UNIT Two

Alterations in Body Defenses

CHAPTER 7

Stress and Adaptation

Stress has become an increasingly discussed topic in today's world. The concept is discussed extensively in the health care fields, and it is found as well in economics, political science, business, and education. At the level of the popular press, the term is exploited with messages about how stress can be prevented, managed, and even eliminated.

Whether stress is more prevalent today than it was in centuries past is uncertain. Certainly, the pressures that existed were equally challenging, although of a different type. Social psychologists Richard Lazarus and Susan Folkman related that as early as the 14th century the term was used to indicate hardship, straits, adversity, or affliction.[1] In the 17th century, *stress* and related terms appeared in the context of physical sciences: *load* was defined as an external force, *stress* as the ratio of internal force created by the load to the area over which the force acted, and *strain* was the deformation or distortion of the object.[1] These concepts are still used in engineering today.

The concepts of stress and strain survived, and throughout the 19th and early 20th centuries, stress and strain were thought to be the cause of "ill health" and "mental disease."[2] By the 20th century, stress had drawn considerable attention both as a health concern and as a research focus. In 1910, when Sir William Osler delivered his Lumleian Lectures on "angina pectoris," he described the relationship of stress and strain to angina pectoris.[3] Approximately 15 years later, Walter Cannon, well known for his work in physiology, began to use the word *stress* in relation to his laboratory experiments on the "fight-or-flight" response. It seems possible that the term emerged from his work with the homeostatic features of living organisms and their tendency to "bound back" and "resist disruption" when

acted on by an "external force."[4] At about the same time, Hans Selye, who became known for his research and publications on stress, began using the term *stress* in a very special way to mean an orchestrated set of bodily responses to any form of noxious stimulus.[5]

The content in this chapter has been organized into three sections: homeostasis, the stress response and adaptation to stress, and the acute and chronic effects of stress.

HOMEOSTASIS

The concepts of stress and adaptation have their origin in the complexity of the human body and the interactions between the body's cells and its many organ systems. The body requires that a level of homeostasis or constancy be maintained during the many changes that occur in the internal and external environments. Stress and adaptation involve feedback control systems that regulate cellular function and integrate the function of the different body systems.

Constancy of the Internal Environment

The environment in which body cells live is not the external environment that surrounds the organism, but rather the local fluid environment that surrounds each cell. Claude Bernard, a 19th century physiologist, was the first to describe clearly the central importance of a stable internal environment, which he termed the *milieu intèrieur*. Bernard recognized that body fluids surrounding the cells and the various organ systems provide the means for exchange between the external and the internal environments. It is from this internal environment that body cells receive their nourishment, and it is into this fluid that they secrete their wastes. Even the contents of the gastrointestinal tract and lungs do not become part of the internal environment until they have been absorbed into the extracellular fluid. A multicellular organism is able to survive only as long as the composition of the internal environment is compatible with the survival needs of the individual cells. For example, even a small change in the pH of the body fluids can disrupt the metabolic processes of individual cells.

The concept of a stable internal environment was supported by Walter B. Cannon. He proposed that this kind of stability, which he called *homeostasis*, was achieved through a system of carefully coordinated physiologic processes that oppose change.[6] Cannon pointed out that these processes were largely automatic and emphasized that homeostasis involves resistance to both internal and external disturbances.

In his book *The Wisdom of the Body*, published in 1939, Cannon presented four tentative propositions to describe the general features of homeostasis.[6] With this set of propositions, Cannon emphasized that when a factor is known to shift homeostasis in one direction, it is reasonable to expect the existence of mechanisms that have the opposite effect. For example, in the homeostatic regulation of blood sugar, mechanisms that both raise and lower blood sugar levels would be expected to play a part. As long as the mechanism responding to the initiating disturbance can recover homeostasis, the integrity of the body and the status of normality are retained.

KEY CONCEPTS

HOMEOSTASIS

- Homeostasis is the purposeful maintenance of a stable internal environment maintained by coordinated physiologic processes that oppose change.
- The physiologic control systems that oppose change operate by negative feedback mechanisms that are composed of a sensor that detects a change, an integrator/comparator that sums and compares incoming data with a set point, and an effector system that returns the sensed function to within the range of the set point.

Control Systems

The ability of the body to function and maintain homeostasis under conditions of change in the internal and external environment depends on the thousands of physiologic *control systems* that regulate body function. A homeostatic control system is a collection of interconnected components that function to keep a physical or chemical parameter of the body relatively constant. The body's control systems regulate cellular function, control life processes, and integrate functions of the different organ systems.

Of recent interest have been the neuroendocrine control systems that influence behavior. Biochemical messengers that exist in our brain control nerve activity, information flow, and ultimately, behavior.[7] These control systems function in producing the emotional reactions to stressors. In persons with mental health disorders, they can interact in the production of

Constancy of the Internal Environment

1. Constancy in an open system, such as our bodies represent, requires mechanisms that act to maintain this constancy. Cannon based this proposition on insights into the ways by which steady states such as glucose concentrations, body temperature, and acid-base balance were regulated.
2. Steady-state conditions require that any tendency toward change automatically meet with factors that resist change. An increase in blood sugar results in thirst as the body attempts to dilute the concentration of sugar in the extracellular fluid.
3. The regulating system that determines the homeostatic state consists of a number of cooperating mechanisms acting simultaneously or successively. Blood sugar is regulated by insulin, glucagon, and other hormones that control its release from the liver or its uptake by the tissues.
4. Homeostasis does not occur by chance, but is the result of organized self-government.

(Cannon W.B. [1932]. *The wisdom of the body* (pp. 299–300). New York: W.W. Norton)

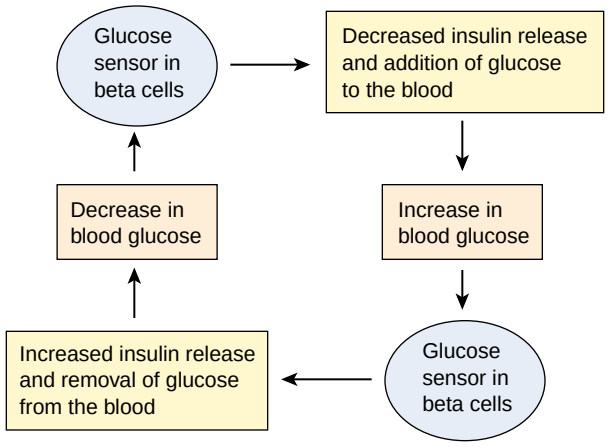
symptoms associated with the disorder. The field of neuropharmacology has focused on the modulation of the endogenous messengers and signaling systems that control behavior in the treatment of mental disorders such as anxiety disorders, depression, and schizophrenia.

Feedback Systems

Most control systems in the body operate by *negative feedback mechanisms,* which function in a manner similar to the thermostat on a heating system. When the monitored function or value decreases below the set point of the system, the feedback mechanism causes the function or value to increase, and when the function or value is increased above the set point, the feedback mechanism causes it to decrease (Fig. 7-1). For example, in the negative feedback mechanism that controls blood glucose levels, an increase in blood glucose stimulates an increase in insulin, which enhances the removal of glucose from the blood. When sufficient glucose has left the bloodstream to cause blood glucose levels to fall, insulin secretion is inhibited and glucagon and other counter regulatory mechanisms stimulate the release of glucose from the liver, which causes the blood glucose level to return to normal.

The reason most physiologic control systems function under negative rather than *positive feedback mechanisms* is that a positive feedback mechanism interjects instability rather than stability into a system. It produces a cycle in which the initiating stimulus produces more of the same. For example, in a positive feedback system, exposure to an increase in environmental temperature would invoke compensatory mechanisms designed to increase, rather than decrease, body temperature.

In summary, physiologic and psychological adaptation involves the ability to maintain the constancy of the internal environment (homeostasis) and behavior in the face of a wide range of changes in the internal and external environments. It involves negative feedback control systems that regulate cellular function, control life's processes, regulate behavior, and integrate the function of the different body systems.



■ **FIGURE 7-1** ■ Illustration of negative feedback control mechanisms using blood glucose as an example.

STRESS

The increased focus on health promotion has heightened interest in the roles of stress and biobehavioral stress responses in the development of disease.[8] Stress may contribute directly to the production or exacerbation of a disease, or it may contribute to the development of behaviors such as smoking, overeating, and drug abuse that increase the risk of disease.[9]

The Stress Response

In the early 1930s, the world-renowned endocrinologist Hans Selye was the first to describe a group of specific anatomic changes that occurred in rats that were exposed to a variety of different experimental stimuli. He came to an understanding that these changes were manifestations of the body's attempt to adapt to stimuli. Selye described *stress* as "a state manifested by a specific syndrome of the body developed in response to any stimuli that made an intense systemic demand on it."[10] As a young medical student, Selye noticed that patients with diverse disease conditions had many signs and symptoms in common. He observed that "whether a man suffers from a loss of blood, an infectious disease, or advanced cancer, he loses his appetite, his muscular strength, and his ambition to accomplish anything; usually the patient also loses weight and even his facial expression betrays that he is ill."[11] Selye referred to this as the "syndrome of just being sick."

In his early career as an experimental scientist, Selye noted a triad of adrenal enlargement, thymic atrophy, and gastric ulcer appeared in rats he was using for his studies. These same three changes developed in response to many different or nonspecific experimental challenges. He assumed that the hypothalamic-pituitary-adrenal (HPA) axis played a pivotal role in the development of this response. To Selye, the response to stressors was a process that enabled the rats to resist the experimental challenge by using the function of the system best able to respond to it. He labeled the response the *general adaptation syndrome* (GAS): *general* because the effect was a general systemic reaction, *adaptive* because the response was in reaction to a stressor, and *syndrome* because the physical manifestations were coordinated and dependent on each other.[10]

According to Selye, the GAS involves three stages: the alarm stage, the stage of resistance, and the stage of exhaustion. The *alarm stage* is characterized by a generalized stimulation of the sympathetic nervous system and the HPA axis, resulting in the release of catecholamines and cortisol. During the *resistance stage,* the body selects the most effective and economic channels of defense. During this stage, the increased cortisol levels present during the first stage drop because they are no longer needed. If the stressor is prolonged or overwhelms the ability of the body to defend itself, the *stage of exhaustion* ensues, during which resources are depleted and signs of "wear and tear" or systemic damage appear.[12] Selye contended that many ailments, such as various emotional disturbances, mildly annoying headaches, insomnia, upset stomach, gastric and duodenal ulcers, certain types of rheumatic disorders, and cardiovascular and kidney diseases appear to be initiated or encouraged by the "body itself because of its faulty adaptive reactions to potentially injurious agents."[11]

The events or environmental agents responsible for initiating the stress response were called *stressors*. According to Selye, stressors could be endogenous, arising from within the body, or exogenous, arising from outside the body.[11] In explaining the stress response, Selye proposed that two factors determine the nature of the stress response: the properties of the stressor and the conditioning of the person being stressed. Selye indicated that not all stress was detrimental; thus, he coined the terms *eustress* and *distress*.[12] He suggested that mild, brief, and controllable periods of stress could be perceived as positive stimuli to emotional and intellectual growth and development. It is the severe, protracted, and uncontrolled situations of psychological and physical distress that are disruptive of health.[11] For example, the joy of becoming a new parent and the sorrow of losing a parent are completely different experiences, yet their stressor effect—the nonspecific demand for adjustment to a new situation—can be similar.

Stressors tend to produce different responses in different persons or in the same person at different times, indicating the influence of the adaptive capacity of the person, or what Selye called *conditioning factors*. These conditioning factors may be internal (*e.g.*, genetic predisposition, age, gender) or external (*e.g.*, exposure to environmental agents, life experiences, dietary factors, level of social support).[11] The relative risk for development of a stress-related pathologic process seems, at least in part, to depend on these factors.

Neuroendocrine-Immune Interactions

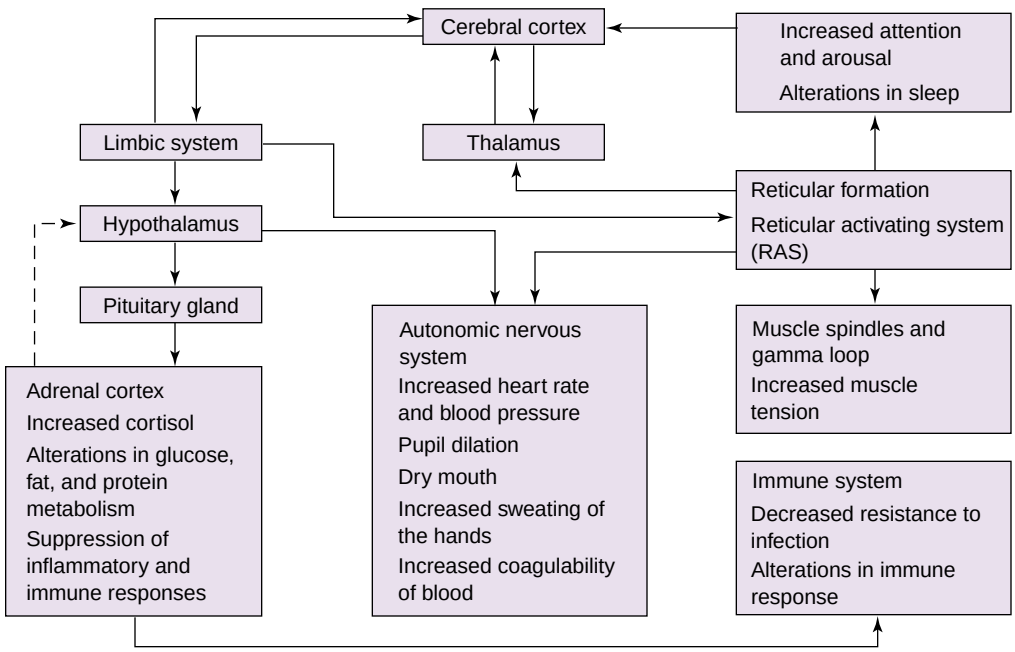
The manifestations of the stress response are strongly influenced by both the nervous and endocrine systems. The neuroendocrine systems integrate signals received along neurosensory pathways and from circulating mediators that are carried in the bloodstream. In addition, the immune system both affects and is affected by the stress response.

The stress response is meant to protect the person against acute threats to homeostasis and is normally time limited. Therefore, under normal circumstances, the neural responses and the hormones that are released during the response are not around long enough to cause damage to vital tissues. However, in situations in which the stress response is hyperactive or becomes habituated, the physiologic and behavioral changes (*e.g.*, immunosuppression, sympathetic system activation) induced by the response can themselves become a threat to homeostasis. If the stress response is hypoactive, the person may be more susceptible to diseases associated with overactivity of the immune response.[9]

Neuroendocrine Responses

The integration of the stress responses, which occurs at the level of the central nervous system (CNS), is complex and not completely understood. It relies on communication along neuronal pathways of the cerebral cortex, the limbic system, the thalamus, the hypothalamus, the pituitary gland, and the reticular activating system (RAS) (Fig. 7-2). The cerebral cortex is involved with vigilance, cognition, and focused attention, and the limbic system with emotional components (*e.g.*, fear, excitement, rage, anger) of the stress response. The thalamus functions as the relay center and is important in receiving, sorting out, and distributing sensory input. The hypothalamus coordinates the responses of the endocrine and autonomic nervous systems (ANS). The RAS modulates mental alertness, ANS activity, and skeletal muscle tone, using input from other neural structures. The musculoskeletal tension that occurs during the stress response reflects the increased activity of the RAS and its influence on the reflex circuits that control muscle tone.

Locus Ceruleus. Central to the neural component of the neuroendocrine response to the stress is an area in the brain stem



■ **FIGURE 7-2** ■ Stress pathways. The broken line represents negative feedback.

called the locus ceruleus (LC).[13] The locus ceruleus is densely populated with neurons that produce norepinephrine (NE) and is thought to be the central integrating site for the ANS response to stressful stimuli (Fig. 7-3). The LC-NE system has afferent pathways to the hypothalamus, the limbic system, the hippocampus, and the cerebral cortex.

The LC-NE system confers an adaptive advantage during a stressful situation. The sympathetic nervous system manifestation of the stress reaction has been called the *fight-or-flight response.* This is the most rapid of the stress responses and represents the basic survival response of our primitive ancestors when confronted with the perils of the wilderness and its inhabitants. The increase in sympathetic activity in the brain increases attention and arousal and thus probably intensifies memory. The heart and respiratory rates increase, the hands and feet become moist, the pupils dilate, the mouth becomes dry, and the activity of the gastrointestinal tract decreases.

The Corticotropin-Releasing Factor. The corticotropin-releasing factor (CRF) is central to the endocrine component of the neuroendocrine response to stress (Fig. 7-3). CRF is a small peptide hormone found in both the hypothalamus and in extrahypothalamic structures, such as the limbic system and the brain stem. It is both an important endocrine regulator of pituitary and adrenal activity and a neurotransmitter involved in autonomic nervous system activity, metabolism, and behavior.[9,14,15] Receptors for CRF are distributed throughout the brain as well as many peripheral sites. CRF from the hypothalamus induces the secretion of the adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH, in turn, stimulates the adrenal gland to synthesize and secrete the glucocorticoid hormones (*e.g.*, cortisol).

The glucocorticoid hormones have a number of direct or indirect physiologic effects that mediate the stress response, enhance the action of other stress hormones, or suppress other components of the stress system. In this regard, cortisol acts both as a mediator of the stress response and an inhibitor of the stress response such that overactivation does not occur.[16] Cortisol maintains blood glucose levels by antagonizing the effects of insulin and enhances the effect of catecholamines on the cardiovascular system. It also suppresses osteoblast activity, hematopoiesis, protein and collagen synthesis, and immune responses. All of these functions are meant to protect the organism against the effects of a stressor and to focus energy on regaining balance in the face of an acute challenge to homeostasis.

Other Hormones. A wide variety of other hormones, including growth hormones, thyroid hormone, and the reproductive hormones, also are responsive to stressful situations. Systems responsible for reproduction, growth, and immunity are directly linked to the stress system, and the hormonal effects of the stress response profoundly influence these systems.

Although growth hormone is initially elevated at the onset of stress, the prolonged presence of cortisol leads to suppression of growth hormone, somatomedin C, and other growth factors, exerting a chronically inhibitory effect on growth. In addition, CRF directly increases somatostatin, which in turn inhibits growth hormone secretion. Although the connection is speculative, the effects of stress on growth hormone may provide one of the vital links to understanding failure to thrive in children.

Stress-induced cortisol secretion also is associated with decreased levels of thyroid-stimulating hormone and inhibition of conversion of thyroxine to the more biologically active triiodothyronine in peripheral tissues. Both changes may serve as a means to conserve energy at times of stress.

Antidiuretic hormone (ADH) also is involved in the stress response, particularly in hypotensive stress or stress caused by

■ **FIGURE 7-3** ■ Neuroendocrine–immune system regulation of the stress response.

fluid volume loss. ADH, also known as vasopressin, increases water retention by the kidneys, produces vasoconstriction of blood vessels, and appears to synergize CRF's capacity to increase the release of ACTH.

The reproductive hormones are inhibited by CRF at the hypophyseal level and by cortisol at the pituitary, gonadal, and target tissue level.[11] Sepsis and severe trauma can induce anovulation and amenorrhea in women and decreased spermatogenesis and decreased levels of testosterone in men.

Immune Responses

The hallmark of the stress response, as first described by Selye, is the endocrine-immune interactions (*i.e.*, increased corticosteroid production and atrophy of the thymus) that are known to suppress the immune response. In concert, these two components of the stress system, through endocrine and neurotransmitter pathways, produce the physical and behavioral changes designed to adapt to acute stress. Much of the literature regarding stress and the immune response focuses on the causal role of stress in immune-related diseases. It has also been suggested that the reverse may occur; emotional and psychological manifestations of the stress response may be a reflection of alterations in the CNS resulting from the immune response (Fig. 7-3). Immune cells such as monocytes and lymphocytes can penetrate the blood-brain barrier and take up residence in the brain, where they secrete cytokines and other inflammatory mediators that influence the stress response. In the case of cancer, this could mean that the subjective feelings of helplessness and hopelessness that have been repeatedly related to the onset and progression of cancers may arise secondary to the CNS effects of products released by immune cells during the early stage of the disease.[17]

The exact mechanism by which stress produces its effect on the immune response is unknown and probably varies from person to person, depending on genetic endowment and environmental factors. The most significant arguments for interactions between the neuroendocrine and immune systems derive from evidence that the immune and neuroendocrine systems share common signal pathways (*i.e.*, messenger molecules and receptors), that hormones and neuropeptides can alter the function of immune cells, and that the immune system and its mediators can modulate neuroendocrine function.[18] Receptors for a number of CNS-controlled hormones and neuromediators reportedly have been found on lymphocytes. Among these are receptors for glucocorticoids, insulin, testosterone, prolactin, catecholamines, estrogens, acetylcholine, and growth hormone, suggesting that these hormones influence lymphocyte function. For example, cortisol is known to suppress immune function, and pharmacologic doses of cortisol are used clinically to suppress the immune response. There is evidence that the immune system, in turn, influences neuroendocrine function.[19] It has been observed that the HPA axis is activated by cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor that are released from immune cells (see Chapter 8).

A second possible route for neuroendocrine regulation of immune function is through the sympathetic nervous system and the release of catecholamines. The lymph nodes, thymus, and spleen are supplied with ANS nerve fibers. Centrally acting CRF activates the ANS through multisynaptic descending pathways, and circulating epinephrine acts synergistically with CRF and cortisol to inhibit the function of the immune system.

Not only is the quantity of immune expression changed because of stress, but the quality of the response is changed. Stress hormones differentially stimulate the proliferation of subtypes of T lymphocyte helper cells. Because these T helper cell subtypes secrete different cytokines, they stimulate different aspects of the immune response. One subtype tends to stimulate the cellular-mediated immune response; whereas, a second type tends to activate B lymphocytes and humoral-mediated immune responses.[7]

Coping and Adaptation to Stress

The ability to adapt to a wide range of environments and stressors is not peculiar to humans. According to René Dubos (a microbiologist noted for his study of human responses to the total environment), "adaptability is found throughout life and is perhaps the one attribute that distinguishes most clearly the world of life from the world of inanimate matter."[20] Living organisms, no matter how primitive, do not submit passively to the impact of environmental forces. They attempt to respond adaptively, each in its own unique and most suitable manner. The higher the organism on the evolutionary scale, the larger its repertoire of adaptive mechanisms and its ability to select and limit aspects of the environment to which it responds. The most fully evolved mechanisms are the social responses through which individuals or groups modify their environments, their habits, or both to achieve a way of life that is best suited to their needs.

Adaptation

Human beings, because of their highly developed nervous system and intellect, usually have alternative mechanisms for adapting and have the ability to control many aspects of their environment. Air conditioning and central heating limit the need to adapt to extreme changes in environmental temperature. The availability of antiseptic agents, immunizations, and antibiotics eliminates the need to respond to common infectious agents. At the same time, modern technology creates new challenges for adaptation and provides new sources of stress, such as increased noise, air pollution, exposure to harmful chemicals, and changes in biologic rhythms imposed by shift work and transcontinental air travel.

Of particular interest are the differences in the body's response to events that threaten the integrity of the body's physiologic environment and those that threaten the integrity of the person's psychosocial environment. Many of the body's responses to physiologic disturbances are controlled on a moment-by-moment basis by feedback mechanisms that limit their application and duration of action. For example, the baroreflex-mediated rise in heart rate that occurs when a person moves from the recumbent to the standing position is almost instantaneous and subsides within seconds. Furthermore, the response to physiologic disturbances that threaten the integrity of the internal environment is specific to the threat; the body usually does not raise the body temperature when an increase in heart rate is needed. In contrast, the response to psychological disturbances is not regulated with the same degree of specificity and feedback control; instead, the effect may be inappropriate and sustained.

KEY CONCEPTS

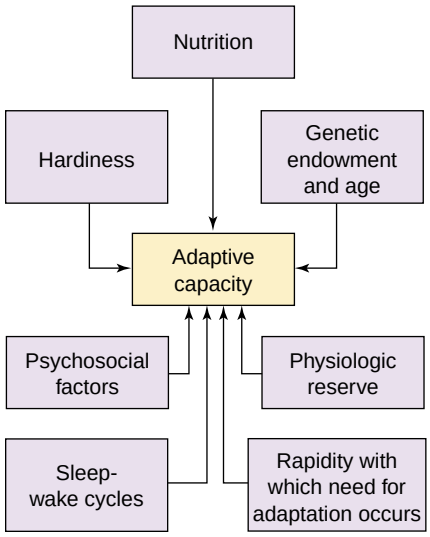
STRESS AND ADAPTATION

- Stress is a state manifested by symptoms that arise from the coordinated activation of the neuroendocrine and immune systems, which Selye called the *general adaptation syndrome.*
- The hormones and neurotransmitters (catecholamines and cortisol) that are released during the stress response function to alert the individual to a threat or challenge to homeostasis, to enhance cardiovascular and metabolic activity in order to manage the stressor, and to focus the energy of the body by suppressing the activity of other systems that are not immediately needed.
- Adaptation is the ability to respond to challenges of physical or psychological homeostasis and to return to a balanced state.
- The ability to adapt is influenced by previous learning, physiologic reserve, time, genetic endowment, age, health status and nutrition, sleep-wake cycles, and psychosocial factors.

Factors Affecting the Ability to Adapt

Adaptation implies that an individual has successfully created a new balance between the stressor and the ability to deal with it. The means used to attain this balance are called *coping strategies* or *coping mechanisms.* Coping mechanisms are the emotional and behavioral responses used to manage threats to our physiologic and psychological homeostasis. According to Lazarus, how we cope with stressful events depends on how we perceive and interpret the event.[21] Is the event perceived as a threat of harm or loss? And, is the event perceived as a challenge rather than a threat? Physiologic reserve, time, genetic endowment and age, health status, nutrition, sleep-wake cycles, hardiness, and psychosocial factors influence a person's appraisal of a stressor and the coping mechanisms used to adapt to the new situation (Fig. 7-4).

Physiologic and Anatomic Reserve. The trained athlete is able to increase cardiac output sixfold to sevenfold during exercise. The safety margin for adaptation of most body systems is considerably greater than that needed for normal activities. The red blood cells carry more oxygen than the tissues can use, the liver and fat cells store excess nutrients, and bone tissue stores calcium in excess of that needed for normal neuromuscular function. The ability of body systems to increase their function given the need to adapt is known as the *physiologic reserve.* Many of the body organs, such as the lungs, kidneys, and adrenals, are paired to provide anatomic reserve as well. Both organs are not needed to ensure the continued existence and maintenance of the internal environment. Many persons function normally with only one lung or one kidney. For example, in kidney disease signs of renal failure do not occur until approximately 90% of the functioning nephrons have been destroyed.



■ **FIGURE 7-4** ■ Factors affecting adaptation.

Time. Adaptation is most efficient when changes occur gradually, rather than suddenly. For instance, it is possible to lose a liter or more of blood through chronic gastrointestinal bleeding during the period of a week without manifesting signs of shock. However, a sudden hemorrhage that causes rapid loss of an equal amount of blood is likely to cause hypotension and shock.

Genetic Endowment. Adaptation is further affected by the availability of adaptive responses and flexibility in selecting the most appropriate and economical response. The greater the number of available responses, the more effective is the capacity to adapt.

Genetic endowment can ensure that the systems that are essential to adaptation function adequately. Even a gene that has deleterious effects may prove adaptive in some environments. In Africa, the gene for sickle cell anemia persists in some populations because it provides some resistance to infection with the parasite that causes malaria.

Age. The capacity to adapt is decreased at the extremes of age. The ability to adapt is impaired by the immaturity of an infant, much as it is by the decline in functional reserve that occurs with age. For example, the infant has difficulty concentrating urine because of immature renal structures and therefore is less able than an adult to cope with decreased water intake or exaggerated water losses. A similar situation, caused by age-related changes in renal function, exists in the elderly.

Health Status. Physical and mental health status determines physiologic and psychological reserves and is a strong determinant of the ability to adapt. For example, persons with heart disease are less able to adjust to stresses that require the recruitment of cardiovascular responses. Severe emotional stress often produces disruption of physiologic function and limits

the ability to make appropriate choices related to long-term adaptive needs. Those who have worked with acutely ill persons know that the will to live often has a profound influence on survival during life-threatening illnesses.

Nutrition. There are 50 to 60 essential nutrients, including minerals, lipids, certain fatty acids, vitamins, and specific amino acids. Deficiencies or excesses of any of these nutrients can alter a person's health status and impair the ability to adapt. The importance of nutrition to enzyme function, immune response, and wound healing is well known. On a worldwide basis, malnutrition may be one of the most common causes of immunodeficiency.

Among the problems associated with dietary excess are obesity and alcohol abuse. Obesity is a common problem. It predisposes to a number of health problems, including atherosclerosis and hypertension. Alcohol is commonly used in excess. It acutely affects brain function and, with long-term use, can seriously impair the function of the liver, brain, and other vital structures.

Sleep-Wake Cycles. Sleep is considered to be a restorative function in which energy is restored and tissues are regenerated.[22] Sleep occurs in a cyclic manner, alternating with periods of wakefulness and increased energy use. Biologic rhythms play an important role in adaptation to stress, development of illness, and response to medical treatment. Many rhythms, such as rest and activity, work and leisure, and eating and drinking, oscillate with a frequency similar to that of the 24-hour light-dark solar day. The term *circadian,* from the Latin *circa* ("about") and *dies* ("day"), is used to describe these 24-hour diurnal rhythms.

Sleep disorders and alterations in the sleep-wake cycle have been shown to alter immune function, the normal circadian pattern of hormone secretion, and physical and psychological functioning.[23] The two most common manifestations of an alteration in the sleep-wake cycle are insomnia and sleep deprivation or increased somnolence. In some persons, stress may produce sleep disorders, and in others, sleep disorders may lead to stress. Acute stress and environmental disturbances, loss of a loved one, recovery from surgery, and pain are common causes of transient and short-term insomnia. Air travel and jet lag constitute additional causes of altered sleep-wake cycles, as does shift work. In persons with chronic insomnia, the bed often acquires many unpleasant secondary associations and becomes a place of stress and worry, rather than a place of rest.[24]

Hardiness. Studies by social psychologists have focused on individuals' emotional reactions to stressful situations and their coping mechanisms to determine those characteristics that help some people remain healthy despite being challenged by high levels of stressors. For example, the concept of *hardiness* describes a personality characteristic that includes a sense of having control over the environment, a sense of having a purpose in life, and an ability to conceptualize stressors as a challenge, rather than a threat.[25] Many studies by nurses and social psychologists suggest that hardiness is correlated with positive health outcomes.[25]

Psychosocial Factors. Several studies have related social factors and life events to illness. Scientific interest in the social environment as a cause of stress has gradually broadened to include the social environment as a resource that modulates the relation between stress and health. Presumably, persons who can mobilize strong supportive resources from within their social relationships are better able to withstand the negative effects of stress on their health. Studies suggest that social support has direct and indirect positive effects on health status and serves as a buffer or modifier of the physical and psychosocial effects of stress.[26]

Social networks contribute in a number of ways to a person's psychosocial and physical integrity. The configuration of significant others that constitutes this network functions to mobilize the resources of the person; these friends, colleagues, and family members share the person's tasks and provide monetary support, materials and tools, and guidance in improving problem-solving capabilities.[26] Persons with ample social networks are not as likely to experience many types of stress, such as being homeless or being lonely.[9] There is also evidence that persons who have social supports or social assets may live longer and have a lower incidence of somatic illness.[27]

Social support has been viewed in terms of the number of relationships a person has and the person's perception of these relationships.[28] Close relationships with others can involve positive effects as well as the potential for conflict and may, in some situations, leave the person less able to cope with life stressors.

In summary, the stress response is an activation of several physiologic systems (sympathetic nervous system, the HPA axis, and the immune system) that work in a coordinated fashion to protect the body against damage from the intense demands made on it. Selye called this response the *general adaptation syndrome.* The stress response is divided into three stages: the *alarm stage,* with activation of the sympathetic nervous system and the HPA axis; the *resistance stage,* during which the body selects the most effective defenses; and the *stage of exhaustion,* during which physiologic resources are depleted and signs of systemic damage appear.

The activation and control of the stress response are mediated by the combined efforts of the nervous and endocrine systems. The neuroendocrine systems integrate signals received along neurosensory pathways and from circulating mediators that are carried in the bloodstream. In addition, the immune system both affects and is affected by the stress response.

Adaptation is affected by a number of factors, including experience and previous learning, the rapidity with which the need to adapt occurs, genetic endowment and age, health status, nutrition, sleep-wake cycles, hardiness, and psychosocial factors.

DISORDERS OF THE STRESS RESPONSE

For the most part, the stress response is meant to be acute and time limited. The time-limited nature of the process renders the accompanying catabolic and immunosuppressive effects advantageous. It is the chronicity of the response that is thought to be disruptive to physical and mental health.

Stressors can assume a number of patterns in relation to time. They may be classified as acute time-limited, chronic intermittent, or chronic sustained. An acute time-limited stressor is one that occurs over a short time and does not recur; a chronic intermittent stressor is one to which a person is chronically exposed. The frequency or chronicity of circumstances to which the body is asked to respond often determines the availability and efficiency of the stress responses. For example, the response of the immune system is more rapid and efficient on second exposure to a pathogen than it is on first exposure, but chronic exposure to a stressor can fatigue the system and impair its effectiveness.

Effects of Acute Stress

The reactions to acute stress are those associated with the autonomic nervous system, the fight-or-flight response. The manifestations of the stress response—a pounding headache, cold moist skin, a stiff neck—are all part of the acute stress response. Centrally, there is facilitation of neural pathways mediating arousal, alertness, vigilance, cognition, and focused attention, as well as appropriate aggression. The acute stress response can result from either psychologically or physiologically threatening events. In situations of life-threatening trauma, these acute responses may be lifesaving in that they divert blood from less essential to more essential body functions. Increased alertness and cognitive functioning enables rapid processing of information and arrival at the most appropriate solution to the threatening situation.

However, for persons with limited coping abilities, either because of physical or mental health, the acute stress response may be detrimental. This is true of persons with pre-existing heart disease in whom the overwhelming sympathetic behaviors associated with the stress response can lead to dysrhythmias. For people with other chronic health problems, such as headache disorder, acute stress may precipitate a recurrence. In healthy individuals, the acute stress response can redirect attention from behaviors that promote health, such as attention to proper meals and getting adequate sleep. For those with health problems, it can interrupt compliance with medication regimens and exercise programs. In some situations, the acute arousal state actually can be life threatening, physically immobilizing the person when movement would avert catastrophe (*e.g.*, moving out of the way of a speeding car).

Effects of Chronic Stress

The stress response is designed to be an acute self-limited response in which activation of the ANS and the HPA axis is controlled in a negative feedback manner. As with all negative feedback systems, including the stress response system, pathophysiologic changes can occur. Function can be altered in several ways, including when a component of the system fails; when the neural and hormonal connections among the components of the system are dysfunctional; and when the original stimulus for the activation of the system is prolonged or of such magnitude that it overwhelms the ability of the system to respond appropriately. In these cases, the system may become overactive or underactive.

Chronicity and excessive activation of the stress response can result from chronic illnesses as well as contribute to the development of long-term health problems. Chronic activation of the stress response is an important public health issue from both a health and a cost perspective. The National Institute for Occupational Safety and Health declared stress a hazard of the workplace.[29] It is linked to a myriad of health disorders, such as diseases of the cardiovascular, gastrointestinal, immune, and neurologic systems, as well as depression, chronic alcoholism and drug abuse, eating disorders, accidents, and suicide.

Occurrence of the oral disease acute necrotizing gingivitis, in which the normal bacterial flora of the mouth become invasive, is known by dentists to be associated with acute stress, such as final examinations.[30] Similarly, herpes simplex type 1 infection (*i.e.*, cold sores) often develops during periods of inadequate rest, fever, ultraviolet radiation, and emotional upset. The resident herpesvirus is kept in check by body defenses, probably T lymphocytes, until a stressful event occurs that causes suppression of the immune system. Psychological stress is associated in a dose-response manner with an increased risk for development of the common cold, and this risk is attributable to increased rates of infection, rather than frequency of symptoms after infection.[31]

In a study in which participants were infected with the influenza virus, persons who reported the greatest amount of premorbid stress reported the most intense influenza symptoms and had a statistically greater production of interleukin-6, a cytokine that acts as a chemotactic agent for immune cells.[32] Elderly caregivers of a spouse with dementia had a significantly higher score for emotional distress and higher salivary cortisol than did matched control subjects. The higher stress was correlated with a decreased immune response to the influenza vaccine.[34] The experience of stress also has been associated with delays in wound healing.

Post-traumatic Stress Disorder

The post-traumatic stress disorder (PTSD) is an example of chronic activation of the stress response as a result of experiencing a potentially life-threatening event. It was formerly called *battle fatigue* or *shell shock* because it was first characterized in men and women returning from combat. Although war is still a significant cause of PTSD, other major catastrophic events, such as major weather-related disasters, airplane crashes, terrorist bombings, and rape or child abuse, also may result in the development of the disorder. The terrorist attacks on the World Trade Center and Pentagon on September 11, 2001, represented an amalgam of interpersonal violence, loss, and threat to tens of thousands of people.[35] These events have influenced and will continue to influence the development of PTSD in a substantial number of people. On the basis of data obtained after the 1995 bombing of the Murrah Federal Building in Oklahoma City, it is predicted that PTSD will develop in approximately 35% of those who were directly exposed to the September 11 attacks.[36]

PTSD is characterized by a constellation of symptoms that are experienced as states of intrusion, avoidance, and hyperarousal. *Intrusion* refers to the occurrence of "flashbacks" during waking hours or nightmares in which the past traumatic event is relived, often in vivid and frightening detail. *Avoidance* refers to the emotional numbing that accompanies this disorder and disrupts important personal relationships. Because a

person with PTSD has not been able to resolve the painful feelings associated with the trauma, depression is commonly a part of the clinical picture. Survivor guilt also may be a product of traumatic situations in which the person survived the disaster but loved ones did not. *Hyperarousal* refers to the presence of increased irritability and exaggerated startle reflex. In addition, memory problems, sleep disturbances, and anxiety are commonly experienced by persons with PTSD.

Although the pathophysiology of PTSD is not completely understood, the elucidation of physiologic changes related to the disorder has shed light on why some people recover from the disorder but others do not. It has been hypothesized that the intrusive symptoms of PTSD may arise from exaggerated sympathetic nervous system activation in response to the traumatic event. Persons with chronic PTSD have been shown to have increased levels of norepinephrine and increased activity of α_2-adrenergic receptors.[35] The increase in catecholamines, in tandem with increased thyroid levels in persons with PTSD, is thought to explain some of the intrusive and somatic symptoms of the disorder.[35,37]

Recent neuroanatomic studies have identified alterations in two brain structures—the amygdala and hippocampus. Positron-emission tomography and functional magnetic resonance imaging (MRI) have shown increased reactivity of the amygdala and hippocampus and decreased reactivity of the anterior cingulate and orbitofrontal areas. These areas of the brain are involved in fear responses. The hippocampus also functions in memory processes. Differences in hippocampal function and memory processes suggest a neuroanatomic basis for the intrusive recollections and other cognitive problems that characterize PTSD.[35]

Despite the observed neuroanatomical changes, persons with PTSD do not uniformly undergo the biological responses associated with other types of stress.[38] For example, persons with PTSD demonstrate decreased cortisol levels, increased sensitivity of cortisol receptors, and an enhanced negative feedback inhibition of cortisol release with the dexamethasone suppression test. Dexamethasone is a synthetic glucocorticoid that mimics the effects of cortisol and directly inhibits the action of CRF and ACTH. This is in contrast to patients with major depression, who have a decreased sensitivity of glucocorticoid receptors, a high plasma level of cortisol, and a decreased dexamethasone suppression.[38] The hypersuppression of cortisol observed with the dexamethasone test suggests that persons with PTSD do not exhibit a classic stress response as described by Selye. Because this hypersuppression has not been described in other psychiatric disorders, it may serve as a relatively specific marker for PTSD.

Little is known about the risk factors that predispose people to the development of PTSD. It is important to note that less than half of all people who are exposed to a traumatic event experience PTSD. For example, only 15% to 30% of soldiers exposed to combat experience the disorder.[39] It also has been found that children exposed to violent events but who have strong family relationships rarely experience PTSD.[40] Statistics indicate there is a need for studies to determine risk factors for PTSD as a means of targeting individuals who may need intensive therapeutic measures after a life-threatening event. Research also is needed to determine the mechanisms by which the disorder develops so that it can be prevented, or if that is not possible, so that treatment methods can be created to decrease the devastating effects that this disorder has on affected individuals and their families.[37]

Health care professionals need to be aware that clients who present with symptoms of depression, anxiety, and alcohol or drug abuse may in fact be experiencing PTSD. The client history should include questions concerning the occurrence of violence, major loss, or traumatic events in the person's life. Debriefing, or talking about the traumatic event at the time it happens, often is an effective therapeutic tool. Crisis teams are among the first people to attend to the emotional needs of those caught in catastrophic events. Some people may need continued individual or group therapy. Often concurrent pharmacotherapy, such as antidepressants and antianxiety agents, is useful and helps the individual participate more fully in therapy.

Most important, the person with PTSD must not be made to feel responsible for the disorder or that it is evidence of a character flaw. It is not uncommon for persons with this disorder to be told to "get over it" or "just get on with it, because others have." There is ample evidence to suggest that there is a biologic basis for the individual differences in responses to traumatic events, and these differences need to be taken into account.

Treatment of Stress Disorders

The treatment of stress should be directed toward helping people avoid coping behaviors that impose a risk to their health and providing them with alternative stress-reducing strategies. Purposeful priority setting and problem solving can be used by persons who are overwhelmed by the number of life stresses to which they have been exposed. Other nonpharmacologic methods used for stress reduction are relaxation techniques, guided imagery, music therapy, massage, and biofeedback.

Relaxation

Practices for evoking the relaxation response are numerous. They are found in virtually every culture and are credited with producing a generalized decrease in sympathetic system activity and musculoskeletal tension. According to Herbert Benson, a physician who worked in developing the technique, four elements are integral to the various relaxation techniques: a repetitive mental device, a passive attitude, decreased mental tonus, and a quiet environment.[41] Benson developed a noncultural method that is commonly used for achieving relaxation (see accompanying box).

Progressive muscle relaxation, originally developed by Edmund Jacobson, who did extensive research on the muscle correlates of anxiety and tension, is another method of relieving tension. He observed that tension can be defined physiologically as the inappropriate contraction of muscle fibers. His procedure, which has been modified by a number of therapists, consists of systematic contraction and relaxation of major muscle groups.[42] As the person learns to relax, the various muscle groups are combined. Eventually, the person learns to relax individual muscle groups without first contracting them.

Imagery

Guided imagery is another technique that can be used to achieve relaxation. One method is scene visualization, in which the person is asked to sit back, close the eyes, and con-

The Relaxation Response

- Sit quietly in a comfortable position.
- Deeply relax all your muscles, beginning at your feet and progressing up to your face.
- Breathe through your nose. Become aware of your breathing. As you breathe out, say the word "one" silently to yourself. Continue for 20 minutes. When you have finished, sit quietly for several minutes, first with your eyes closed and then with them open.
- Do not worry about whether you are successful in achieving a deep level of relaxation. Maintain a positive attitude and permit the relaxation to occur at its own rate. Expect distracting thoughts, ignore them, and continue repeating "one" as you breathe out.

(Modified from Benson H. [1977]. Systemic hypertension and the relaxation response. *New England Journal of Medicine* 296, 1152)

centrate on a scene narrated by the therapist. Whenever possible, all five senses are involved: the person attempts to see, feel, hear, and taste aspects of the visual experience. Other types of imagery involve imagining the appearance of each of the major muscle groups and how they feel during tension and relaxation.

Music Therapy

Music therapy is used for both its physiologic and psychological effects. It involves listening to selected pieces of music as a means of ameliorating anxiety or stress, reducing pain, decreasing feelings of loneliness and isolation, buffering noise, and facilitating expression of emotion. Music is defined as having three components: rhythm, melody, and harmony.[43,44] Rhythm is the order in the movement of the music. Rhythm is the most dynamic aspect of music, and particular pieces of music often are selected because they harmonize with body rhythms, such as heart rhythm, respiratory rhythm, or gait. The melody is created by the musical pitch and distance (or interval) between the musical tone. The melody contributes to the listener's emotional response to the music. The harmony results from the way pitches are blended together, with the combination of sounds described as consonant or dissonant by the listener. Music usually is selected based on a person's musical preference and past experiences with music. Depending on the setting, headphones may be used to screen distracting noises. Radio and television music is inappropriate for music therapy because of the inability to control the selection of pieces that are played, the interruptions that occur (*e.g.*, commercials and announcements), and the quality of the reception.

Massage Therapies

Massage is the manipulation of the soft tissues of the body to promote relaxation and relief of muscle tension. The technique that is used may involve a gentle stroking along the length of a muscle (effleurage), application of pressure across the width of a muscle (pétrissage), deep massage movements applied by a circular motion of the thumbs or fingertips (friction), squeezing across the width of a muscle (kneading), or use of light slaps or chopping actions (hacking).[45] Massage may be administered by practitioners who have received special training in its use or by less prepared persons, such as parents of small children[46,47] or caregivers of confused elders.[48] It often is used as a means of physiologic relaxation and stress relief in critically ill patients.[49]

Biofeedback

Biofeedback is a technique in which an individual learns to control physiologic functioning. It involves electronic monitoring of one or more physiologic responses to stress with immediate feedback of the specific response to the person undergoing treatment. Several types of responses are used: electromyographic (EMG), electrothermal, and electrodermal (EDR).[50] The EMG response involves the measurement of electrical potentials from muscles, usually the forearm extensor or frontalis. This is used to gain control over the contraction of skeletal muscles that occurs with anxiety and tension. The electrodermal sensors monitor skin temperature in the fingers or toes. The sympathetic nervous system exerts significant control over blood flow in the distal parts of the body such as the digits of the hands and feet. Consequently, anxiety often is manifested by a decrease in skin temperature in the fingers and toes. EDR sensors measure conductivity of skin (usually the hands) in response to anxiety. Fearful and anxious people often have cold and clammy hands, which leads to a decrease in conductivity.

In summary, stress is neither negative nor deleterious to health. The stress response is designed to be time limited and protective, but in situations of prolonged activation of the response because of overwhelming or chronic stressors, it could be damaging to health. PTSD is an example of chronic activation of the stress response as a result of experiencing a severe trauma. In this disorder, memory of the traumatic event seems to be enhanced. Flashbacks of the event are accompanied by intense activation of the neuroendocrine system.

Treatment of stress should be aimed at helping people avoid coping behaviors that can adversely affect their health and providing them with other ways to reduce stress. Nonpharmacologic methods used in the treatment of stress include relaxation techniques, guided imagery, music therapy, massage techniques, and biofeedback.

REVIEW QUESTIONS

- Describe the concept of homeostasis as it relates to a specific body function.
- State Selye's definition of stress.
- Relate Selye's description of the general adaptation syndrome to the signs and symptoms experienced by a person with a condition such as hemorrhagic shock.
- Describe the contributions of the autonomic nervous system, endocrine system, and the immune system to the stress response.
- List at least six factors that influence a person's adaptive apacity.

- Describe the physiologic and psychological effects of a chronic stress response.
- Describe the three states characteristic of post-traumatic stress disorder.
- Describe at least five nonpharmacologic methods of treating stress.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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