1995, July). *Singular and combined efficacy of in vivo exposure and CBT in the treatment of panic disorder with agoraphobia*. Paper presented at the World Congress of Behavioural and Cognitive Therapies, Copenhagen, Denmark.
- Telch, M. J., Brouillard, M., Telch, C. F., Agras, W. S., & Taylor, C. B. (1989). Role of cognitive appraisal in panic related avoidance. *Behaviour Research and Therapy*, 27, 373–383.
- Tellegen, A. (1985). Structure of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In A. H. Tuma & J. D. Maser (Eds.), *Anxiety and the anxiety disorders* (pp. 681–706). Hillsdale, NJ: Erlbaum.
- Testa, T. J. (1975). Effects of similarity of location and temporal intensity pattern of conditioned and unconditioned stimuli on the acquisition of conditioned suppression in rats. *Journal of Experimental Psychology: Animal Behavior Processes*, 1, 114–121.
- Thorn, G. R., Chosak, A., Baker, S. L., & Barlow, D. H. (1999). Psychological theories of panic disorder. In D. J. Nutt, J. C. Ballenger, & J.-P. Lepine (Eds.), *Panic disorder: Clinical diagnosis, management, and mechanisms* (pp. 93–108). London: Martin Dunitz.
- Thyer, B., & Himle, J. (1985). Temporal relationships between panic attack onset and phobic avoidance in agoraphobia. *Behaviour Research and Therapy*, 23, 607–608.
- Timberlake, W. (1994). Behavior systems, associationism, and Pavlovian conditioning. *Psychonomic Bulletin & Review*, 1, 405–420.
- Timberlake, W., & Grant, D. L. (1975). Auto-shaping in rats to the presentation of another rat predicting food. *Science*, 190, 690–692.
- Timberlake, W., & Silva, K. M. (1995). Appetitive behavior in ethology, psychology, and behavioral systems. In N. S. Thompson (Ed.), *Perspectives in ethology* (Vol. 11, pp. 211–253). New York: Plenum.
- Timberlake, W., Wahl, G., & King, D. (1982). Stimulus and response contingencies in the misbehavior of rats. *Journal of Experimental Psychology: Animal Behavior Processes*, 8, 62–85.
- Tolman, E. C. (1932). *Purposive behavior in animals and men*. New York: Century.
- Trapold, M. A., & Overmier, J. B. (1972). The second learning process in instrumental learning. In A. H. Black & W. F. Prokasy (Eds.), *Classical conditioning. II: Current research and theory* (pp. 427–452). New York: Appleton-Century-Crofts.
- Tuma, A. H., & Maser, J. D. (Eds.). (1985). *Anxiety and the anxiety disorders*. Hillsdale, NJ: Erlbaum.
- Turkat, I. (1982). An investigation of parental modeling in the etiology of diabetic illness behavior. *Behaviour Research and Therapy*, 20, 547–552.
- Tweed, D. L., Schoenbach, V. J., George, L. K., & Blazer, D. G. (1989).

- The effects of childhood parental death and divorce on six-month history of anxiety disorders. *British Journal of Psychiatry*, 154, 823–828.
- Uhde, T., Boulenger, J., Roy-Byrne, P., Geraci, M., Vittone, B., & Post, R. (1985). Longitudinal course of panic disorder: Clinical and biological considerations. *Progressive-Neuro-psychopharmacology & Biological Psychiatry*, 9, 39–51.
- Van den Hout, M. A. (1988). The explanation of experimental panic. In S. Rachman & J. D. Maser (Eds.), *Panic: Psychological perspectives*. Hillsdale, NJ: Erlbaum.
- Van Houten, R., O'Leary, K. D., & Weiss, S. J. (1970). Summation of conditioned suppression. *Journal of the Experimental Analysis of Behavior*, 13, 75–81.
- VanDercar, D. H., & Schneiderman, N. (1967). Interstimulus interval functions in different response systems during classical discrimination conditioning of rabbits. *Psychonomic Science*, 9, 9–10.
- Wagner, A. R. (1969). Stimulus selection and a modified continuity theory. In G. H. Bower & J. T. Spence (Eds.), *The psychology of learning and motivation* (Vol. 36, pp. 1–41). New York: Academic Press.
- Wagner, A. R. (1976). Priming in STM: An information-processing mechanism for self-generated or retrieval-generated depression in performance. In T. R. Tighe & R. N. Leaton (Eds.), *Habituation: Perspectives from child development, animal behavior, and neurophysiology* (pp. 95–128). Hillsdale, NJ: Erlbaum.
- Wagner, A. R. (1981). SOP: A model of automatic memory processing in animal behavior. In N. E. Spear & R. R. Miller (Eds.), *Information processing in animals: Memory mechanisms* (pp. 5–47). Hillsdale, NJ: Erlbaum.
- Wagner, A. R., & Brandon, S. E. (1989). Evolution of a structured connectionist model of Pavlovian conditioning (AESOP). In S. B. Klein & R. R. Mowrer (Eds.), *Contemporary learning theories: Pavlovian conditioning and the status of traditional learning theory* (pp. 149–189). Hillsdale, NJ: Erlbaum.
- Watson, D., & Clark, L. A. (1984). Negative affectivity: The disposition to experience negative emotional states. *Psychological Bulletin*, 96, 465–490.
- Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Child Psychology*, 3, 1–14.
- Weiss, J. (1971). Effects of coping behavior in different warning-signal conditions on stress pathology in rats. *Journal of Comparative and Physiological Psychology*, 77, 1–13.
- Weiss, S. J., & Emurian, H. H. (1970). Stimulus control during the summation of conditioned suppression. *Journal of Experimental Psychology*, 85, 204–209.
- White, T. L., & Depue, R. A. (1999). Differential association of traits of fear and anxiety with norepinephrine- and dark-induced pupil reactivity. *Journal of Personality and Social Psychology*, 77(4), 863–877.
- Whitehead, W. W., Bush, C., Heller, B., & Costa, P. (1986). Social learning influences of menstrual symptoms and illness behavior. *Health Psychology*, 5, 13–23.
- Whitehead, W. W., Winget, C., Fedoravicius, A., Wooley, S., & Blackwell, B. (1982). Learned illness behavior in patients with irritable bowel syndrome and peptic ulcer. *Digestive Diseases and Science*, 27, 202–208.
- Williams, J., & Maier, S. (1977). Transituational immunization and therapy of learned helplessness in the rat. *Journal of Experimental Psychology: Animal Behavior Processes*, 3, 240–252.
- Williams, S. L., Kinney, P. H., Harap, S. T., & Liebmann, M. (1997). Thoughts of agoraphobic people during scary tasks. *Journal of Abnormal Psychology*, 106, 511–520.
- Wittchen, H. U., & Essau, C. A. (1991). The epidemiology of panic attacks, panic disorder and agoraphobia. In J. R. Walker, G. R. Norton, & C. A. Ross (Eds.), *Panic disorder and agoraphobia* (pp. 103–149). Monterey, CA: Brooks/Cole.
- Wolpe, J., & Rowan, V. C. (1988). Panic disorder: A product of classical conditioning. *Behaviour Research and Therapy*, 26, 441–450.
- Woods, S. C., & Strubbe, J. H. (1994). The psychobiology of meals. *Psychonomic Bulletin & Review*, 1, 141–155.
- Zinbarg, R. E., Barlow, D. H., Liebowitz, M., Street, L., Broadhead, E., Katon, W., Roy-Byrne, P., Lepine, J. P., Teherani, M., Richard, J., Brantley, P. J., & Kraemer, H. (1994). The DSM-IV field trial for mixed-anxiety depression. *The American Journal of Psychiatry*, 151, 1153–1162.
- Zinbarg, R., Brown, T., Barlow, D., & Rapee, R. (in press). Fear responses to hyperventilation and 5.5% carbon dioxide enriched air and anxiety sensitivity: A reanalysis of Rapee, Brown, Antony, & Barlow (1992). *Journal of Abnormal Psychology*.
- Zinbarg, R., & Mohlman, J. (1998). Individual differences in the acquisition of affectively valenced associations. *Journal of Personality and Social Psychology*, 74, 1024–1040.
- Zucker, D., Taylor, C. B., Brouillard, M., Ehlers, A., Margraf, J., Telch, M., Roth, W. T., & Agras, W. S. (1989). Cognitive aspects of panic attacks: Content, course, and relationship to laboratory stressors. *British Journal of Psychiatry*, 155, 86–91.

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