

1 THE NATURE OF STRESSORS

MONDAY MORNING

Can hardly get myself out of bed. It's just way too early. Why do they have classes at 8:30? It's inhuman. Well, I better move my butt. I've missed a couple of classes already and I'm pretty far behind, and sometimes I can't even figure out what the Prof is talking about. I borrowed some notes, but I might as well be reading hieroglyphics. I wish I had the time to go through the book, but between working at the restaurant at night and meeting with Jesse on weekends, there don't seem to be enough hours in the day. I can't put Jesse off any longer as I'm sensing annoyance because I'm never around. I really don't want to end up being dumped. Until I met Jesse I felt pretty alone, and didn't have much of a social group to hang with. Aw hell, I can't think about that now. I just remembered that the clock's ticking and those two essays and the class presentation are sitting on my head. I don't even know where to start. It almost seems as if my Profs are colluding against me. The exam schedule is nuts. My two toughest exams are on the same day, and then I've got six days to study for that no-brainer course that is easier than what we took in high school. I've also got to get home before the exams to see Dad. He didn't sound good last time I spoke to him and Mom. I really miss them, and I think they're not telling me everything about Dad's heart problems. I don't even know where to begin. I just want to stay in bed and cover my head.

There are certain topics that encourage opinions from everybody and their cousin, and on which people seem willing to make statements with absolute certainty regardless of their knowledge of the subject. It's unlikely you would overhear conversations regarding heavy topics in physics, such as quark-gluon-plasma or the space and time continuum. However, you might catch snippets of conversations about how to fix the ailing economy (opposite

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opinions all being dogmatically pushed), about how badly international affairs have been bungled by this or that political party, and about the stresses of modern life. Here, though, people often divide into two camps. There are those who view modern life as a grind with a variety of stressors appearing everywhere, exacerbated by work/school and unhelpful mothers and fathers as well as disloyal friends, and there are those who believe that stressors of modern life are vastly over-rated and that the daily challenges that people are said to experience are something of a fiction, or perhaps it's something that only others need to endure. In short, stress is something everybody talks about with the view that they have special insights into the topic.

I confess that this drives me nuts. I'm supposed to be an expert in a field in which everybody feels they also have remarkable expertise. On more than a single occasion one of my relatives (on the other side) has even offered advice as to what direction my research should be going and offered suggested readings (this relative, incidentally, is adamant that we only use 10% of our brain, something he learned from his Grade 2 teacher). The fact that these events bother me as they do also means that I'm not handling it well. It has clearly frustrated me, at least to the extent that I'm venting about it (and I don't even know you!). It seems that although I'm really good at giving advice about stress, I'm just not very good at dealing with my own distress.

Regardless of whether or not this confession has undermined my credibility, you ought to believe me when I say that stressful events are linked to a wide range of mental health problems, and are among the prime suspects in the provocation of several physical illnesses. For this reason, it's important for us to learn how to recognize and deal with stressful events that entangle us every day (have you noticed that it's a jungle out there?), and major life stressors that most of us will invariably encounter at some time or other.

Does the text in the box at the outset of this chapter sound at all familiar? And if it does, upon finding yourself in a similar situation would you do anything about it or would you just hope everything will get better, eventually? As indicated in the Preface, this book might not help you solve your specific problems. However, it will provide you with information about stress and coping processes, and insights into a constellation of psychosocial, experiential and developmental factors and how these relate to a wide variety of illnesses that have been associated with stressful events. You'll also learn about various aspects of our biological defense systems, and some of the psychological consequences of not keeping stressful events in check. In essence, the book's core goal is to give you a comprehensive and integrated understanding of stress processes and their relation to health. What I want to emphasize is not only that these various elements are all important facets of human psychology (and its interaction with other dimensions of the human condition; e.g., biological, social, economic), but also that stressful events can have consequences that you might never have considered. Beyond having immediate effects on your well-being, stressful experiences can also mark you for decades. In fact, the stressors you encounter, depending on when they occurred and how severe they were, can have intergenerational effects.

This chapter will introduce you to some basic definitions and concepts, with the goal of acquainting you with some of the key variables that influence or determine the impact of stressful events. This will entail:

- a description of what a stressor comprises, and that stressors come in various forms. These include challenges that are of a purely psychological nature, those that have direct physical effects, and those that cause a dysregulation of internal processes, but nonetheless act as stressors, even if we aren't consciously aware of them;
- analyses of the attributes of a stressor that result in it having greater or lesser effects. In this regard, we will discuss the contribution of the stressor's severity, controllability, predictability, uncertainty, ambiguity, and chronicity;
- how stressors are assessed in a laboratory context or in community samples, including analyses of those stressors that appear as nothing more than minor inconveniences, and stressors that represent major life events, as well as traumatic experiences that are endured.
- the individual factors that influence vulnerability to the effects of stressors as well as variables that imbue us with resilience so that we can overcome the potential adverse consequences of stressful experiences. To this end, we'll consider the individual and interactive influences of genetic, environmental, experience-related, personality variables, early experiences, and age-related factors on well-being.

SOME BASIC DEFINITIONS AND CONCEPTS

It's a good idea to begin by defining some key terms so that we're all on the same page. For starters, what do we mean when we use the terms 'stress' and 'stressor'? This sounds fairly mundane, doesn't it? Nevertheless, just humor me, and assume that differentiation of these terms might be useful. A 'stressor' is a stimulus or event that is *appraised* or perceived as being aversive and causes a 'stress response' that comprises a series of behavioral, emotional, and biological changes aimed at maintaining an organism's well-being. Among other things, these stress responses involve biological changes that occur so that energy resources are directed towards the places they are needed, and away from processes that are not essential at the moment (e.g., reproduction, eating, digestion). Simultaneously, multiple brain regions are activated to help us appraise and then deal with the stressful event.

So what exactly are these stressors? In fact, there is no easy definition of 'stressor', since appraisals of events may vary with contextual factors and change yet again over time, and they are also interpreted differently across individuals. In response to a similar definitional problem of pornography, US Supreme Court Justice Potter Stewart famously observed 'I can't define it, but I know it when I see it' (Jacobellis vs. Ohio, 1964). In much the same way, what constitutes a stressor may be highly subjective, and it needs to be acknowledged that individual differences that exist can be fairly pronounced. In effect, one person's poison is another person's meat.

There is enormous variability regarding the degree to which stressors can affect different people. Events or stimuli that are stressful to one individual might not be similarly appraised by a second individual. For example, jumping out of a plane (with a parachute, of course) might be exciting for some individuals, whereas it might be exceptionally distressing for others. Even if two individuals appraise a stressor similarly, they might display different emotional reactions. As well, even if their emotional reactions were the same, they might display different methods of coping with the stressor. Finally, the fact that individuals' appraisals, coping, and emotional responses are comparable does not mean that their biological responses will necessarily be the same, and hence different psychological outcomes (including pathologies) might evolve over

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TABLE 1.1 Factors that influence the stress response

Stressor type
Processive (neurogenic or psychogenic)
Systemic (immune insults)
Stressor characteristics
Controllability
Predictability
Ambiguity/ uncertainty
Chronicity
Intermittence
Organismic variables
Species
Strain
Sex
Age
Experiential variables
Previous stressor experiences (sensitization/desensitization)
Prenatal events
Early life events (maternal factors, trauma)
Attachment (bonding)
Personal characteristics
Self-esteem
Self-efficacy
Hardiness
Optimism
Neuroticism
Social characteristics
Social support and unsupportive interactions
Appraisal styles
Coping skills

time. These individual differences in stress responses might come about as a result of several factors, some of which are listed in Table 1.1. We'll go through each of these systematically, and revisit them in ensuing chapters, as they have important implications for the development of stressor-induced biological and pathological outcomes. Obviously, assessing the link between stressor encounters and the emergence of psychological or physical disturbances isn't easy, but the progress that has been made is significant and has resulted in the development of several effective strategies for preventing illness and treating pathology once it has emerged.

CHARACTERIZING STRESSORS

Even at this very early point you've learned something important about stressors. First, not all stressors have the same impact, and second, individuals differ remarkably with respect to how they appraise stressful events and how they respond to them. You've also learned that there are

multiple factors responsible for these individual differences. Some of these differences might be related to the stressor, whereas others might be related to characteristics of the individual and their varied experiences. We'll now move to a more detailed analysis concerning why we respond to certain stressors as we do, beginning with a discussion of their features.

TYPES OF STRESSORS

Stressors generally come in multiple flavors, and we'll start by distinguishing between these as they don't necessarily result in identical outcomes. A stressor that involves information processing (e.g., asking ourselves 'Is that dog drooling and does that glare and posture mean it's dangerous?', or 'Does this guy with the mask covering his face seem like a mugger?') is referred to as a *processive* stressor. Understanding the threat (stressor) involves several complex cognitive processes that engage numerous brain regions. These include neural circuits responsible for executive functioning that involves appraisal and decision making (e.g., frontal cortex; anterior cingulate cortex), memory processes (e.g., hippocampus and several cortical brain regions), and those involved in anxiety and/or fear responses (e.g., prefrontal cortex, amygdala, and hippocampus). Broadly speaking, processive stressors can be of a purely psychological (psychogenic) nature, or of a physical nature (termed 'neurogenic' stressors), such as those associated with certain illnesses or painful stimuli (e.g., burns). Not surprisingly, psychogenic and neurogenic stressors may elicit similar outcomes in some respects, but as we will see, they can also have several very different consequences.

Another type of challenge, referred to as a 'systemic' stressor, does not involve the same type of information processing, as it entails an insult to our biological systems. Systemic challenges include, but are not limited to, marked changes of glucose concentrations in our blood (as occur in diabetes), the presence of inflammation or the production of certain proteins evoked by inflammation (as occurs with heart problems), and numerous other biological changes. In these instances, we might not be processing the information with the question 'Is this a threat to my well-being?', as we do when confronted by some processive stressors, but our body might be interpreting these challenges as threats, and sending messages to the brain so that certain actions are taken to meet the immediate needs. For instance, the pain associated with a broken bone (a processive stressor) might make us more cautious and protective of the injured area, and thus will increase the likelihood that it will heal without being perturbed. Likewise, the fatigue and achiness associated with influenza (a systemic stressor) pushes us into bed so that we can rest and thus recuperate more readily. The behavioral changes that occur in response to processive or systemic insults involve the integration of several biological and cognitive systems. It seems that multidirectional communication occurs between various facets of our brain, peripheral nervous system, hormonal systems and the immune system so that coordinated responses occur.

PSYCHOGENIC STRESSORS

Different types of stressors (psychogenic vs neurogenic vs systemic) do not necessarily lead to identical outcomes. For example, in rodents, a purely psychogenic stressor, such as being exposed to predator odors, gives rise to neurochemical changes within the brain (e.g., the release

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of chemicals from brain neurons) that are different in several respects from those elicited by a neurogenic stressor (a painful stimulus). In fact, even among psychogenic stressors, marked differences occur as a function of the specific stressor encountered. Those psychological stressors that reflect innate challenges (e.g., predator odors) instigate neurobiological changes that are distinguishable from those elicited by conditioned or learned stressors, such as cues that had previously been associated with a neurogenic stressor. In light of the specific neural circuits activated by these stressful events, it might be expected that they would also be associated with the emergence of different behavioral outputs or even pathophysiological processes, and might require different strategies to attenuate the negative reactions that might occur.

At one time scientists had thought that we had a 'stress center' in our brain, just as it was mistakenly thought that there was a 'pleasure center'. The neural circuitry associated with stressors is much more complex; we do not have 'a' stress system, but instead there appear to be multiple pathways that respond preferentially to different types of stressors (Merali et al., 2004). When we examine these systems from a perspective relevant to humans, their importance takes on more tangible meaning and significance. For example, some stress responses reflect outcomes associated with something that has already happened (the loss of a loved one, a business failure, a hurricane, or being ostracized by your friends), and not surprisingly, these stressors might be associated with different psychological outcomes.

One can intuitively appreciate that certain conditions, particularly those that involve interpersonal events (e.g., the death of a loved one), might favor certain types of responses and lead to depression, but these processes might be distinct from those involving adverse achievement-related events (work-related stress), although these too can favor depressive affect (Mazure et al., 2000). Moreover, gender differences appear to exist with respect to the types of stressors that lead to pathological outcomes. In this regard, it has been suggested that psychosocial stressors may have more dramatic effects in females than in males, whereas those related to job strain/competition may have more profound effects in males (Kendler et al., 2001; Mazure et al., 2000). Other stress responses, especially those that are of an anticipatory nature (e.g., imminent surgery, anticipation of an upcoming exam or public speaking, taking a plane flight if you have a plane phobia, an imminent tax audit, the chance of seeing the bully in the schoolyard), are likely to be accompanied by anxiety (Harkness, 2008). Still other types of stressors, notably those that are ambiguous in nature (e.g., the 'possibility' of a terrorist attack, or a pilot announcing that 'we have to return to the airport' without further explanation) might be accompanied by disorganized cognitions while the situation plays out.

Some stressors involve an evaluative component (e.g., public speaking or asking questions in class, activities in front of an audience, a job interview), a social component (e.g., a fight with your best friend), one that involves a degree of embarrassment (e.g., certain visits to the doctor if you're a 50+ year-old male), and some that instigate particularly aversive emotional responses (e.g., shame, humiliation). Some psychological stressors may have profound effects, but their actions are fairly transient, whereas others may be remarkably powerful, so much so that they can have life-long effects (Robinaugh & McNally, 2010).

NEUROGENIC STRESSORS

Physical stressors can be brief (stubbing your toe), moderate in duration (e.g., a slight burn, a back strain, or a slightly sprained ankle), they can be persistent (e.g., rheumatoid

arthritis, sustained or recurrent migraine headaches), or they can be both persistent and severe (severe burns, injuries sustained from accidents, or the pain associated with certain diseases such as cancer). There's little question that the more intense stressors call upon an incredible portion of a person's psychological and physiological resources. As well, these neurogenic stressors typically don't appear in isolation from psychogenic stressors. Whether these entail financial difficulties brought about owing to physical illness, repeated trips to doctors or hospitals, having to rely on others when one would prefer not to, or the anticipation that the distress will continue, it seems that complex multidimensional processes are often at work. As a result, diverse psychological processes might be necessary to cope with these multipronged insults. Often, our abilities may simply be insufficient to deal with events, and external mechanisms that enable us to withstand these challenges (e.g., our social support resources) may become essential.

SYSTEMIC STRESSORS

Psychogenic and neurogenic stressors are all in some sense tangible (i.e., we can see or feel them), but we can encounter stressors that we might not be conscious of, and hence we might not be aware that we are experiencing any strain. Thus, we typically wouldn't think of them as stressors. Nevertheless, it has been suggested that challenges, such as immune activation, should be considered as stressors given that they elicit a cascade of biological changes that in many ways are akin to those associated with psychogenic and neurogenic insults. Among other things, systemic stressors may affect our neuroendocrine functioning, our brain neurochemical processes, and elicit several depression-like behavioral changes (Anisman & Merali, 1999). However, because we might be unaware that something is happening in our body that might adversely affect us (certainly this is the case soon after infection), there is seemingly no opportunity to take steps that might facilitate coping with the challenge. From this perspective, systemic stressors reflect silent, insidious attackers that can have negative repercussions for well-being beyond their potential direct effects. We'll be dealing with this in considerable detail later (see Chapter 5), but for the moment just keep in mind that stressors aren't always obvious, but may nevertheless have pernicious repercussions.

STRESSOR CHARACTERISTICS

Every stressor that we encounter may have unique elements about it and thus may have very different repercussions. By example, let's consider one broad stressor category, that of being ill, and examine the various elements that make up this type of challenge. An illness can be a brief one (a bad case of the flu, or appendicitis requiring surgery), or one that is less intense, but can still wreak havoc on a person's general well-being owing to the fact that the condition lasts for some time, and there are some illnesses that are chronic and/or progressive (gets worse over time). Some illnesses might allow individuals to function more or less normally despite the symptoms being exceptionally disturbing (e.g., tinnitus), whereas in other instances (e.g., arthritis, lupus erythematosus, Parkinson's disease) the features of the illness might interfere with multiple aspects of daily life. There are also illnesses, such as Type 2 diabetes, that necessitate changes in lifestyle, and can have drastic

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long-term implications for further diseases, but early on might have few discernible negative effects. Worst of all, for the patient and the family members, are disturbances that rob you of yourself (Alzheimer's Disease), illnesses that might or might not lead to death (cancer, heart disease, HIV), or those that are physically incapacitating (e.g., ALS, paralysis). Some illnesses 'just show up' without any apparent cause, whereas others occur as a result of traumatic events (a head injury, paralysis) stemming from one's own behaviors (engaging in certain sports), those of others (drunk or incompetent drivers), or acts of nature (flood, hurricane, earthquake). In each instance the illness trajectory may vary over months and years, and the needs of the affected individuals might differ accordingly. The psychological aspects related to the illness, the attributions regarding the cause of the illness, as well as the extent to which the illness *allows* the engagement of effective coping, differs with the individual's condition.

SEVERITY

Because each stressor we encounter might have numerous unique characteristics, it is difficult to compare whether one stressor is more severe than another. This is made still more difficult as our perception of stressors may be influenced by the context in which they occur and may vary over time. Furthermore, there are stressors that simply can't be compared to one another in terms of their relative severity (e.g., the death of a child vs dealing with a severe incapacitating illness) as they are on entirely different dimensions, and are often so severe that comparisons become meaningless. Nevertheless, most people would agree that certain stressors are more profound than others (e.g., the loss of a loved one vs getting a parking ticket), and thus most of us could guess that some stressors are apt to have greater pathophysiological consequences than others.

CONTROLLABILITY

The notion that control over one's destiny is important in determining psychological health has been around for a long time. The classic studies in the 1950s by Brady (1958) indicated that a monkey that was responsible for making certain responses in order to avoid an aversive stimulus developed ulcers more readily than a monkey that received an identical amount of unpleasant stimulation over which it had no control. Termed the *Executive Monkey Studies*, this research suggested that having control (and responsibility) was a daunting stressor that could lead to stress-related pathology. These studies had obvious implications for business leaders and they became an important talking point for psychologists working with executives in large organizations, essentially telling them that being an executive has its hardships. In essence, being in control also means being responsible, and with this comes considerable psychological strain that could lead to pathological outcomes. This view held considerable intuitive appeal, but later studies contradicted these findings, and it is now commonly accepted that having control over both stressor occurrence and its termination is psychologically and physically advantageous.

NASTY LITTLE CREATURES

For some time it was thought that ulcers arose as a result of stressful experiences. However, it seems that the bacterium *Helicobacter pylori* is responsible for ulcers (Marshall & Warren, 1984), and in recent scientific discussions the contribution of stressful experiences has taken a back seat. Nevertheless, it does appear that stressors may affect gastrointestinal ulcers, and that stressful events and *Helicobacter pylori* may act synergistically to promote ulceration.

For their work in identifying *Helicobacter pylori* as the main culprit responsible for peptic ulcer disease, Marshall and Warren received the Nobel Prize in Physiology or Medicine (2005). To make the point concerning their hypothesis, which most scientists had dismissed, Marshall drank a brew of *Helicobacter pylori* to demonstrate that this bacterium would, indeed, cause ulcers. It would, after all, have been tough to get experimental participants for this study or even to get the study through an ethics review panel.

Experiments conducted almost a decade after the Brady studies, using a similar paradigm, documented one of the best-known phenomena in stress research. In particular, these studies demonstrated a phenomenon known as the ‘learned helplessness’ effect, whereby stressors over which the animal had no control provoked marked behavioral impairments in animals. It was shown that animals exposed to an escapable stressor (a shock to their feet), or that had not been stressed at all, subsequently displayed proficient performance in a test where they were required to escape from a stressor. However, animals that had been exposed to an uncontrollable stressor (a footshock that they could not escape) later exhibited profound behavioral impairments in an escape test where an active response would have terminated the footshock stressor. In these studies, the animal in the ‘uncontrollable’ stressor condition received the stressor at exactly the same time and for the same duration as the animal in the escapable shock condition. However, unlike the animals that were exposed to an escapable stressor, those in the uncontrollable condition were unable to control stressor termination. Instead, stressor offset occurred whenever animals in the escape condition made an appropriate response. Thus, animals received the same duration of the stressor, but differed with respect to the psychological dimension of having control over the stressor termination (this is referred to as a ‘yoked’ paradigm). As only animals in the uncontrollable condition later showed impaired performance, it was concluded that it was not the stressor itself that was responsible for the behavioral impairments. Rather, it was the animal’s inability to exert control over stressor termination that was crucial in determining whether or not the adverse effects of the treatment would become apparent (Seligman & Maier, 1967).

In describing the results of these experiments, it was indicated that those animals who confronted an uncontrollable stressor subsequently did not make overt attempts to avoid or escape the footshock, even though they could now escape if they made a simple response of moving from one side of the test chamber to the other. Instead, they seemed to passively accept the stressor. Indeed, when an animal made an occasional escape response, this was

not predictive of further escape attempts. The investigators suggested that these animals had learned to become helpless. Cognitive processes were thought to occur whereby they *learned* that their responses were unrelated to outcomes ('nothing I do matters'), and as they had no control over the situation they stopped trying to escape. Indeed, if animals were initially trained to make an appropriate response and then exposed to the uncontrollable situation, they did not display behavioral disturbances when subsequently exposed to a controllable stressor. These animals, having first learned that they control their destiny, were essentially immunized against the effects of the uncontrollable stressor.

The behavioral disturbances elicited by uncontrollable stressors have been seen across a variety of species, but in rodents it is typically seen only in certain situations. It seems that when the stressor is administered to rodents, the high degree of reactivity that is elicited favors an appropriate escape response being emitted (i.e., running from one chamber in which the stressor is administered to an adjacent 'safe' chamber) and thus potential behavioral deficits are obfuscated. Eventually, it was observed that if the response required of the animal to escape entailed a motor response that was relatively difficult to accomplish or where an active response had to be maintained for several seconds before successful escape was possible, then performance deficits could be elicited. Such findings gave rise to the suggestion that performance disruption was not a reflection of a cognitive disturbance, such as helplessness, but instead stemmed from brain biochemical changes that hindered the rodents' ability to maintain prolonged or complex active responses (Anisman et al., 1978; Glazer & Weiss, 1976).

Failure experiences in humans may have effects vaguely reminiscent of those associated with uncontrollable stressors in animals. For instance, university students exposed to unsolvable problems subsequently displayed impaired performance in a problem-solving task, as did depressed students who had not been exposed to the unsolvable task. Although these outcomes have often been attributed to learned helplessness, there are other explanations that might have little to do with helplessness. For instance, there might be a mismatch between the participant's expectancy regarding their performance, and their failure to meet this expectancy might have induced frustration that was responsible for the subsequent impaired performance. These differing positions notwithstanding, since these early studies, much has been made of the importance of stressor controllability in determining later psychological and physical disturbances.

STRESSOR PREDICTABILITY, UNCERTAINTY, AMBIGUITY, AND BLACK SWANS

The impact of stressors on psychological and physical well-being is influenced by their predictability, uncertainty, and ambiguity. There are occasions on which the occurrence of stressors is very predictable, but there are also those where stressors are entirely unpredictable, and our responses in these situations are likely to be quite different. Who among us would have predicted 9/11, or that an earthquake or tsunami would hit a particular region, causing the deaths of thousands upon thousands? In contrast, tax time is a stressor, particularly for accountants or those who owe the government a lot of money, and its occurrence is predictable (the behavior of governments may not always be predictable, but you can count on them being systematic when it comes to taxes).

Uncertainty is related to unpredictability, but they can be distinguished from one another. We all will die eventually (that is a certainty), but when this will happen is often unpredictable. Essentially, when we talk about predictability, it is usually in the context of events that will happen; it is simply a matter of knowing when they might happen, whether there will be a warning of their occurrence, and on what schedule they might occur (e.g., a single event, repeated events, events that occur intermittently). Uncertainty, in contrast, deals with events that might or might not occur (e.g., it is uncertain whether this new flu virus will end up as a pandemic). When there is uncertainty about the occurrence of a stressor, individuals may take on a cavalier attitude that essentially comprises ‘whatever happens, happens’. Others, however, seem to have great difficulty dealing with uncertain situations, and for these individuals their stress reactions could potentially be pathogenic.

Another similar construct is that of ambiguity. We say that a situation is ambiguous when the stimulus context does not provide sufficient information, or provides multiple but inconsistent bits of information, so that it becomes difficult to determine whether and when the event might occur. By example, ambiguity exists when one has a set of symptoms, but they do not form a coherent pattern that allows for a firm diagnosis. Likewise, when government agencies are trying to determine the imminence of a terrorist attack they might encounter a set of stimuli that suggests that something is up (e.g., increased internet chatter, certain individuals or groups have suddenly dropped off the grid), but otherwise things seem much the same as they usually are. The situation here is thus an ambiguous one.

An old proverb has it that ‘*mann tracht unt got lacht*’, literally translated as ‘man thinks (plans) and god laughs’. On a daily basis, most individuals typically behave as if the events in their lives are predictable and that they can reasonably anticipate what the future holds for them, and that they even have some control over their lives. Even though most of us know that this sense of control is an illusion, many of us operate as if we have some say regarding what happens to us: we have expectations for the future, and planning is viewed as necessary given our apparent need for order and predictability. Thus, it shouldn’t be surprising that adverse events that are unpredictable are generally viewed as being more unpleasant than predictable events (Baker & Stephenson, 2000), and are more likely to be associated with disturbed brain neuronal functioning, the excessive activation of some stress hormones, and altered immune functioning (Pitman et al., 1995).

So, what is it about the unpredictability and uncertainty regarding bad events that makes them so aversive? What differentiates the aversiveness of predictable vs unpredictable events is, to a significant extent, related to the anticipatory period. When we know that an event will happen at a particular time, there may be great anxiety about the impending event, and waiting itself, coupled with the probability of events occurring during specified periods, may be stressful (Osuna, 1985). Yet knowing that the event will or is about to happen gives us the opportunity to prepare or adjust our behaviors and expectancies. Unpredictable events, however, don’t allow us to prepare in a similar manner, and we may be on edge for extended periods of time. Most people are familiar with the first part of Franklin D. Roosevelt’s statement in relation to the Great Depression, but less familiar with the second part; ‘the only thing we have to fear is fear itself – nameless, unreasoning, unjustified terror which paralyzes needed efforts to convert retreat into advance’. This very well describes the response to unpredictable, ambiguous, but potentially very stressful situations: irrational, inappropriate

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and immobilizing behaviors that reflect our inability to appraise and cope with situations, so that our ability to strategize becomes entirely ineffective.

As with unpredictability, in most situations uncertainty is also seen as being more aversive than is certainty. However, there are instances where this isn't the case. For instance, some people who are at risk for a genetic disorder, such as Huntington's Disease, want to know whether they carry the gene for this illness, and hence will invariably be affected. These individuals don't want to live in suspense, essentially with a sword hanging over their heads, and choose to know whether or not they carry the gene. Others, however, would rather not know and appear to be able to vanquish their thoughts so that their daily routine is not affected. It seems that individuals differ in their *intolerance for uncertainty*. The level of uncertainty that can be tolerated is a trait that individuals bring into situations that involve an ambiguous or uncertain component (Rosen et al., 2007). High intolerance for uncertainty has been found to exacerbate the anxiety associated with daily stressors, and increased intolerance for uncertainty, as well as the desire to reduce uncertainty, was found to predict increased information seeking (Rosen et al., 2007), which could potentially increase the adverse effects of stressors. Unpredictable events obviously have the potential for turning our lives upside down. The death of loved ones, sudden illness, catastrophic natural disasters, are all events that we know are possibilities, but we really don't expect them to happen to us. Yet the probability of dying of heart disease is about 34% and that of cancer is about 16–17% (although survival rates have been increasing for several cancers), Type II diabetes occurs in about 3.5% of individuals and is climbing, autoimmune disorders occur at 3.1%, and then there's kidney, pancreatic or liver disease, and serious automobile accidents that lead to severe disability or death at a rate of about 1.7% each year. There is also a chance of being hit by lightning or a brick falling off a building and onto your head (events that are admittedly rare), or the possibility of being in a plane crash (although for the people on the plane or the person hit by the brick, such probabilities simply don't count). The point of all of this is simple. We might not know how we'll fare in the future, but given the number of bad things that can happen to us, and the additive probabilities of these events, we can pretty much count on not getting away untouched. We don't know whether, how, or when we'll encounter these nightmares, but it's almost a certainty that we'll encounter some bad dreams.

Uncertainty and ambiguity are frequent in our experiences and they are known to promote anxiety. For example, consider what your own reactions to symptoms of an illness might be (e.g., 'Is this lump I feel something I should worry about?' 'This feeling in my chest seems like indigestion, but it might also be a heart attack. What do I do now?'). This, in turn, might lead to further uncertainties pertaining to the illness and its prognosis ('What are the odds that the treatment will work?'), and the availability of a competent and experienced medical practitioner ('Does this doctor have the experience and skill that will be needed?').

From what has been said to this point, it's fairly clear that unpredictability, uncertainty and ambiguity can be exceedingly stressful. But there is also a different spin that has been applied regarding the role uncertainty might play in the context of serious illnesses (Mishel, 1999). From this perspective uncertainty involves two distinct appraisal processes, namely *inference* and *illusion*. If uncertainty exists, then individuals can reconstrue a largely negative situation (inference) to extract a glimmer of hope despite the odds (illusion). Because uncertain situations are vague and changeable, in the context of events that are spiraling

downward (e.g., when all treatment efforts to stall the progress of a cancer have failed), individuals can capitalize on uncertainty so that their appraisals take on a positive hue, no matter how limited this might be. Uncertainty, essentially, allows a person to expect the worst, but still hope for the best.

DUMBASS GAMBLERS

It seems that for many of us, there is a need to maintain a semblance of control over our own destinies. Even when a situation is entirely unpredictable and individuals have absolutely no control over the outcome, those who are self-assured are more likely to choose to exercise their own judgment in determining that outcome, despite this semblance of control being illusory. The fact is that when situations are unpredictable and where outcomes are entirely out of our control, our participation in decision making (e.g., how to treat an illness) is not that far removed from that of engaging in a game of chance (gambling).

We see this desire or need for control across various domains. For example, when given the opportunity to play a game of chance (say roulette) where individuals either have absolutely no control over outcomes, or are allowed to ‘pay’ a premium to press a button to stop the wheel (in this instance they have a semblance of control insofar as the wheel will stop, but they have no control with respect to where the ball lands), they will more often pick the latter. Similarly, when people buy lottery tickets, they will often prefer to choose their own numbers rather than have a series of numbers generated through a computer (as if they have a divine connection with the odds maker in the sky, which the computer, of course, doesn’t). It also seems that some people feel that they (or others) are endowed with a trait characteristic of being lucky (‘I’m a lucky person’, as opposed to ‘This was my lucky day’), and so might get involved in events that involve high risk (e.g., gambling), which they believe doesn’t apply to them since they are, after all, lucky. If that isn’t dopey enough, there are others who develop an ‘illusion of control by proxy’ wherein they find a ‘lucky person’ to buy their lottery tickets for them (Wohl & Enzle, 2009). One wonders whether stock market players, at least to some extent, are affected by some of these characteristics.

I was recently introduced to the ‘Black Swan theory’ advanced by Taleb (2007) to explain irrational behaviors that people often endorse in the context of making decisions. The implications of this perspective for the stress field are enormous, and so I figured it should be brought up fairly early in this volume. Essentially, from Taleb’s position there are events that occur very infrequently and are essentially unpredictable, have a major impact on the individual (or society, or the economy), and often have people rationalizing, in hindsight, that the event might have been predictable if only the right data had been available. For instance, could we have predicted 9/11 and the ensuing stock market debacle, or in Japan the earthquake and resulting tsunami and the potential for a nuclear meltdown? Probably not, but it can be argued that even though any single event is an outlier (a black swan), there are so many possible things that could go wrong, one or

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more of these will eventually occur. Black swans don't simply refer to 'major' events like a 9/11, a crash in the housing market, or the possibility of another war breaking out somewhere (the latter aren't really black swans, but more like albino squirrels, which I've seen several times). There are individual tragedies that can also occur, such as being diagnosed with a rare disease, sitting at lunch and having part of a building suddenly collapse with you as collateral damage, or a piece of space junk reentering the atmosphere and taking direct aim at your house. We can't know what will befall us, as there are simply too many 'unknown unknowns'; so many that the odds of dodging all of them are slight. However, they can and do occur, and their ramifications can be enormous.

THE BRAIN'S RESPONSE TO KNOWING AND THE UNKNOWNABLE

Given that we often find ourselves in situations where the information available is ambiguous and making decisions entails a degree of risk (e.g., the behavior of stock markets), there has been increasing interest in determining which brain regions might be engaged for decision making under such conditions. For instance, which brain regions are activated under conditions that involve risk (i.e., where the outcome probabilities are known), ambiguity (a situation where there is a lack *information* about outcome probabilities), or ignorance (a condition wherein the outcomes were completely unknown and even unknowable)? It was observed that relative to the risk situation, ambiguous information provoked a greater activation of certain brain regions (inferior frontal gyrus and posterior parietal cortex), and this same outcome was apparent when participants were presented with non-useful information (the ignorance context) (Bach et al., 2009). Perhaps these regions are activated in an effort to make sense of this situation. It might simply be the case that the brain doesn't like uncertainty and tries to set things in order. It has been suggested that the individual differences observed in these situations might be related to differences in intolerance for uncertainty, and it is important to consider this variable in assessing neural systems that are involved in the decision-making process.

CHRONICITY

There are stressors that, unfortunately, must be endured on a chronic basis: these can be psychosocial or family-related issues, financial impositions, health problems, discrimination or stigma, or a combination of different factors. When stressors are chronic and occur on a predictable basis, we are often able to adapt and perhaps even take charge of our situation. Studies of animals suggested that the neurochemical changes that occur in response to acute stressors will diminish with chronic predictable, invariable stressor experiences (stressors that are chronic but don't change are termed 'homotypic' stressors). Sometimes, however, the stressors we experience might be chronic, intermittent, unpredictable, ambiguous and uncontrollable, and vary across days (the latter are referred to as 'heterotypic' stressors), making it difficult to establish adequate coping methods, or even to take preparatory steps

to enable effective coping. Under such conditions, the usual adaptation that occurs in response to homotypic stressors might be less likely to develop (Anisman et al., 2008). Thus persistent stressors, such as acting as a caretaker (e.g., for a parent with Alzheimer's or a child with exceptional needs), or dealing with chronic illness or financial problems, each of which involves multiple challenges that might change from day-to-day, might strain our ability to cope effectively and lead to psychological or physical disturbances.

Chronic unpredictable stressors needn't be severe in order to elicit pathophysiological outcomes. Several studies in animals showed that a regimen that comprised a series of mild uncontrollable stressors was effective in this regard (Willner et al., 1992), although this outcome was not universally observed, tending to appear more readily with somewhat stronger stressors. The chronic mild stress model, perhaps because it has a degree of intuitive appeal (i.e., it 'sounds' right), has received wide recognition and attention, but it seems the effects of stressor treatments depend on a number of other factors, such as the individual's previous stressor experiences, the way stressors are appraised, and the coping methods used.

ALLOSTATIC OVERLOAD

In recent years, the concepts of stasis and allostatic overload have evolved to explain the impact of severe or chronic stressors. Under normal conditions biological changes occur to meet the ebb and flow of environmental demands, thus maintaining stability within the organism. This essentially describes homeostasis. In response to strong or sudden stressful challenges, and to severe chronic events, greater and more rapid biological changes are instigated to restore and maintain stability, and we refer to this as allostasis (Sterling & Eyer, 1988). As adaptable as humans and animals might be, when a strain on the system is excessive, our adaptive biological systems might eventually become overly taxed, resulting in *allostatic overload*. Under these conditions the organism may become ill or more vulnerable to the negative impact of new stressors that might be encountered (McEwen, 2000; Schulkin, 2003).

In addition, allostatic overload may occur through a more insidious process. In particular, 'Type 2' allostatic overload occurs as a result of social conflict or other forms of social disturbances. These threats do not necessarily elicit strong coping responses as do severe or traumatic stressors, but over time their toll might become enormous, unless measures are taken to modify the social structure that imposes itself adversely on the individual (McEwen & Wingfield, 2003). This is especially the case as the social challenges that affect us (e.g., in the workplace) might be insidious, essentially creeping up on us without our conscious awareness.

MEASURING STRESSORS

We all seem to know what we mean by a stressor, but for experimental purposes we need to be able to distinguish between different types of stressors and how intense these stressors are perceived to be. Later, we'll be discussing individual differences in how stressors are appraised and perceived, but for the moment we'll examine how stressor experiences are measured, and a few of the limitations of these procedures.

MAJOR LIFE EVENTS

Stressful events are known to promote psychological disturbances, and severe stressors are more likely to do so than are relatively mild stressors. In an effort to analyze the impact of stressors, several variants of major life events scales have been developed, which have been used to predict the relations between stressors and the occurrence of illness or disturbed quality of life. One approach was based on the notion that a stressor ought to be considered in terms of the social adjustment that is required to deal with it (e.g., the Social Readjustment Scale; Holmes & Rahe, 1967). Others simply focus on major life stressors that had been encountered over a set period of time (e.g., six months or one year), basing their severity on responses from a normative group of participants (Paykel et al., 1971). Other questionnaires are available that focus on particular types of events, such as traumatic experiences that might have occurred at some specific time over the course of the life span (e.g., the Traumatic Life Events Questionnaire; Kubany et al., 2000), or particular stress-related pathological conditions, such as posttraumatic stress disorder (PTSD; Weiss & Marmar, 1997). There are also scales that deal with specific types of events ranging from psychological abuse to breast cancer and other types of challenges.

These scales share certain essential attributes (they do, after all, give us an idea of what an individual has experienced), but they also share several deficiencies. First, an evaluation of the distress experienced by an individual over some set period of time is often based on scaled scores. For instance, in the Social Readjustment Scale, 'death of a child' receives a score of 100, 'trouble with in-laws' gets a score of 29, 'changes in work hours' a score of 20, 'revisions of personal habits' 24, and 'pregnancy' 40. So getting pregnant, changing our personal habits, altering our work hours, and having issues with our in-laws are worse than having our own child die. Doesn't make a lot of sense, does it? Furthermore, certain items on the list seem to have a positive valence (e.g., an outstanding personal achievement), others a negative valence (e.g., the death of a close friend), and still others depend on an individual's perspective (e.g., a major change in responsibilities at work, e.g. a promotion, demotion, lateral transfer). So the scale doesn't necessarily reflect adverse events, but instead deals with 'life changes' that might or might not be interpreted as stressors. Of course, the scales don't consider the context in which a stressor had occurred. For instance, the death of a loved one is typically a severe stressor, but it might vary as a function of whether the person had been going through a severe illness or had died suddenly in an accident. Likewise, as we'll see, even apparently minor stressors can have relatively pronounced consequences when these occur within the background of a series of other, more distressing events.

A further problem with each of these approaches is that they ask individuals to report on events that had previously occurred, and hence are subject to 'retrospective bias'. That is, the way individuals interpret or even remember the past may be colored by how they feel at the moment. If an individual is feeling really great, then past negative events might not seem so bad and they might not even recall that certain adverse events had ever occurred. In contrast, if the individual is currently dejected, then all events in their past may be perceived as

the slings and arrows of outrageous (mis)fortune and they might even dredge up events that were insignificant. Further to this point, when individuals are ill they often want to know why this occurred. Is it something they did, or something that somebody else did? Or is it just bad luck? In the case of people who are depressed they might be looking for causes and might attribute their depression, sometimes inappropriately, to particular past events. In short, as most defense and prosecution lawyers know, we can't be trusted to recollect our past experiences accurately.

DAILY HASSLES VERSUS MAJOR LIFE EVENTS

One typically presumes that the more intense the stressor the more profound the consequences. To a certain degree this is certainly the case. But what are the consequences of those day-to-day annoyances that can really bug you, especially when they appear repeatedly or are superimposed on the backdrop of other ongoing stressors (it's not from nowhere that we have expressions such as 'the straw that broke the camel's back')? Most of us know the experience of having to deal with a new stressor when were in the midst of dealing with an earlier challenge; our immediate response when this occurs is something like 'Oh no! Not now'. It's hard enough to deal with one event, but when coping resources have to be redirected to a second stressor, even if it's a fairly trivial one, our abilities to deal with these situations may become stretched. Most of us certainly have to deal with multiple concurrent challenges at some time or other. For some, juggling different tasks is so much part of their repertoire that they can't see how anyone would ever have a problem in this respect. For others, however, juggling multiple demands is exceptionally difficult, taxing their resources, and ultimately leading to illness.

Hassles can certainly be a pain and even small increases in these experiences may result in individuals being more prone to illness and mood disturbances. The relations between such 'daily hassles' and pathology have been evident across a range of illnesses, including depression, irritable bowel syndrome and diabetes (Blanchard et al., 2008; Ravindran et al., 1999), although this doesn't necessarily mean that the hassles caused the pathology, as those who are already ill may be more sensitive to day-to-day annoyances. Nevertheless, these seemingly inconsequential stressors, when they continue for long enough, can have a cumulative effect.

The formal publication of the Hassles and Uplifts Scale (Kanner et al., 1981) provided an instrument to show that hassles are related to poor well-being. Since the initial publication of this scale, other similar instruments have been developed for particular groups (e.g., caregivers) or circumstances (e.g., transition to university). Investigations using daily hassles scales typically report an overall score, but it may well be that specific types of hassles are more germane to some individuals than to others. Thus, analyses might be considered in terms of the different types of challenges experienced (e.g., partner, friends and family hassles, as well as those that are related to home, work, health, and financial strains). This hasn't been widely done, but if it were, then it might be observed that illness varies as a function of both the severity and type of the stressor encountered, and that certain illnesses are more closely related to particular types of hassles.

A TAXONOMY OF HASSLES – CHANGING TIMES

In their original report, Kanner et al. outlined the 10 most frequent hassles and uplifts reported. These hassles comprised: (1) Concerns about weight; (2) Health of family member; (3) Rising prices of common goods; (4) Home maintenance; (5) Too many things to do; (6) Misplacing or losing things; (7) Yard work or outside home maintenance; (8) Property, investment, or taxes; (9) Crime; and (10) Physical appearance. This paper was published thirty years ago, but some of those same hassles are still pertinent. Today, however, we might find that frustration with our computer, loud people talking on cell phones, emails from work when you're at home, junk emails (including word that a long-lost cousin in Nicaragua has left you \$12.5M) might break into the top 10. Importantly, these were the top 10 items for the population at large, but might not be the top 10 for those dealing with particular issues experienced by some individuals, such as caregivers who deal with illness or any of numerous other major problems. Again, when hassles are superimposed on major life stressors, then we're dealing with exponentially greater problems.

Given that hassles can be draining, you might be asking what can be done about these stressors. Causal observation suggests that having people to whom you can vent and who can help you with minor problems is useful, as social support usually is. However, there are limits to what your social support network is willing to put up with. Using them excessively for the purpose of venting, and putting upon them for very minor reasons (and not giving anything in return), may end up being counterproductive, as friends might abandon you or offer unsupportive reactions and you might get to be known as a whiner. Of course, mutual whining might diminish this problem, and although it doesn't eliminate stressors, it is a way of coping.

Most of us probably already know the key element that needs to be considered in relation to hassles, namely, don't have a meltdown. It's not productive, and excessive reactions to mild events can act as stress generators, causing further problems that need to be dealt with (like fixing the broken laptop that you whacked when you forgot to save the data). Second, put things in perspective; losing your keys or having a minor skin blemish doesn't rate as all that terrible in comparison to some serious events that can be encountered. Heart disease, cancer, and paralysis are all horrible experiences, and are difficult to deal with. Day-to-day hassles aren't, and usually can be dealt with readily. In Chapter 12 we'll be talking about various stress management procedures and treatments. One that is currently in vogue is mindful meditation (mindfulness). A key precept of this procedure is 'think in the moment'. In part, this means appraise the *present* situation properly, without worrying about secondary issues, and don't go into an automatic negative response mood. Once appropriate appraisals have been made (i.e., 'this is just a minor hassle'), then with proper deliberation, effective coping strategies can be used. Of course for some people (especially the perfectionist types and likely the Type A personalities) those little things left undone sit there sneering at them annoyingly, to the extent that they are incapable of focusing on important issues. Basically, the best advice that can be offered is what my kids (annoyingly) say to me when I'm on the verge of a meltdown over something minor, 'Chill, Dad'.

ENOUGH IS ENOUGH

A newspaper headline had a story about a Dalhousie University professor who, after standing in line for about an hour to get a rare on-campus parking pass (even though he'd been teaching at the university for thirty years), walked up to the administration offices and handed in his resignation. I can visualize his frustration when he was likely already very busy with classes about to start, and at a certain point he just said 'Screw it'. A small part of me wondered whether he was a flake, but a larger part was in admiration, given that as a university professor, I know some of the administrative aggravations that are often experienced (like completing form after form after form). Still, the event described had occurred yesterday, and today he's out of work. It may be that he won't miss the job (he was near retirement) and/or has other options. Alternatively, this might be an instance of stress generation. (Incidentally, as a result of such frustration I've developed a 'request a request form' so that when I'm asked to fill out a form, I ask them to complete my form so that I can determine whether they have the authority and justification to request that I complete their form – I'll be happy to share this form if you email me, and you won't have to complete a form to get it.)

STRESSOR INTERVIEWS AND DIARIES

To overcome some of the limitations associated with retrospective analyses, several researchers have attempted to obtain confirmation of stressful experiences by interviewing friends and family members. Although, at first blush, this might seem reasonable, the fact is that such reports can reflect the observers' own spin or bias, and hence can be just as flawed. Besides this, stress, like beauty, is ultimately in the eye of the beholder, and it's hard to know what a particular person feels by asking someone else. Judicial courts don't allow witnesses to testify about what was happening in the mind of someone else, and researchers are equally skeptical of this approach.

Ultimately, the best way to evaluate the relations between stressful events and later outcomes is by prospectively assessing stressor experiences and then relating them to particular outcomes, such as aspects of health. Not unexpectedly, this can be an onerous task that takes an awfully long time to complete, and participant loss (referred to as subject attrition) can be very high. Thus, one might end up with only those participants who are most dedicated to the project, so that the data collected might not be representative of individuals at large. If the study is relatively short term, say for a matter of weeks or even a couple of months, a diary approach can be used (e.g., Holtzman et al., 2004). This can be conducted using a format in which participants answer a brief set of questions at the end of each day (or week) indicating what they've experienced. This requires that the investigator meet with participants and form some sort of relationship with them so that they will be motivated to engage in the study on a daily basis. As useful as this approach might be, its use in long-term studies is obviously limited by logistical considerations.

INDIVIDUAL DIFFERENCE FACTORS

VULNERABILITY AND RESILIENCE

Up until this point, we've focused on the different characteristics of stressors that could potentially influence behavioral or physiological outcomes. Of course, these features are only a few of the many factors that influence how stressors affect us. To a considerable extent, previous life experiences, characteristics of the organism (animal or human), and personality variables determine the nature of the stress responses that occur. In the next section we'll focus on the influence of these variables. In assessing these factors, we will not only think about what makes us vulnerable to pathological outcomes related to stressful experiences, but also what goes into an individual being more or less resilient in the face of different challenges. Some of the factors that seem to make individuals resilient in fending off or preventing the adverse effects of stressors have been identified (see Figure 1.1), but it's certainly the case that there are enormous differences across individuals in this regard.

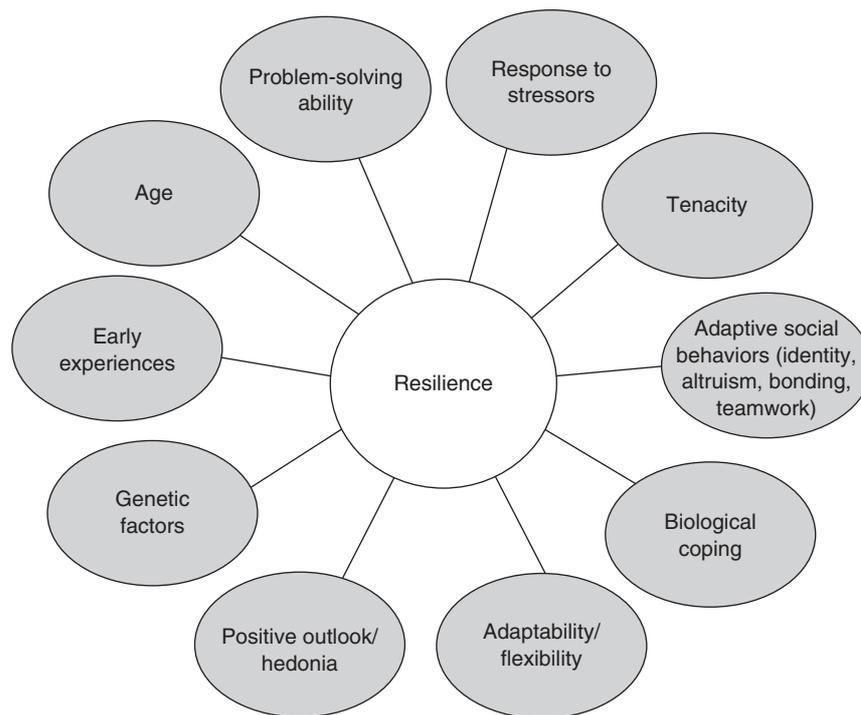


FIGURE 1.1 Numerous factors might be important in preventing the development of stress-related pathology. These range from personality characteristics, genetic factors, and a variety of experiences. Some, but certainly not all, of the important ingredients are provided in Figure 1.1. The effectiveness of these resilience factors is likely dependent on the stressor situation, will vary over time as the stressor is experienced, and will also vary across individuals.

VULNERABILITY VS RESILIENCE

In the context of illness, vulnerability refers to the susceptibility of a person (or a group, or even a whole society) to increased psychological or physical poor health as might occur in response to particular environmental or social challenges. Resilience, by contrast, refers to factors that limit or prevent these events from having adverse effects or, more often, resilience refers to the ability to recover from illness. The two aren't necessarily at opposite ends of a continuum. Moreover, the absence of factors that increase vulnerability doesn't necessarily imbue resilience. A person can, theoretically, have many factors that engender stressor resilience, but a single catastrophic vulnerability factor might be sufficient to undo all that fitness. By example, how often have you heard of a person being perfectly healthy who suddenly dies? It took only one malfunction, an aneurysm or a pulmonary embolism, for instance, to undo all that was 'healthy' about that individual. In this regard, one could take the view that stressors act on weak links within a system. A person may have all sorts of strong links, but when stressors come along, they have the most profound impact on the weakest link, causing damage at that point.

For an individual to be resilient, numerous ingredients might have to come together in exactly the right amounts. Charney (2004) suggested that neural mechanisms related to reward and motivation (hedonia, optimism), responsiveness to fear and fear-related situations, and adaptive social behaviors (altruism, bonding, and teamwork) all acted to influence character traits that affected resilience to severely traumatic events. Another perspective has it that resilience increases with increased tenacity, trust in one's instincts, acceptance of change, control, and spirituality. Still another perspective attributes resilience to the ability to adapt and be flexible to changes, the ability to problem solve, and possessing a positive outlook on life. No doubt, other resiliency factors, including early experiences and genetic factors, contribute to the ability to withstand the potential for stressors to harm us. Moreover, it is possible that certain characteristics exist that might enhance well-being even in the presence of factors that would otherwise increase vulnerability to pathology. For instance, an individual with many factors that make him or her vulnerable to stress-related pathology may overcome challenges by having an excellent social support network or perhaps by espousing a religious belief that allows them to endure the worst challenges. This is not to suggest that religiosity is the way to go, but it seems to work for some people.

Most studies that assessed the relationship between stressful events and pathology have addressed questions related to what makes us ill and what the characteristics are of individuals who are most likely to become ill. Much less information is available regarding what makes us resilient. Where we most often encounter this topic is in considering the resilience of some individuals in coping with illness, and the findings from such studies have been especially constructive. There are some individuals who, in the context of serious illnesses, are particularly resilient and are able to maintain, or regain, their mental health readily. Among individuals who have previously encountered a severe illness, the cognitive restructuring that might have occurred previously (e.g., finding meaning in their illness, which we'll come back to in Chapter 2) may have facilitated their ability to appraise and cope with a

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further stressor. In other instances, however, the previous stressful experiences might not have served in this capacity, but instead acted against well-being. Having gone through a traumatic experience, individuals might simply be too worn down or they may be sensitized so that later stressors in the form of severe illness might simply be too difficult to handle.

Resilience in relation to illness can be influenced by several personality characteristics, such as self-efficacy, self-esteem, internal locus of control, optimism, mastery, hardiness, hope, self-empowerment, determination, and acceptance of illness. Knowing this, unfortunately, isn't going to be of much help in advising anyone how to deal with illness as we can't easily get people to develop better self-esteem or greater hardiness. However, the way individuals appraise and cope with their illness may have profound repercussions for their well-being. Specifically, positive cognitive appraisal, spirituality, and active coping, which are considered in Chapter 2, were associated with resilience, and these attributes can be promoted with proper training (e.g., using cognitive behavioral therapy or mindfulness training as described in Chapter 12).

GENETIC FACTORS

When I was an undergraduate and first introduced to genetics, it was described in the form of Mendelian inheritance (that stuff about pea plants), and most of us came to believe that we inherited certain genotypes (specific genes we received from our parents) which then affected our phenotype (what we looked like), although it was acknowledged that inheritance could be incomplete and hence we might not be exactly like either of our parents on any given domain. So, unlike pea plants, people aren't simply tall or short, green or yellow, or round or wrinkled: there are all sorts of levels in between. A second premise that was drilled into us was that whatever genes you inherited were those that you were stuck with forever, and that was that. A third premise was that for some unknown reason, genes could interact with the environment, but nobody ever explained how or why this could happen. In the last decade there has been a revolution within molecular biology and all fields of medicine and neuroscience. Scientists have not only unraveled the genome, they have also found ways of modifying genes, and identifying how and where genetic changes occur naturally or in response to environmental factors or in response to stressful events. We now know that the potential actions or effects of genes can be suppressed by environmental triggers or specific experiences and hence might promote (or limit) pathology. We also know that genes can be inserted or deleted, and thus might affect phenotypes, and we have discovered many subtle inherited mutations or variants that occur within genes (referred to as 'polymorphisms') that can have profound effects on pathology.

SO, WHAT'S THIS STUFF ABOUT GENES CAUSING BEHAVIOR?

There is this odd notion that genes cause behavioral phenotypes. That seems pretty vague; it's as if you inherit some gene or set of genes, et voila, a behavior appears as if by magic. Moreover, it's often thought that the effects of genes are immutable. In fact, however, the job of genes is to

produce proteins, including hormones, peptides, neurotransmitters, enzymes and receptors that, in turn, influence behaviors. The effects of these genes aren't immutable, but are influenced by environmental factors that moderate how these gene effects are expressed. So, you might have genes that dispose you to particular characteristics, but whether these characteristics are expressed can be influenced by day-to-day events or events that occurred way back when, even when you were just a fetus.

As you know, the chromosomes you inherit from your parents comprise a lengthy DNA strand that's made of many genes, each of which comprises a set of nucleotide bases (guanine, adenine, cytosine, and thymine; the latter is replaced by uracil in an RNA strand) that reflect the gene playbook. Using the DNA as a template, RNA is formed through a process called transcription. The messenger RNA (mRNA) produced through this process is then decoded so that a specific amino acid chain, or polypeptide, is created that will in turn produce a protein (e.g., a hormone or neurotransmitter). When the characteristics of the DNA are altered, as occurs when even a single nucleotide is changed, the message that's delivered can potentially change and have some pretty significant consequences.

The genes on a DNA strand are interspaced by a bunch of additional nucleotides, much of which we know little about. But, in this pile of 'junk DNA' we also find strands that precede the gene. These are known as 'promoters' or 'promoter regions' (there are other names used as well, such as 'response elements') that are thought to act as activators or repressors. Essentially, the promoter serves as an instruction manual for the gene that follows it. These promoter regions can tell a gene when to turn on or off, or even when to interact with other genes. Importantly, environmental events, including stressors, influence these promoters by affecting other chemicals present in cells as well as extracellularly, which can then affect the influence of the gene on hormonal and neurotransmitter processes, and all those other biological factors that come to affect behavior.

Genes, therefore, have the potential to affect behavior in one way or another (e.g., increasing certain proteins that favor a disposition towards behavioral phenotypes, such as depression or anxiety), but in most instances they don't directly cause the behaviors. Ultimately, what we do is dictated by much more than just our genes. Face it, whether it's God or Nature, neither fully transcribes our lives before we are born. That would be pretty boring. Instead, we're faced with multiple paths that can be taken, ways to deal with environmental insults and social relations, and these affect the way genes get to express themselves.

APPROACHES IN HUMANS

There have been many studies showing that genetic factors might be related to various psychopathological states. These studies have included pedigree analysis in which a particular phenotype has been traced through families in an attempt to identify the presence of particular genes, and studies that compared pathology in monozygotic and dizygotic twins (identical vs fraternal twins) to determine the degree to which a particular phenotype was inherited or induced by environmental factors, and often these phenotypes were linked to

inheriting certain biological substrates. In more recent years, one of the most common approaches has involved the identification of particular genes or gene polymorphisms in relation to the presence of pathological states. In some instances this has entailed finding a sample (cohort) of affected and non-affected individuals (who have, or do not have, a particular phenotype or a family history for a particular phenotype), and then doing genomic analyses to see whether there is a match between the presence of certain genes or mutations and the appearance of a pathology. The idea is that if we could identify the gene associated with an illness, then determining what proteins this gene is responsible for making (e.g., levels of hormones and neurotransmitters and their receptors, and all sorts of other essential biological factors) would facilitate the development of treatments to attenuate or prevent pathology.

It sounds simple enough to find a proper cohort and then do the genetic analysis. However, if it actually were that simple, then many of the problems in the field might already have been solved. First, the diagnosis of an illness needs to be correct, which isn't always a simple matter as different illnesses have overlapping symptoms. Second, individuals might have similar symptoms, but that doesn't necessarily mean that these stem from the same underlying biological causes (including genetic and biochemical processes). Two individuals can come to have a particular chemical modification, but this might have involved different routes (much in the same way as your bank account can be low either because you're spending too much, not earning enough, a bank error, or unknown to you someone had been removing money from your account). Finally, there are potentially millions of mutations that can occur across the genome (more than a single mutation can also appear on any given gene), and most of these will be entirely unrelated to the pathology being studied. As a result the number of participants needed to do the studies appropriately is huge. In retrospect, it is understandable that the data from studies that have been conducted, probably because so many mutations occur concurrently and due to the small numbers of participants used, have not been particularly reliable. What has been clear, however, is that for certain pathologies, as well as the underlying biological processes, the expression of genetic effects was not always evident. Instead, the contribution of genetic factors was most evident in the presence of particular challenges, such as life stressors.

APPROACHES IN ANIMALS

Studies conducted using rodents have made it clear that genetic factors are fundamental in determining several stress responses and the pathological outcomes associated with stressors. In this regard, several approaches can be adopted to evaluate these relationships. A good first step is the use of inbred strains that naturally differ with respect to a given phenotype (the behavior or physiological characteristics of the animal) and genotype (the animal's genetic makeup) and relating these characteristics to neurochemical or hormonal differences in response to stressors (Crawley et al., 1997). Of course, simply because a strain is high (or low) with respect to both a given behavioral outcome and particular biological change doesn't mean that these factors are connected. But as described in the insert, this observation can be followed by further analyses to determine whether a correspondence between behavioral and biological factors is evident when various crosses between the strains are assessed (e.g., within F_1 , F_2 and backcross generations).

GENETIC ANALYSES IN PAST DECADES

There are occasions on which it might be suspected that the effect of a stressor is determined by the genetic backdrop upon which it is superimposed; that is, having a particular gene doesn't cause the development of a particular psychological or physical illness, but it might be permissive in that it allows for stressors to have adverse effects. There are some fairly simple, if somewhat tedious, manipulations that can be conducted to evaluate these possibilities.

When two inbred strains are crossed, the offspring (referred to as the F_1 generation) will all be genetically identical to one another. For example, one parent might be dominant for both components of a gene (AA), whereas the other parent may be homozygous recessive (aa). As the offspring inherit one gene from each parent, the offspring will necessarily be Aa. With respect to another gene, both parents may be BB, and so the offspring will necessarily be BB. The same will apply to every gene and hence all F_1 animals will be identical to all others. When we cross two F_1 s, we can then begin to see differences in the genotype: the offspring of an Aa \times Aa cross can potentially carry the AA, aa, or Aa combination. Within this F_2 generation (also referred to as the 'first segregating generation') we can determine whether a particular gene and phenotype are linked to one another (either in the absence of a stressor or following exposure to a stressor). For instance, if every mouse that has inherited the 'AA' genotype exhibits a particular phenotype, and every mouse with the 'aa' genotype exhibits a different characteristic, then the two might be related. This doesn't mean they are causally related, as this is once again simply a correlation between variables. However, if those mice that exhibit a given phenotype carry the AA, Aa or the aa combination, then we would know with a fair degree of certainty that these genotypes and the phenotype are unrelated. There are still more sophisticated variations of this approach (e.g., QTL analysis), but their description will have to be passed over for now.

There are occasions where a single gene can have more than a single phenotypic outcome. This is referred to as 'pleiotropy'. Pleiotropy can occur because genes on a chromosome are inherited as a group (termed 'linkage') or because one phenotype (e.g., a biological change) may directly or indirectly lead to a second phenotypic change. Assessing genes across successive crosses also allows us to see whether certain characteristics always appear together (e.g., Does a certain chemical always end up being present in conjunction with a particular heart problem?; Does having a certain coat color predict the occurrence of epilepsy?). In effect, we could be able to develop 'biomarkers' that predict later disease occurrence.

As well, one could determine whether genetic influences interact with maternal factors in determining outcomes. As we have just learned, all F_1 s of inbred strains are identical to one another. If a particular trait is entirely due to genetic factors, then it shouldn't matter who their mom is (i.e., from one strain or the other). However, F_1 mice can be produced where the dam (mom) is a member of a particular strain, whereas in another cross the dam is of the alternative strain (this is referred to as a 'diallel cross'). In this instance the F_1 s will all be identical, but if they differ from one another on some phenotype, then we'd likely ascribe this to characteristics of the mom.

26 AN INTRODUCTION TO STRESS AND HEALTH

With the remarkable advances in our understanding of molecular biological processes and the related technologies, newer and more sophisticated methods have been developed, including those in which specific strains of mice can be engineered. Specifically, mice (and in some instances rats) have been developed in which genes can be directly manipulated (engineered). Thus, one can assess the effects of stressors on a particular outcome in the presence of a specific genotype. For instance, a gene can be deleted from (knock-out) or added to (knock-in or transgenic) the genome of a mouse, and then bred so that numerous identical mice are obtained. This allows for analysis of the role of a particular gene or small set of genes in relation to particular pathophysiological outcomes, and how stressors influence vulnerability to pathology. So, if one believes that stressors cause a rise in chemical X, which then promotes depressive-like symptoms, then strains can be developed that lack the gene responsible for producing chemical X and thus determine whether the depressive-like behaviors are prevented. Conversely, mice can be developed that overexpress the gene that determines the presence of chemical X, with the expectation that depressive-like features would be more prominent. In theory, this approach is potentially revealing and might prompt important hints for human pathology. Yet, as most complex human pathologies likely involve many genes, the effectiveness of this approach is necessarily limited, and certainly doesn't reflect the full spectrum of the disorder. Furthermore, in mice born with a particular gene deleted, there is a fair possibility that other genes may compensate for the deleted genes. With respect to the latter issue, approaches have been developed so that the gene deletion will occur at specific times in life (thereby handling the adaptations that could occur through early development) and these can be targeted at specific brain regions. The possibility of using this 'conditional knockout' in relation to pathology has been very exciting, and opportunities exist to assess the combined role of more than a single gene.

The key point for us here is that when these genetic approaches are coupled with the analysis of stressor effects (and other factors that may favor the provocation of behavioral disturbances) and other experiential factors (e.g., early life experiences), it may be possible to identify the array of factors that contribute to stress-related disturbances. This approach can also be used to identify the relative contribution of different biological processes to specific features (symptoms) of illness, and may ultimately provide markers that can be used to predict an individual's vulnerability to disease states.

As will be seen in ensuing sections, the data supporting genetic involvement in stress-related pathology are overwhelming, and the data derived from such studies have been critical in the development of new targets for the treatment of several illnesses. One can't say, however, to what extent genetic and environmental factors influence pathology, as among other things, their relative contributions likely vary with the specific disease being assessed. Understandably, most of the molecular genetic analyses that have been conducted have involved animals (primarily mice), and studies of the interactive effects of stressors and genes in affecting illness in humans have been limited. Nevertheless, as we'll see, when these factors were examined concurrently, the results obtained were impressive.

ENDOPHENOTYPIC ANALYSES

Before closing off this section one further issue ought to be introduced. Because of the diversity of symptoms associated with most psychiatric disturbances, the variability in the effectiveness of pharmacological treatments of such disorders, and the presumed array of neurochemical and hormonal processes that might underlie these disorders, it was suggested that analyses of these illnesses might not be best served by assessing them as syndromes. Instead, as illustrated in Figure 1.2, it might be more profitable to assess the ‘endophenotypes’ that comprise the disorder. This would involve tying specific *symptoms* of a disorder to specific genetic components and neurochemical processes that might be related to the efficacy of treatment responses (e.g., Gottesman & Gould, 2003). This is not an easy thing to do, but calls for this approach have become more common, and it has led to the idea that rather than treating all individuals diagnosed with a syndrome in a particular way, it would be propitious to identify the biological and behavioral characteristics of each individual, and then to apply ‘individualized’ treatments accordingly. This might be expensive in the short run, but more economically sensible over the long term.

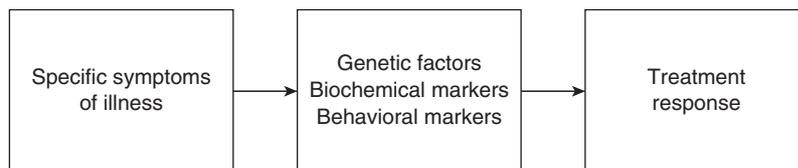


FIGURE 1.2 An endophenotypic approach attempts to link the specific symptoms of an illness to specific biological factors, such as genetic markers, and then to link these factors to particular treatment responses. There are likely many factors that are associated with illness, but not all will be predictive of a treatment response. However, identifying those that do, even if they are not causally related to the illness, may be an important element in developing individualized treatment strategies.

PERSONALITY

We all know those individuals who, given the least encouragement, seem to turn into Henny-Penny shouting that the sky is falling, and others, in contrast, who seem stoic even under the worst of conditions. As we’ve already seen, there are several factors that make us different from one another in this regard. An important set of characteristics engendering diversity of responses to stressors concerns personality attributes. In particular, there appear to be relatively stable features of individuals that appear to be important in determining whether they will be more or less vulnerable or resilient to the impact of stressors (Suls et al., 1996). Certain personality traits might influence the stress process by affecting the way we appraise

or cope with stressors, whereas others might make us more sensitive or reactive to stressors, and there seem to be characteristics that are actually instrumental in getting us into aversive situations (e.g., high risk takers are more likely to get into certain stressful situations relative to those low in this feature). Many of these factors may have evolved through the parenting individuals received, the socialization that occurred in early life, experiences that shaped particular responses, and it is probable that genetic factors also contribute in this regard.

One of the best studied views of personality has comprised the analysis of the Big Five or Five Factor Model. This conceptual framework has a lengthy history that culminated (more or less) with the model provided by Costa and McCrae (1992). The Five Factors comprise Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. One could argue that each of these dimensions could influence stress responses indirectly, but it is Neuroticism (or emotional stability) which largely comprises the disposition to experience unpleasant emotions readily (anger, anxiety, depression, or vulnerability), which seems most closely related to stressor reactivity. In this regard, some of the questions from the Big Five Factor inventory ('I get stressed out easily'; 'I worry about things'; 'I get irritated easily') tell us this factor is indeed targeted at stress-related reactivity (Vollrath, 2001).

Of course, the Big Five represent only one perspective concerning the personality dimensions that might influence the stress response. In fact, because of the broadness of this framework, it isn't clear that it is the best approach to evaluate predictors of stress reactivity, and numerous other factors have been proposed that are viewed as personality-based moderators of the stress response. Of these, *resilience* has received increasing attention, although it is not viewed as a trait. Resilience is seen as a process (or a constellation of factors) leading to changes that make individuals better able to deal with stressors or to bounce back from the adverse effects otherwise elicited by stressful experiences. Based on the many components that influence the stress response, it can be deduced that there are certain characteristics that lead to an individual being more or less resilient (e.g., early life experiences, developmental trajectory related to dealing with novel events, appraisals and coping abilities), taking into account that stress responses are governed by multiple contextual factors.

Not surprisingly, individuals who approach situations with an upbeat and optimistic outlook will have a very different view of that situation than do individuals who enter it with a pessimistic perspective. Scheier and Carver (1985) developed the Life Orientation Test (LOT), which was later revised (LOT-R), to measure the attributes of personality that make up optimism/pessimism. There are other instruments to measure this characteristic, but it seems that the LOT-R is the most widely used. Based on studies using the LOT-R it was shown that optimism/pessimism represents a personality trait that was associated with stress reactions and the ability to meet fairly severe life challenges. In this regard optimism/pessimism influenced how individuals deal with severe stressors, including breast cancer in females and radical prostatectomy in men, moderated hormonal changes and immune responses ordinarily elicited by stressors, and was related to stress reactions, such as burnout (Carver & Connor-Smith, 2010; Carver et al., 1993).

As in the case of optimism, it seems that an individual's *self-efficacy* (the belief that tasks can be accomplished and difficulties resolved through one's own efforts) can act as a moderator of the stress response, and thus influence well-being. Likewise, it seems that our *locus*

of control may influence how we appraise or respond to stressful events. Specifically, those with a high internal locus of control tend to have the view that events in life arise primarily because of their own behaviors and actions, whereas individuals with a low internal locus of control generally believe that fate, chance, or powerful others determine what events they encounter. These characteristics are thought to influence how individuals interpret or appraise situations and their own abilities to deal with them, and thus will affect psychological stress responses (we'll be coming back to this in Chapter 8, when we discuss depressive illness).

There are many personality factors that play into how we deal with stressors, but only a small number of these have even been mentioned to this point. Numerous volumes have been written on this issue, and trying to cover this broad field wouldn't do it any justice, certainly not in just a few pages. As we move forward, however, the contribution of several of these many personality traits will emerge, but for the moment, the important message here is that you should not assume that the things that bother you, and the way you think stressful issues should be dealt with, necessarily apply to everyone.

AGE

An individual's age has a lot to do with how they react to stressors emotionally and physically, and whether pathology will arise. Lupien et al. (2009), in their timely and thoughtful review, indicated that regardless of whether stressors occur prenatally, in infancy, childhood, adolescence, adulthood or in those who are aged, profound brain changes and mental health problems can emerge. These outcomes, as already mentioned, can reflect the interaction with genetic and other psychosocial factors, but the nature of the pathology that emerges may be dependent on the timing of the stressor experience. My inclination is to start this section with a discussion of older age, as this is of particular importance to me at the moment. But for the sake of a good orderly description, we'll follow a chronological order.

PRENATAL EXPERIENCES

Stressors experienced by a pregnant female may have effects on the fetus that will be manifested at various times following birth. In humans, the offspring of mothers who had experienced chronic or severe stress during pregnancy subsequently exhibited cognitive, behavioral and emotional problems during both childhood and adulthood. However, studies that evaluated these relations in retrospective analyses were troubled by some of the factors typical of self-report studies. Moreover, prospective analyses of children born following natural disasters were confounded by changes in quality of life that extended well beyond the primary stressful period (e.g., earthquakes, hurricanes, and tsunami are followed by multiple financial and health repercussions). This, however, does not belie the fact that the perceived severity of natural disasters was a strong predictor of mental health problems among pregnant and postpartum women, which was related to perinatal health outcomes in the offspring.

The fetus' intrauterine environment might profoundly influence its brain development, and hence stressful events that influence this prenatal environment may have repercussions

that carry through postnatal periods. For example, stressful events will give rise to elevated levels of a stress hormone (corticotropin releasing hormone), which may appear in the placenta, ultimately affecting the fetal brain (Charil et al., 2010). In addition, among rodents, the offspring of mothers that had been stressed during pregnancy showed elevated activity of the stress hormone corticosterone when they encountered stressors postnatally, and this outcome was evident even when the pregnant dam had experienced a stressor on only a single occasion. Furthermore, these experiences influenced particular neurochemical receptors present within the hippocampus, a brain region that is fundamental in regulating biological stress responses and cognitive functioning. It might be particularly relevant that the effects of maternal stressors have especially profound effects in female offspring, and might be an important element responsible for differences between males and females in the development of stress-related pathology. In Chapter 11, which largely deals with the intergenerational transmission of trauma, a lengthier discussion of prenatal stressor effects is provided.

STRESSORS AS TERATOGENS

Teratogenic agents (those that cause disturbances and malformations of the fetus) are dependent on the stage of development at which the compound is encountered. Typically, the most harmful effects occur during the first trimester, but can vary with the species, the nature of the teratogenic agent, as well as particular phases of developmental growth. In the case of stressors, it has been suggested that the mid-term period is particularly sensitive to the adverse effects of stressors, possibly because placental adaptation can be achieved early in pregnancy, thus limiting adverse outcomes. However, the data from human studies and those from non-human primates and rodents have not been entirely uniform, and this issue has yet to be fully resolved. This is particularly the case as most strong stressors encountered by humans are often chronic in nature (especially when the aftermath of the initial trauma is considered) and hence span a lengthy period of fetal development (Charil et al., 2010).

EARLY POSTNATAL EXPERIENCES

Stressors have profound effects on children, and events early in life may subsequently affect biological responses to stressors in adulthood (see Chapters 3–5), and encourage psychological disturbances, such as depressive disorders, a variety of anxiety disorders and drug addiction (Chapters 8, 9 and 10), and may even have effects that are manifested across generations (Chapter 11). There are a wide range of stressors that infants and children can experience, ranging from physical, psychological, or sexual abuse, through to neglect or socioeconomic difficulties (poverty). However, children may not appraise specific challenges in the same way that adults do and therefore it is sometimes difficult to discern how they are being affected by adverse events (e.g., Compas et al., 2001). As well, the social, cognitive,

emotional, and tangible resources to deal with stressors are not as well developed in children as they are in adults. Thus, it can reasonably be expected that stressful events might have marked immediate effects on children's well-being, and the notion is intuitively appealing that stressors experienced early in life would have profound repercussions on long-term well-being.

Early studies conducted by Harlow indeed revealed that monkeys raised in isolated environments later became asocial and had vastly deficient parenting skills. It has likewise been known for decades that raising children in deprived environments where they were not stimulated by touch or caress, as in the case of hospitals or orphanages, gave rise to frequent psychological and physical disturbances and exceptionally high levels of infant mortality. In fact, profound behavioral and biological disturbances are seen even when humans or rodents are brought up in environments that are not nearly as severe as those experienced by children in orphanages or monkeys in Harlow's studies. Early experiences, and in particular maternal care and factors related to socioeconomic status, most certainly influence developmental trajectories and ultimately adult behaviors (Shonkoff et al., 2009). Among other things, children from a nurturing early life environment were subsequently found to have a hippocampus that was larger (by about 10%) than children from a less nurturing environment (Luby et al., 2012), which could have enormous repercussions for stress responses and mental health, as well as learning and memory processes. Furthermore, stressful early life experiences have been associated with greater adult anxiety, depression, and chronic fatigue syndrome, and have also been implicated in favoring the development of a variety of diseases of aging, such as vascular disease and autoimmune disorders, and premature mortality (Shonkoff et al., 2009).

RE-PROGRAMMING BIOLOGICAL FUNCTIONS AND EPIGENETIC PROCESSES

To account for why early events might have repercussions many years later, it was proposed that psychological stressors result in the programming of various types of biological signals, including those that involve hormonal and immunological processes. Further, adverse early life experiences give rise to several behavioral and cognitive changes (e.g., high threat vigilance, mistrust of others, disrupted social relations, disturbed self-regulation, and unhealthy lifestyle choices) that might engender further stressors or result in these individuals being highly reactive to threats. These behavioral factors, and the stress reactions they elicit, might exacerbate already disturbed hormonal and immunological functioning associated with the early experiences, and eventually might culminate in pathology.

In considering the effects of early life experiences, one should not just focus on severe cases, such as abuse. Indeed, simply having an inattentive or neglectful parent can have profound and lasting repercussions on cognitive functioning and on vulnerability to stress-related disturbances. Studies with rodents indicated that early life neglect may engender disturbed adult behavioral and biological functioning, whereas stimulation may enhance an animal's ability to contend with later stressor experiences. In this regard, it seems that if pups had an attentive mom who cared for them well (in the case of rodents this involves lots

of licking and grooming of pups), then these animals grew up to be fairly resilient in the face of stressors (Kaffman & Meaney, 2007). In contrast, extended periods of separation from the mom, or having an inattentive mom, resulted in animals being more stress reactive as adults, relatively resistant to the extinction of fear responses, and even after extinction had taken place, the fear response could readily be reinstated (Callaghan & Richardson, 2011). Essential questions that have emerged have concerned which neurobiological processes are involved in these outcomes, and whether the adverse effects of early adverse experiences can be reversed, or if there are variables that may compensate for poor parenting.

In their influential review and commentary, Shonkoff et al. (2009) indicated that numerous diseases that appear in adulthood, including psychiatric disorders, diabetes, heart disease, and various immune-related disorders, might have their roots in childhood stressor experiences. They suggested that the cumulative effects of life stresses contribute to allostatic overload that might eventually lead to pathology, or alternatively, that stressful experiences in childhood may become biologically 'embedded' (either through epigenetic processes or via sensitized biological responses) so that their consequences might appear years later. These investigators distinguished between 'positive' or 'tolerable' stressors that, with appropriate social support, might allow individuals to learn how to cope with such events, from those described as 'toxic' stressors (extreme poverty, psychological or physical abuse, neglect, maternal depression, parental substance abuse, and family violence) that are more likely to lead to pathology. In effect, there are challenges that are basically part of growing up, that have positive effects as they allow individuals to learn how to appraise and cope with events properly. However, there are also 'toxic' challenges that no one should have to endure. Shonkoff et al. didn't simply indicate that there were problems, rather they called for changes in public policy to attenuate these problems. They suggested that an increased focus be placed on: (a) reducing toxic childhood environments; (b) greater provision of early care and education programs that might not only serve as appropriate learning environments, but could also foster 'safe, stable and responsive environments; (c) evidence-informed interventions and treatments to deal with family mental health problems; and (d) expanding the role of child welfare services so that they undertake comprehensive developmental assessments in order that professionals be able to apply appropriate interventions. To what extent these straightforward suggestions will be endorsed by policy makers will be seen.

EPIGENETIC PROCESSES

A fairly hot topic in recent years has been the possibility that stressful events (as well as other factors) may affect the expression of genes, without altering the sequence of amino acids that make up these genes. This has been termed 'epigenetics', which essentially refers to the study of heritable changes in gene expression that result in a phenotypic change, but without fundamentally altering changes in the underlying DNA sequence (Bird, 2007). Some event, say one that had been experienced early in life, may have caused a series of changes within cells, so that the expression of the gene is suppressed. This gene suppression could affect whether or not

certain neurochemical processes, including the neurochemical receptors, are operating appropriately, and hence could have effects with respect to how individuals deal with stressors, or they could have effects directly on processes that lead to illness. Importantly, these changes could persist over the course of an organism's life, and could also be transmitted across successive generations (if the epigenetic change occurred within the germ line, i.e., the sperm or ovum), hence affecting the biological and behavioral processes of the children and grandchildren of the individual that had initially been affected. Epigenetic changes have been shown to contribute to some forms of cancer, as well as autoimmune disorders, such as rheumatoid arthritis. Although epigenetic mechanisms have been linked to stressful experiences encountered at any time in life, there has been considerable interest in determining to what extent early life events (abuse or neglect) might have long-term consequences owing to epigenetic changes. In this regard, analyses of the brain tissue of depressed individuals who died by suicide revealed epigenetic changes in the genes associated with stress-relevant neurochemical responses among those individuals that had experienced early life parental neglect (McGowan & Szyf, 2010; Poulter et al., 2008).

TRANSITIONAL PERIODS

In addition to the impact of prenatal and early postnatal periods, there are other developmental times during which an organism might be especially sensitive to stressors. These include those phases of life that are referred to as transitional periods. We all go through events in life that involve change or transitions that call upon our adaptive resources. Entering kindergarten, for instance, is one of these life transitions. You're suddenly a big boy or big girl, having graduated from day care, but you also suddenly find yourself in a new social context, where it's not just you, mom and dad anymore. Likewise, entering high school, college, university, or the workforce is also an exciting major life transition during which we might experience insecurities and may be particularly vulnerable to the adverse effects of stressors. Leaving home, living with someone else, getting married (or divorced), moving cities and retirement, represent life transitions, and at these times the responses to stressors might be altered.

Most animal studies that assessed the effects of early life events on later stressor vulnerability have focused on events experienced during the early postnatal period (postnatal days 1–10), and as we've seen, stressors experienced at this time alter the developmental trajectory of stress relevant processes. However, it also seems that the juvenile (early adolescent) period, spanning postnatal days 28–35 in rodents, is exquisitely sensitive to stressors and has protracted ramifications on vulnerability to the stressor-provoked neurochemical and behavioral changes that occur in adulthood (Jacobson-Pick et al., 2008; Spear, 2009). The sensitivity of this developmental phase may be related to reorganization of many neurotransmitter systems that occur at this time. As well, it is a developmental phase during which rodents display increased socialization (play) with conspecifics and increased independence from the dam. In fact, stressors in the form of social instability encountered at

this age may influence brain development, particularly the hippocampus, and thus may affect some forms of memory in adulthood, including those associated with fear (McCormick et al., 2011). Moreover, as adults, these rats exhibited elevated levels of the stress hormone corticosterone and reduced numbers of receptors in the hippocampus that are sensitive to corticoids. Interestingly, in both rodents and humans, the adolescent period is one during which fear responses are especially difficult to overcome relative to those seen in younger or older individuals. Once an anxiety or fear response is established it may persist even after the danger is no longer present, and among adults with fear-related disorders, about 75% of cases have their roots in anxiety that developed at earlier ages. These fear responses are not immutable, as they could be attenuated with appropriate treatment; however, this was more difficult to achieve in adolescent rodents and humans (Uys et al., 2006).

Adolescence in humans is a period in which individuals are highly focused on ‘fitting in’, developing an adult-like identity, finding a peer group that will accept them and with whom they feel comfortable, showing interest in a sexual partner, and even concerns about events that they will be facing some time down the road. These issues become particularly acute as young people move from secondary school to university, as this transition requires considerable adaptation in the face of psychosocial and environmental changes. During this stage of life, many individuals leave behind long-standing social networks and form new ones, including changes in their romantic relationships, and efforts to gain social, economic, and emotional independence. In effect, just when young people are expected to establish their independence, they encounter a transition replete with factors that destabilize their support systems, and individuals may struggle with a collision between expectations of autonomy and contending with a series of novel and stressful experiences that would be best met with the support of others.

Given the distress associated with transitions into adulthood, a considerable number of young people experience clinical levels of major depression, dysthymia (i.e., chronic low-grade depression), and anxiety disorders that were estimated to be as high as 25% (Mackenzie et al., 2011). Moreover, many may have undiagnosed or subsyndromal symptoms of depression and anxiety that could reflect the antecedent conditions of major depression (Offer & Spiro, 1987). Thus, although the transition into adulthood can be seamless and exciting for some, for many others it is a challenging process that seems to last forever, and every day is filled with hardships.

OLDER AGE

Before starting a discussion of stress and aging, we need to distinguish what we mean by aged or aging. When I was young, and the mean life span was somewhere around 75 for females and 70 for males, someone at retirement age (65) was considered to be fairly old. With changes in lifestyle (diet, exercise) and medical treatments, life expectancy has increased appreciably, and 65 is hardly seen as ‘old’, and certainly not by others who are about that age (am I sounding a bit defensive?). Still, being old is no picnic, and getting old also has significant down-sides. With age comes a decaying system; young guys no longer want to

play tennis as they ‘want a good game’, and flirting is interpreted as coming from an ‘old lech’. Worse still, disease states generally become more common: neurodegenerative and cardiovascular diseases appear; kidney, liver, and lung diseases are on the horizon; and prostate problems, even those of a minor sort, can cause social distress (if this is too ambiguous, think of ‘Depends’). Aging also influences the extent to which stressors affect well-being. Whether an individual ages ‘successfully’ or not depends (there’s that word again) on, among other things, complex interactions that involve genetic factors, environmental influences, concurrent morbidities, and the ability to cope with stressors.

Studies in rats have pointed to yet another age-related factor that interferes with well-being in association with stressors. In older rats, the release of several brain neurotransmitters, such as norepinephrine, as well as the stress hormone corticosterone, is elevated under basal conditions (as it is in humans), and increases appreciably in response to acute stressors. However, normalization (the return to basal levels) may take longer to occur than it does in younger animals. It is thought that hormonal and neurochemical responses elicited by stressors are of adaptive value, but once the stressor terminates, things ought to return to normal relatively quickly. The sluggish normalization of neurotransmitter release and corticosterone levels, as we’ll see in Chapters 3–5, in older individuals might have some fairly unfavorable repercussions.

A good conceptual framework to use in regard to stress and aging is that of allostasis and allostatic overload (Goldstein, 2011). Let’s face it, the wear and tear on a 70 year-old person (like a 70 year-old car), will be much greater than the load that has been put on a much younger model. The greater the strain an individual had encountered previously, and the greater the challenge they are currently undergoing, the more likely it is that the bumper will fall off. However, as individuals age, vulnerability to pathology might not only stem from decaying biological processes, but might also be a result of the dwindling availability of resources that lend themselves to effective coping, including the reduced availability of social support from family and from friends who might not be able to help (or who might have predeceased them).

WHO WOULD SCAM OLD PEOPLE?

Of the many illnesses faced by older people, one of the most dreaded is dementia. The loss of self and the indignities that can be experienced in relation to many diseases are often beyond what anyone envisions for themselves. Significantly, among the elderly, cognitive decline is linked to stressful experiences. A prospective study among elderly individuals conducted over just 2.5 years revealed that protracted, highly stressful experiences were associated with increased conversion from individuals exhibiting mild cognitive impairments to moderate levels of dementia. Studies in rats also suggested that cognitive deficits and ‘tau pathology’ (a substance implicated in Alzheimer’s disease) are influenced by cumulative stressor experiences (Sotiropoulos et al., 2011).

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There are all sorts of scams being perpetrated, particularly through the internet. Over the course of two days I learned that my long-lost cousin in Italy, Giorgio Anisman, and my similarly lost cousin in Russia, Yvegeny Anisman, had died suddenly and I was their only known living relative. I stood to inherit millions! Who falls for these transparent and patently ridiculous efforts? Apparently there are some people who do, but it's a subset of older folks that are the most frequent victims of telephone and internet scams. It could potentially be that an age-related loss of neurons has made them 'less smart', or it might be that they're more trusting or, phrased differently, that they are deficient in their ability to 'doubt' information that would ordinarily appear suspicious. It seems that with age, a region in the brain associated with appraisals and decision making, the prefrontal cortex, may undergo changes for the worse. In this regard, even among otherwise intelligent people, when the dysfunctionality occurred in one aspect of this region, namely the ventral medial prefrontal cortex, individuals experienced difficulty in the effortful process necessary for disbelief, and hence they were more likely to be the victims of fraud. Being scammed is embarrassing and stressful for pretty well anyone, but for the elderly it's yet another slap in the face that highlights their limitations.

For some 'seniors', particularly those who've aged successfully (healthy in body and mind), this time of life can be wonderful. For many others, however, aging is the pits, and they certainly don't refer to it as 'the golden years'. Besides being accompanied by health problems and repeated visits to different doctors, aging is associated with difficulties getting around, the loss of friends (through death or translocation), the dispersal of family members as children find employment or other opportunities elsewhere, and diminished coping resources, including a progressively smaller social support network. In fact, loneliness, which is stressful for individuals of any age, is often notable in the elderly as their social network might have dissipated, and certain types of stressors produce especially marked physiological changes (e.g., cardiovascular responses) relative to those apparent at earlier ages (Ong et al., 2011). Beyond these stressors, aged individuals might suffer multiple indignities, including unsupportive interactions (often being patronised, talked down to, dismissed, made to feel invisible, or made to feel like a burden) and stigmatization. In light of these factors, it seems that the coping strategies endorsed by older individuals might shift away from ones that reflect a sense of control over their own lives, to those that are reliant on others. Is there any wonder that depression rates in older people are as high as they are?

SEX

It's hardly news that women in much of the world have it much harder than do men. Whether it involves issues related to the job front, taking care of the home or children, or illness, women seem to carry a greater load than do men. Certain illnesses, such as mood

disorders and autoimmune disorders (those in which the immune system turns on the individual, as in the case of multiple sclerosis, lupus erythematosus, arthritis) also occur more frequently in women than in men. In the case of major depression the ratio is about 2:1, and this increases to 3:1 in the case of atypical depression (i.e., where symptoms comprise increased sleep, increased eating, and mood reactivity). Likewise, posttraumatic stress disorder (PTSD) that develops in response to traumatic events occurs more frequently among females than males. These sex differences might occur for any number of reasons, including differences in the stressors actually experienced, greater stress-relevant neurochemical disturbances in females, the influence of particular sex hormones, socialization processes that promote certain behavioral styles being adopted, the endorsement of less adaptive coping strategies to deal with stressors, or psychosocial or personality factors that favor the development of illness. To the extent that sensitivity or reactivity to stressors differs between sexes, one might expect to find that the treatment of stress-related disorders would likewise differ in this regard.

In animal studies sexual dimorphisms (differences in phenotypes as a function of gender) are also apparent in neurobiological responses to stressors. In rodents, females are generally more behaviorally reactive to stressors than males, typically being associated with greater stressor-related neuroendocrine changes, such as variations of the stress hormone corticosterone (Rivier, 1999). Moreover, neuronal activity is increased in numerous brain regions that govern behavioral and cognitive responses to stressors (e.g., frontal, cingulate, and piriform cortices, and the hippocampus, hypothalamic paraventricular nucleus, medial amygdala, and lateral septum), and the extent of the activation varies over the estrous cycle, implicating a role for sex hormones in determining these outcomes (Figueiredo et al., 2002).

In humans, however, the effects of stressors on cortisol (the equivalent of corticosterone in rodents) were greater in males than in females, or were found not to differ as a function of gender (Kajantie & Phillips, 2006). It seems that these effects might vary with the estrous cycle, with greatest cortisol responses in women occurring during the luteal phase (the later part of the menstrual cycle during which the hormone progesterone is very high). It was also reported that the effects of social stressors on cortisol levels in women are blunted among those using oral contraceptives, indicating interactions between stressors and estrogen in provoking the stress response. No doubt there are numerous factors that could account for the difference between cortisol responses in human males and females, including those related to the nature of the stressor (intrapersonal stressors might have greater effects in females, whereas performance pressures have greater effects in males) and the appraisal/coping that might be instigated by the stressor in particular situations.

As we cover successive topics, it will become clear that the greater stress-vulnerability of females regarding depressive and anxiety disorders is also apparent with respect to autoimmune disorders and some types of heart disease. Despite these health inequities, it seems that on average, women still outlive men just as they did fifty years ago, although the gap has been closing. This is not simply due to a bias regarding who is in the workforce, as the same statistics are apparent in both industrialized and non-industrialized countries.

IF THEY'RE THE WEAKER SEX, HOW COME WOMEN LIVE LONGER THAN MEN?

The greater life span of women doesn't seem to simply be a result of estrogen levels, although it can't readily be ruled out that estrogen can interact with other factors to increase well-being. It could be related to women having two XX chromosomes, whereas men have an X chromosome replaced by a puny Y. Tom Persl had an interesting perspective on this (Lauara Blue, *Time Magazine*, 6 August 2006; www.time.com/time/health/article/0,8599,1827162,00.html). He suggested that several factors converge to produce the gap. First, men *smoke a lot more than women (or at least they used to)*; second, *they eat more food that promotes elevated cholesterol levels*; third, *men generally are not as effective in coping with stressors, tending to internalize rather than letting go and externalizing*. This said, I've heard from women that men complain vociferously about every little thing, and if, God forbid, they get a cold you'd think the world was coming to an end (incidentally, these women even referred to this as a 'man cold'). There is another factor that should be considered: it is possible that *testosterone may somehow come to affect longevity*. It has, in fact, been reported that eunuchs in Korea between the fourteenth and nineteenth centuries lived about fifteen years longer than other people. Doesn't sound like a great method for extending life, does it?

PREVIOUS EXPERIENCES AND SENSITIZATION

There is no question, as we've seen in our discussion of early life experiences, that an individual's previous experiences may influence the response to later stressor encounters. It's not simply a matter of our memories of previous experiences influencing our responses to stressors. The characteristics of the neurons themselves may have changed, so that the response to later stimulation is enhanced (this is known as 'sensitization').

Studies in animals indicated that stressor encounters influence the neurochemical responses elicited by subsequent insults. For instance, the brain's neurochemical changes exerted by acute stressors can be induced more readily if mice had previously encountered stressful experiences (Anisman et al., 2008). It's still a bit early in the book to explain how stressful events might come to change the characteristics of neurons so that they would become more responsive (or conversely, less responsive, which is termed 'desensitized' or 'down-regulated') to later challenges. In fact, there are several ways in which these sensitized responses can develop, but what must be recognized at this point is that many biological systems are subject to this sort of effect. You might come across the concept of plasticity in regard to neuronal processes. This refers to the ability of the synapses to change, or the connection between neurons to change in strength as a result of experiences (use) or lack of use. Plasticity is a fundamental feature of the brain that is required for, among other things, learning and memory, and sensitization is an instance of this neural plasticity. However, when we deal with sensitization it should be considered that processes responsible for the sensitization of a given neurotransmitter system may differ from those associated with the sensitization of a second transmitter system. For instance, it is possible that sensitization of

some systems may involve altered expression or sensitivity of relevant receptors, whereas sensitization of other systems may involve the synergistic (multiplicative) effects of two or more biological substrates. Finally, the effects of stressors on sensitized neuronal responses may persist for many months following a stressor event, and it is possible that sensitization processes contribute to the long-term influence of stressors on psychological states.

Based on such findings, it was suggested (Post, 1992) that the biological substrates of depressive illness may evolve over time with repeated stressor experiences and recurrent depressive episodes. With each stressor experience, or with each episode of depression, the stressor severity needed to elicit the depressive mood becomes smaller, until eventually, very little is needed to encourage a depressive state. There have, indeed, been numerous reports showing that although the first episode of depression is preceded by fairly strong stressors, the severity of the stressor necessary to cause illness recurrence is smaller (Kendler et al., 1995). In fact, among individuals who experienced recurrent episodes of depression, very mild stressors were needed to re-induce the depressive state, and even reminders of stressful experiences were sufficient to produce this outcome (Monroe & Harkness, 2005).

In addition to sensitization of biological systems, how we appraise (evaluate) the world around us can be influenced by our previous stressor experiences. By example, it isn't hard to imagine that if individuals encounter a stressor that traumatized them, later reminders of these same experiences will have profound psychological and physical repercussions. This also applies to adverse experiences that occurred in early childhood. Children who experience a trauma will, as adults, be much more likely to develop depressive illness (Kendler et al., 2004), and importantly, this is apparent even when statistically controlling for the family and contextual factors that have been associated with depressive illness. This effect of early life adversity is not limited to young children, having similarly been observed in women that had experienced physical or sexual abuse in adolescence (Harkness et al., 2006). It might be the case that when certain stressors are encountered, they cause changes in numerous aspects of an individual's life, altering the trajectory of life experiences (friendships and other support networks, coping processes, lifestyles, general world view, and even the propensity for further stress encounters), and culminating in a greater vulnerability to psychological and physical illness.

STRESS GENERATION

Stress generation refers to occasions on which individuals, because of their circumstances, may bring stress onto themselves. This doesn't mean that we should blame the victim for finding themselves in adverse situations. Instead, it means that sometimes, through any number of factors, people are disposed to doing the wrong thing at the wrong time, and they might even do this repeatedly. Depressed individuals, by their behaviors, are thought to be a particularly vulnerable group for stress generation (Liu & Alloy, 2010). For instance, one partner in a romantic relationship may tire of always having to deal with the other person's depressive state (poor mood, negativity, lethargy, and aggressive behaviors that might occur), hence leading to the dissolution of the relationship. Essentially, the depressed partner, by not altering their negative behaviors (typically these involve behaviors of a dependent nature),

contributed to the break-up and the loss of an important relationship that might have served as a stress buffer. Likewise, the depressed individual, who tends to be inactive and withdrawn, may also alienate their co-workers, and ultimately find themselves out of a job. Stress generation is also more common among those high in neuroticism (emotional instability), which is not surprising as their emotional sensitivity might favor interpersonal conflicts (Poulton & Andrews, 1992). It has also been reported that perfectionism contributed to interpersonal stressors (Flett et al., 1996), as did sociotropy (a personality trait in which individuals exhibit high levels of dependence and an excessive need to please others; Daley et al., 1997). This is in line with the perspective that individuals whose self-esteem is based largely on their relationship with others place themselves in a situation where interpersonal conflicts will be tied to depression and thus will contribute to further stress generation.

In a sense, it seems that stress breeds stress. In fact, in some instances, by their behaviors and attitudes individuals are able to make their worst fears turn into reality. Let's have a look at one example where this appears, namely that of dating abuse, which occurs in about 20% of dating relationships among university-aged individuals (the abuse, incidentally, goes in both directions, as males when asked are as likely to report psychological abuse as are women). Significantly, however, women who had previously been abused were reported to be at increased risk of being in further abusive relationships. In our research conducted with undergraduate women, 70.4% of those who encountered dating abuse reported a previous assaultive experience (childhood assault, assault by a previous partner), whereas only 24.6% of those in non-abusive relationships had such a history (Matheson et al., 2007). It was not a matter of women who experienced abuse generally being more likely to encounter traumatic experiences, as other forms of trauma (e.g., accidents, witnessing violent events, and the death of someone close to them) were not more common among abused women. Instead, it seemed as if an experience of abuse that occurred earlier in life effectively set in motion a cascade of changes that favored increased vulnerability to later stressors, which provoked depression and PTSD. What exactly this process entails isn't known, but it is possible that the initial abusive experience engendered a set of beliefs and learned coping responses that facilitated women's ability to endure or tolerate their abusive situations, or alternatively, the experience may have limited their capability to leave a bad relationship. Additionally, early abuse experiences may limit the development of social and emotional intelligence skills, and such skill deficits undermined the ability to appraise and respond appropriately to emotionally charged stressor situations (Terrance & Matheson, 2003). In view of the relations between dating abuse and earlier abusive experiences, increased incidence of stress generation, diminished self-esteem and self-worth, depression and PTSD, it would be inappropriate to consider an adult experience in isolation from other factors that might be tied to stress generation.

CONCLUSION

Stressful events are common life experiences whose effects can be negligible and brushed off readily, or they can be extremely severe, affecting individuals for years. Numerous factors can contribute to our vulnerability to stressor-elicited illnesses, and likewise being resilient

in the face of severe stressors and pathology involves complex interactions between a constellation of variables. To a significant extent, however, the impact of stressors will be determined by how these stressors are viewed or appraised and how individuals cope with them. In Chapter 2 we'll be covering these topics in the hope that this will give us a better perspective of what to do when we encounter adverse events. However, if there's a single take-home message from Chapter 1, it's that stressful events and their effects are not only complex, but also that there are marked interindividual differences in their effects. What might be stressful to you might be a walk in the park for someone else, and conversely someone else's greatest distress may be a mild annoyance for others. Without considerable experience (and perhaps not even then), don't presume to understand another person's stress responses.

SUMMARY

- Stressors come in multiple flavors and vary across numerous dimensions. The extent to which stressors affect our well-being is related to the nature of the stressor and the psychological attributes of that stressor, such as the controllability, predictability uncertainty, and ambiguity of stressors or threats of impending stressors.
- The impact of stressors may be governed by the chronicity of stressor experiences as well as stressors that had previously been encountered (e.g., early in life).
- Individual difference factors are fundamental in determining to what extent a stressor might have severe adverse consequences. In this regard, genetic make-up, age, gender, and personality factors all are effective in moderating stress responses.
- Factors that contribute to these individual differences, including the phenotypic expression of genes, can be influenced by previous stressor experiences that can potentially shape the way in which individuals respond to psychological, physical, or even systemic challenges.