Chapter 4
Stress-Related Disease: A Review

I'm at the mercy of any rogue who cares to annoy and tease me.

John Hunter, eighteenth-century physician

There has been skepticism that emotions aroused in a social context can so seriously affect the body as to lead to long-term disease or death. But the work, such as that of Wolf, shows that machinery of the human body is very much at the disposal of the higher centers of the brain…. Given the right circumstances, these higher controls can drive it mercilessly, often without awareness on the part of the individual of how close he is to the fine edge.

(Henry & Stephens, 1977, p. 11)

To review what we have covered so far, Chap. 2 proposed a model of how psychosocial factors can activate a complex myriad of neurological, neuroendocrine, and endocrine response axes. Similarly, Chap. 2 reviewed the physiological constituents of these stress axes in considerable detail. Chapter 3 reviewed the link from stress arousal to disease by summarizing several noteworthy models constructed to elucidate how stress arousal can lead to disease and dysfunction, that is, mechanisms of pathogenesis that link causally stress arousal to target-organ pathology. The goal of this chapter is to review some of the most common clinical manifestations of excessive stress, and more specifically, to familiarize the reader with some of the most frequently encountered target-organ disorders believed to be related to excessive stress arousal.

Gastrointestinal Disorders

Excessive stress and the diseases of the gastrointestinal (GI) system have been thought to be related for decades. The most commonly encountered stress-related GI disorders are peptic ulcers, ulcerative colitis, irritable bowel syndrome, and esophageal reflux.

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Gastrointestinal Physiology

Before reviewing specific disorders, let us briefly review the basic physiology of the GI system. As described by Weinstock and Clouse (1987), the GI system involves a series of sequentially arranged tubular organs separated by sphincters. This system includes the esophagus, the stomach, the duodenum, the small intestine, and the large intestine (colon). See Fig. 4.1.

The esophagus provides a tubular canal for the connection of the mouth and the stomach. The activity of the esophagus is primarily under vagal control and neural mechanisms are primarily responsible for esophageal motility. The upper border of the esophagus is the cricopharyngeus (upper esophageal sphincter). The lower border is the lower esophageal sphincter, the gateway to the stomach.

The basic functions of the stomach are to receive, pulverize, nutritionally regulate, and temporarily store the food one consumes. The stomach is lined with a mucosal tissue that serves to protect it from its own digestive processes. Under the influence of factors such as gastrin, histamine, and vagal and sympathetic stimulation, intragastric dynamics involving the release of hydrochloric acid, pepsin, and mucus, as well as muscular contractions, act upon food that has been delivered to the stomach from the esophagus.

From the stomach, the food passes through the pyloric sphincter to the duodenum. The gallbladder is responsible for releasing bile into the duodenum.

The small intestine and its specialized mucosal lining serves as the primary location for digestion and nutrient absorption. Finally, the large intestine is designed for the absorption and orderly evacuation of concentrated waste products (Weinstock & Clouse, 1987). Let us now review several common stress-related GI disorders.

Peptic Ulcers

Peptic ulcers are usually further classified by their location in the GI system: gastric or stomach ulcers and duodenal ulcers. The incidence of peptic ulcer disease is about 18 in 10,000, with duodendal ulcers accounting for about 75% of those cases.

It was demonstrated many years ago that emotions of anger and rage are related to increased secretion of acid and pepsin by the stomach and that this secretion decreased with depression (Mahl & Brody, 1954; Mittelman & Wolff, 1942; Wolf & Glass, 1950). Although it might be concluded that what one sees in gastric ulcers, that is, an erosion of the wall of the stomach by the acid and enzyme it produces, is simply an exaggeration of a normal physiological response; actually it is not quite so simple. Certainly, emotions can raise gastric acid secretion and exacerbate an already existing ulcer, but normally the stomach wall is protected from the acid within it by a lining of mucus secreted by other cells in its wall. How this protective system breaks down and what predisposes a person to such an event remains elusive.

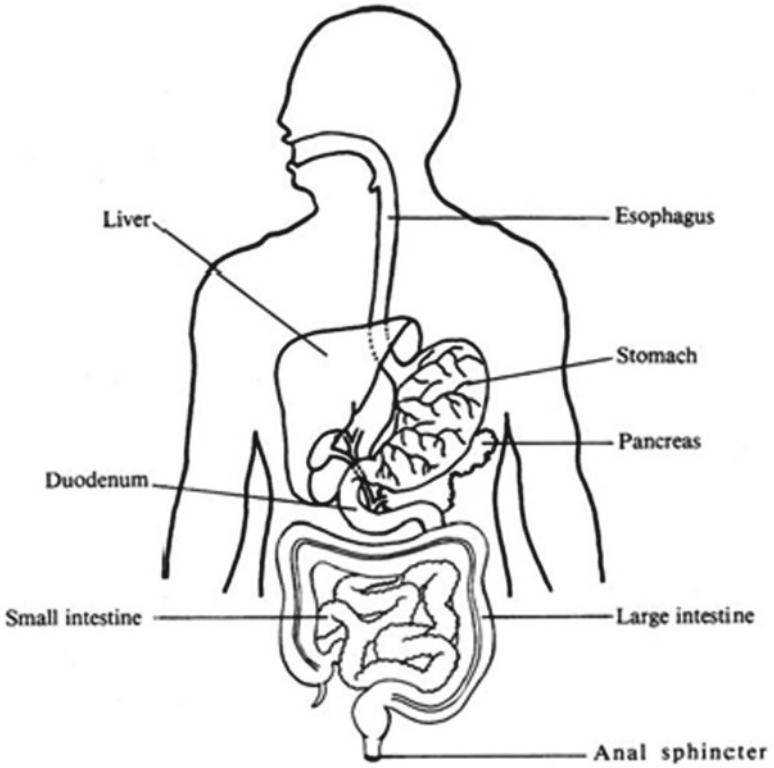

Fig. 4.1 The gastrointestinal system. (*Source*: Daniel A. Girdano and George S. Everly, Jr. (1986). *Controlling Stress and Tension: A Holistic Approach*, 2nd ed., pp. 36, 39. Reprinted by permission of Prentice-Hall, Inc., Englewood Cliffs, NJ)

There seems to be a combination of emotional and genetic factors involved in the pathogenesis of gastric ulcers, and such studies as that of Weiner, Thaler, Reiser, and Mirsky (1957) have demonstrated this quite well. These investigators were able to predict which individuals in a group of recruits in basic training in the army would develop gastric ulcers on the basis of serum pepsinogen levels—a genetic trait that is apparently a necessary but not sufficient factor in the formation of gastric ulcers. Gastric ulcers were also of interest to Selye (1951), who described ulcers apparently in response to chronic arousal of the endocrine stress axes in the general adaptation syndrome. One could thus conceive of a mechanism whereby stress, through the intermediation of neural or hormonal mechanisms, could result in significant irritation. In individuals who are so predisposed, ulceration of the stomach would occur given sufficient time and continued exposure to the stress. The picture is less clear-cut, however, in that it has been suggested that the duodenal ulcer results from changes in the mucosal wall "associated with sustained activation and a feeling of being deprived" (Backus & Dudley, 1977, p. 199).

Therefore, strongly implicated in the stress response, the specific causal mechanisms involved in peptic ulcer formation are probably multifactorial. Vagus-stimulated gastric hypersecretion as well as glucocorticoid anti-inflammatory activity on the mucous lining has been implicated. Yet conclusive data are lacking at present with regard to the selective activation of each mechanism. Bacteriological infections have most recently been implicated in ulcer formation, but a primary main effect seems doubtful. Rather, some complex interaction effect between arousal and bacteria seems more likely in instances where bacteria are, indeed, implicated.

Ulcerative Colitis

Ulcerative colitis is an inflammation and ulceration of the lining of the colon. Research by Grace, Seton, Wolf, and Wolff (1949) and Almy, Kern, and Tulin (1949) produced evidence that the colon becomes hyperactive and hyperemic with an increase in lysozyme levels (a proteolytic enzyme that can dissolve mucus) under stress. The emotions of anger and resentment are reported to create observable ulcerations of the bowel (Grace et al.). "Sustained feelings of this sort might be sufficient to produce enough reduction in bowel wall defenses to the point that the condition becomes self-sustaining" (Backus & Dudley, 1977, p. 199).

The predominant symptom of ulcerative colitis is rectal bleeding, although diarrhea, abdominal cramping and pain, and weight loss may also be present. Ulcerative colitis is sometimes associated with disorders of the spine, liver, and immune system. Rosenbaum (1985) has stated, "The frequency with which emotional precipitating-factors are identified varies, being as high as 74% in adults and 95% in children" (p. 79). Personologic investigations of colitis patients commonly find them to possess an immature personality structure often demonstrating extreme compulsive traits.

Irritable Bowel Syndrome

Mitchell and Drossman (1987) refer to irritable bowel syndrome (IBS) as the most common of the functional disorders. It is viewed as a syndrome of dysfunctional colonic motility; that is, the colon proves to be overreactive to psychological as well as physiological stimuli.

The diagnostic criteria for IBS include atypical abdominal pain, altered bowel habits, symptomatic duration of 3 months or more, and disruption of normal lifestyle (Latimer, 1985). Abdominal distention, mucus in the stools, fecal urgency, nausea, loss of appetite, and even vomiting are other IBS symptoms.

The pathophysiology of IBS is clearly multifactorial, with abnormal myoelectric phenomena, altered gut opiate receptors, abnormal calcium channel activity, and increased alpha-adrenergic activity. Personality characteristics of IBS patients often

Table 4.1 Psychological stimuli and gastrointestinal responses

Psychological state	GI response
Anxiety	Increased esophageal motility
	Increased colonic contractions
	Increased intraluminal pressure of the colon
Hostility, resentment, aggression (without somatomotor expression)	Increased colonic contractions
	Increased gastric acid
	Increased contractile activity of stomach
Depression	Decreased gastric acid
	Decreased colonic contractions
Wish to be rid of trouble	Rapid colonic transit with diarrhea

include compulsiveness, overly conscientious behavior, interpersonal sensitivity, and nonassertiveness (Latimer, 1985). Whitehead (1992) found stress to be related to acute IBS exacerbation and disability.

Esophageal Reflux

Before leaving this section on GI disorders it would be prudent to mention gastroesophageal reflux and its frequent corollary, esophagitis. Dotevall (1985) has indicated that these syndromes are common stress-related disorders. According to Young, Richter, Bradley, and Anderson (1987):

> Heartburn, a common GI symptom, generally is experienced as a painful substernal burning sensation. However, sensations can radiate into the arms or jaw and mimic pain associated with coronary artery disease. Heartburn [esophageal reflux] symptoms typically occur after eating, when lying down, or during bending or straining. The symptoms result from frequent irritation of the sensitive mucosal lining of the esophagus by the usually acidic gastric contents. (p. 8)

Although the primary physiological cause of esophageal reflux and esophagitis is a weakened lower esophageal sphincter, psychological factors are known to contribute to the reflux phenomenon (Dotevall, 1985).

In his superb review of GI physiology and stress, Dotevall (1985) listed the known effects of varied emotional reactions on GI activity. These are summarized in Table 4.1.

Cardiovascular Disorders

The cardiovascular system is thought by many researchers and clinicians to be the prime-target end organ for the stress response. The cardiovascular disorders most often associated with excessive stress are essential hypertension, migraine headache, and Raynaud's disease.

Cardiovascular Physiology

Before reviewing those specific disorders, a brief review of cardiovascular physiology is appropriate. Figure 4.2 details the cardiovascular system.

The heart is the key component in the cardiovascular system. It pumps nutrient-rich, oxygenated arterial blood to the cells of the body while at the same time pumping venous blood, which carries the various metabolic waste products.

The heart is divided into two halves: a right heart and a left heart. The circulatory cycle begins with blood entering the right heart. This blood supply is waste-filled venous blood. It has traveled throughout the venules and veins once it left the capillary beds, where the nutrient and gaseous exchanges initially took place within the body. The venous blood enters the resting heart and fills a small feeder chamber called the right atrium. Blood then passively moves through the tricuspid valve into the pumping chamber of the right heart, the right ventricle. Once the right ventricle is almost completely filled, an electrical impulse begins in the sinoatrial conducting node so as to contract the right atrium. This action forces any remaining blood into the right ventricle.

More specifically, the electrical impulse transverses the atrium until it reaches the atrioventricular node, where there is a fraction-of-a-second delay completing the filling of the right ventricle. Then the electrical impulse is sent through the ventricle, forcing it to contract and pump the venous blood through the pulmonary valve toward the lungs via the pulmonary artery. Once the blood arrives in the lungs, waste products such as carbon dioxide are exchanged for oxygen and the blood is returned to the heart.

The left heart receives the fresh, oxygenated blood from the lungs via the pulmonary vein. This blood enters the left heart at the point of the left atrium. From here the blood is moved through the mitral valve into the left heart's pumping chamber, the left ventricle. Once again, when the heart beats, it sends the electrical impulse from the sinoatrial node through the left atrium to the atrioventricular node, ultimately culminating in the contraction of the left ventricle. Blood pumped from the left ventricle passes through the aortic valve through the aorta into the arterial system, including the coronary arteries. The arteries narrow into arterioles, which feed the capillary beds where the cells exchange gases and nutrients. Then the capillaries feed the venules, which feed the veins, and the cycle is repeated.

Both the right and left hearts pump simultaneously; therefore, blood is being pumped to the lungs at the same time it is being pumped out to the body.

The cardiovascular system is a closed-loop system. As such, pressure within the system is a necessary driving force. The arterial system, including the left heart, is a high-pressure system driven by the contraction of the left ventricle. The venous system, including the right heart, is a low-pressure system, assisted in venous return by the contraction of the skeletal muscles during movement. Blood pressure, as it is typically measured and expressed, relates to the arterial system pressures. Blood pressure is measured in millimeters of mercury (mmHg) and is expressed in terms equivalent to the amount of pressure required to raise a column of mercury so many

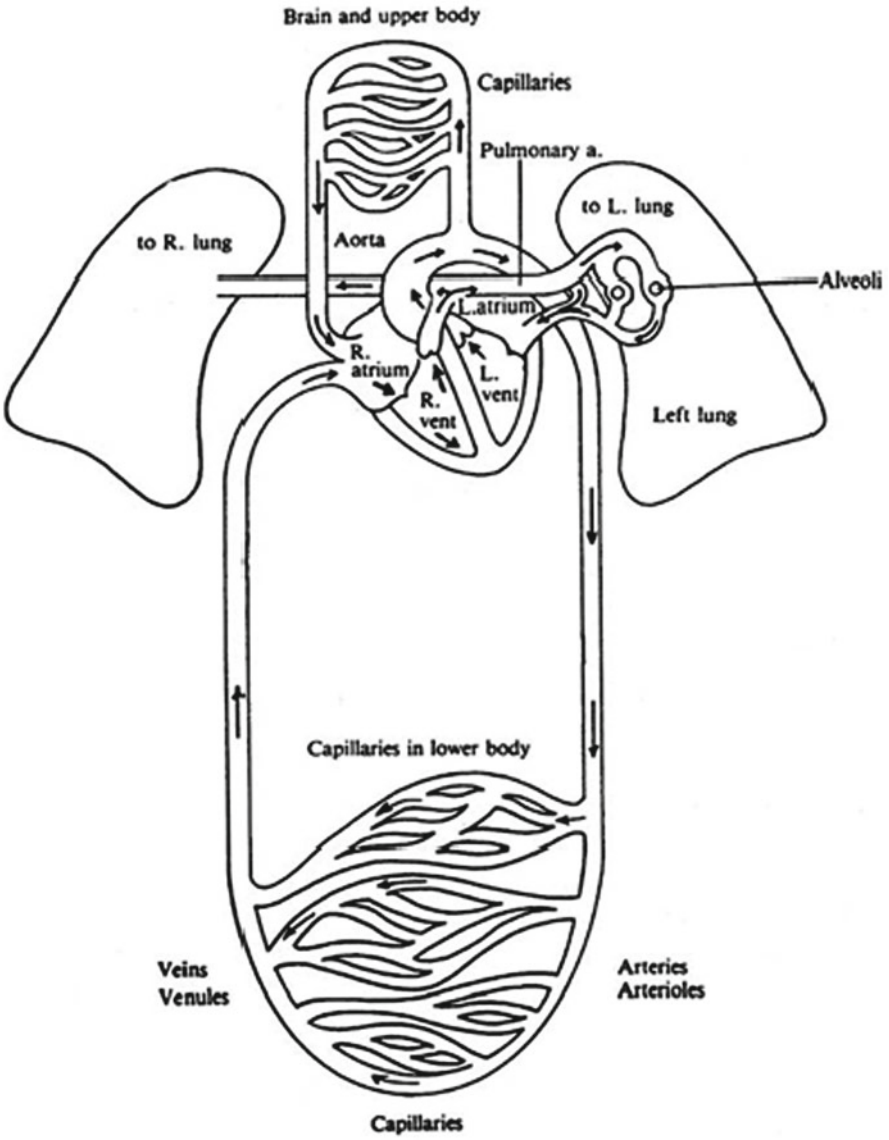

Fig. 4.2 The cardiovascular system. (*Source*: Daniel A. Girdano and George S. Everly, Jr. (1986). *Controlling Stress and Tension: A Holistic Approach*, 2nd ed., pp. 36, 39. Reprinted by permission of Prentice-Hall, Inc., Englewood Cliffs, NJ.)

millimeters. Blood pressure is expressed in terms of the systolic pressure (the pressure within the arteries during the contraction of the ventricles—called *systole*) and the diastolic pressure (the pressure within the arteries when the ventricles are filling at rest—called *diastole*).

Essential Hypertension

According to current estimates, 33% of adult Americans suffer from "the silent killer," cardiovascular hypertension. Cardiovascular hypertension is usually defined as arterial pressures over 140 mmHg systolic pressure and/or 80 mmHg diastolic pressure, although many authorities will adjust these figures upward (especially the systolic pressure) if the patient is advanced in age.

There are basically two types of cardiovascular hypertension: secondary and essential. Secondary cardiovascular hypertension represents a status of elevated blood pressure due to some organic dysfunction, for example, a pheochromocytoma (tumor of the adrenal gland). Essential hypertension has been loosely interpreted as being related to stress and such factors as diet. The term "essential" reflects the once-held notion that with advancing age one always acquired elevated blood pressure. This notion has been refuted (Henry & Stephens, 1977).

In a review of the pathophysiology of hypertension, Eliot (1979) states that in less than 10% of the cases, organic disorders explain hypertension. However, he suggests that both the SAM and the anterior pituitary–adrenocortical stress axes are capable of increasing blood pressure in response to psychosocial factors alone. This may occur through a wide range of diverse mechanisms (see also Selye, 1976). With chronic activation, he concludes, the deterioration of the cardiovascular system may be irreversible.

Henry and Stephens (1977), in a useful review of psychosocial stimulation and hypertension, present evidence similar to that of Eliot. In their review of animal and human studies, they point to the ability of the psychophysiological stress mechanisms to effect an increase in blood pressure. They point to the role of medullary norepinephrine as a vasoconstrictive force capable of increasing blood pressure. In addition, they point to the notion that increased sympathetic tonus (apparently regardless of origin) will lead to further increased sympathetic discharge. The end result may well be the tendency for the carotid sinus and aortic baroreceptors to "reset" themselves at a higher level of blood pressure. The normal effect of the baroreceptors is to act to moderate blood pressure elevations. However, if they are reset at higher levels, they will tolerate greater blood pressure before intervening. Therefore, resting blood pressure may be allowed to rise slowly over time. Finally, these authors point to the role of the adrenocortical response in the elevation of blood pressure, perhaps through some arterial narrowing or sodium-retaining mechanism. They suggest that psychosocial disturbance can play a major role in blood pressure elevations that could become chronic in nature (see Steptoe, 1981).

Weiner (1977), however, states that "psychosocial factors do not by themselves "cause" essential hypertension" (p. 183). They do, however, "interact with other predispositions" to produce high blood pressure (p. 185). He concludes that the available data point toward the conclusion that hypertension essentially can be caused by a wide variety of influences and that psychological and sociological factors "may play a different etiological, pathogenetic, and sustaining role in its different forms" (p. 185).

Vasospastic Phenomena

Stress-related vasospastic phenomena include migraine headaches and Raynaud's disease. These disorders involve vascular spasms; more specifically, their phenomenology involves spasms of the arterial vasculature induced by excessive neurological tone (usually SNS activity) (see Ganong, 1997).

Migraine headaches may affect as many as 29 million Americans. There are two basic subtypes: classical migraine and common migraine. Although both are characterized by vasomotor spasms, the classical migraine is accompanied by a prodrome. The prodrome often manifests in the form of visual disturbances, hearing dysfunction, expressive aphasia, and/or GI dysfunction. The most common form of prodrome is the visual prodrome, for example, the development of an acute visual scotoma. The prodrome is a symptom of severe arterial vasoconstriction. The pain that accompanies migraine headaches occurs on the "rebound," that is, the point at which the arterial vasculature vasodilates in response to the original vasoconstriction. It is unclear whether the pain actually results from the physical dystension of the arterial vasculature or from associated biochemical processes (see Raskin, 1985; Wolff, 1963).

Raynaud's disease is another vasospastic disorder characterized by episodic pallor and cyanosis of the fingers and/or toes. Upon rebound vasodilation, there can be extreme pain characterized by sensations of aching and throbbing. Both exposures to cold and psychosocially induced stress can induce an attack of Raynaud's (Taub & Stroebel, 1978) (see Appendices C and D).

Myocardial Ischemia and Coronary Artery Disease

Myocardial ischemia is a condition wherein the heart muscle endures a state of significantly reduced blood flow. "Myocardial ischemia occurs frequently in patients with coronary artery disease (CAD) and is a significant predictor of future cardiac events" (Gullette et al., 1997, p. 1521). Using a case-crossover design, Gullette and her colleagues demonstrated that mental stress can induce myocardial ischemia. Electrocardiogram (ECG) data were gathered with specific foci upon the emotions of negative tension, sadness, and frustration. Results of this investigation indicated that these negative emotions during daily life can more than double the risk of myocardial ischemia in the subsequent hour. Such ischemic findings were not in evidence subsequent to the states of happiness and feeling in control.

Previous studies have shown a significant correlation between myocardial episodes and the emotion of anger (Mittleman et al., 1995). Other studies have shown a significant relationship between the stress associated with mass disasters (Leor, Poole, & Kloner, 1996) and even missile attacks (Kark, Goldman, & Epstein, 1995), and subsequent cardiac death. Yet the Gullette et al. (1997) study is important in that the mechanisms of pathogenesis were observed rather than inferred.

Finally, the relationship between stress and CAD has been vigorously debated. In a review of investigations, Niaura and Goldstein (1995) conclude, "Our review of sociocultural and interpersonal factors … has identified evidence for a positive association among the following factors and CAD: occupational factors (e.g., job strain, low control, few possibilities for growth, low social support, life stress, and social isolation" (pp. 45–46). An important paper by Manuck, Marsland, Kaplan, and Williams (1995) that reviewed animal research concluded that psychosocial variables and social stress are associated with the promotion of coronary atherogenesis, impaired vasomotor responses of the coronary arteries, coronary lesions, and specific injury to arterial endothelium.

While more research is clearly needed, the argument in support of a significant role for stress in the etiology of CAD appears to be growing.

Respiratory Disorders

Allergy

An allergy is a hypersensitivity that some people develop to a particular agent. The patient's body reacts with an exaggerated immune-defensive response when it encounters the agent (antigen).

One of the most familiar forms of allergy is hay fever. In this condition, the individual is sensitive to some forms of plant pollen, and when these are inhaled from the air, mucous membranes swell, nasal secretion becomes excessive, and nasal obstruction can occur. Because other particles in the air do not seem to elicit such a response, this is clearly an overreaction to a stimulus. However, hay fever has been generally thought to be a phenomenon related only to the body, as opposed to the mind. Yet the mind–body dualism is once again questioned by the finding that some subject with hay fever may respond minimally, if at all, when challenged with the allergenic substance in an environment in which he or she feels secure and comfortable, whereas in other, more stressful situations, the same challenge is met with the usual nasal hypersecretion, congestion, and the like (Holmes, Trenting, & Wolff, 1951).

Bronchial Asthma

Although sharing some similarities with allergy, asthma is a more complex and potentially serious disorder. In asthmatic patients, bronchial secretions increase, mucosal swelling takes place and, finally, smooth muscle surrounding the bronchioles contracts, leading to a great difficulty in expiring air from the lungs. This "inability to breath" is, of course, anxiety producing, and this stress itself leads to a need for more oxygen, thus exacerbating the stress response caused by the original stimulus no matter what its nature. That bronchial asthmatic attacks can be caused

by or at least exacerbated by psychosocial stimulation is no longer in question. Research reviewed by Lachman (1972) warrants such a conclusion, as does the work of Knapp (1982). Stress-related asthma appears to be related to activation of the parasympathetic nervous system (Moran, 1995).

Hyperventilation

Hyperventilation may be considered an example of an acute stress response. However, episodic hyperventilation can become a long-standing problem that goes undiagnosed for long periods of time in patients presenting vague problems that do not fit any particular pattern, such as vague aches and pains, nausea, vomiting, chest pains, and the like. The clinician must be on guard for this particular manifestation of the stress response, in order to protect the individual from unnecessary suffering and expense while searching for the cause. This, again, is a part of the fight-or-flight response in which the body is readied for action by increasing O_2 and decreasing CO_2; however, no action takes place. It has been suggested that any time a patient presents such vague problems that seem elusive, the clinician should maintain a high degree of suspicion regarding hyperventilation. Consideration may then be given to asking the patient to hyperventilate in the office. If the symptoms are reproduced, much time and effort of both physician and patient may be saved. For methods and cautions, refer to articles by Campernolle, Kees, and Leen (1979) and Lum (1975); see also Knapp (1982).

Musculoskeletal Disorders

This system comprises, as its name implies, all the body's muscles and bony support. It is thus the system that is responsible for the body's mobility and therefore plays one of the more obvious roles in a fight-or-flight type of response. At such a time, the muscles tense, blood flow is increased to them, and the very word "tension" associated with emotions such as anger or anxiety relates to this state of the musculoskeletal system (Tomita, 1975).

The stress-related disorders here are quite predictable. Low back pain may often be produced in a situation in which there is contraction of the back muscles as if to keep the body erect for fleeing a situation. If the contraction continues but there is no associated action (and therefore the stress situation remains), blood flow to the muscles decreases, metabolites increase, and pain is produced (Dorpat & Holmes, 1955; Holmes & Wolff, 1952).

Tension headache is a similar situation. The muscles of the head and neck are kept in prolonged contraction, resulting in pain by the same mechanism. This is to be differentiated from the pain of vascular headaches, which seems to begin in periods *following* tension.

There have even been some studies that indicate a possible role for stress in the development or influence of the course of the inflammatory joint disease, rheumatoid arthritis (Amkraut & Solomon, 1974; Heisel, 1972; Selye, 1956).

Skin Disorders

The skin is thought to be a common target end organ for excessive arousal (Musaph, 1977). Common stress-related disorders include eczema, acne, urticaria, psoriasis, and alopecia areata (patchy hair loss) (Engels, 1985; Lachman, 1972). According to Medansky (1971), 80% of dermatological patients have a psychological overlay. Supporting such a conclusion is empirical evidence that various neurodermatological syndromes have either been initiated or exacerbated through the controlled manipulation of psychosocial variables (Engels, Lachman). The specific mechanisms of pathogenesis have yet to be satisfactorily detailed in most instances, however. Folks and Kinney (1995) provide a useful review of the role of psychological factors and various dermatological conditions.

Immune System

Perhaps the most intriguing and complex somatic target organ in the human body is the immune system. The implications for health and disease are literally profound. Imagine if psychological process can affect the immune system then virtually every cell in the human body can be a target of excessive stress and both noncommunicable and even communicable diseases then have the potential to be "stress-related" diseases. Let us explore the fascinating target organ in greater depth.

The immune system basically serves to protect the body from invading toxins and microorganisms that may damage organs and tissues. Some of the protective functions of the immune system are to eliminate bacteria and to reject foreign substances, known as antigens, that have entered the body. In addition, the immune system possesses a "memory" for encounters with foreign substances, such that a subsequent encounter induces a more rapid and potent response (Borysenko, 1987; Guyton & Hall, 2006). The immune system is often conceptually divided into innate or nonspecific immunity, which provides a general defense, and specific or acquired immunity, which acts against particular threatening antigens.

Innate Immunity

As the term implies, *innate immunity* refers to processes that are apparent from birth and provide a general or nonspecific defense by acting against anything identified

as foreign or *not self* (Thibodeau & Patton, 1993). There are many variations of innate immunity. For example, species-resistant, innate immunity makes the human body unsuitable to some potentially lethal animal diseases such as distemper. Conversely, dogs and cats are resistant to human diseases such as mumps or measles. Other nonspecific types of immunity include physical barriers, such as the skin's outer keratin layer, which limits entry into the body, and biochemical substances, such as tears, saliva, and perspiration, which contain enzymes that digest or weaken the walls surrounding bacterial cells (Parslow, 1994). These anatomical and chemical barriers serve as the body's *first line of defense* against invading toxins (Abbas & Lichtman, 2011; Guyton & Hall, 2006; Thibodeau & Patton, 1993).

If bacteria or other microorganisms penetrate this first line of defense, the body has a second, nonspecific or general line of innate protection that incorporates phagocytosis, natural killer (NK) cells, interferon, and inflammation. Phagocytosis, which involves the destruction and absorption of microorganisms, utilizes cells known as phagocytes to eliminate pathogens (any organism causing disease). Nearly all tissues and organs possess inhabitant phagocytes. There are a variety of phagocytic cells, including (1) neutrophils, the most numerous type, accounting for one-half to two-thirds of circulating white blood cells (which are primarily involved in destroying pathogens); (2) monocytes, which are relatively large cells produced in the bone marrow and released into the blood for about 1 day before settling in a selective tissue; and (3) macrophages, the settled or mature monocytic cells, which are large, avid eliminators of foreign particles and debris (Abbas & Lichtman, 2011; Guyton & Hall, 2006).

In addition to phagocytes, the body possesses natural killer (NK) cells, which are lymphocytes (one type of white blood cell) that kill various tumor cells and cells infected by viruses. One of the common ways NK cells function is by breaking down or lysing cells by damaging their plasma membrane. NK cells are currently considered to be an initial or frontline protective response that is utilized before a more specific response can be exhibited (Imboden, 1994). Therefore, although probably related to cytotoxic T lymphocytes (see acquired immunity below), NK cells serve a broad surveillance-like function that, unlike T cells, do not require prior antigen interaction (McDaniel, 1992). Therefore, NK cells are often included as part of the nonspecific immune functions.

About 40 years ago, it was discovered that some cells exposed to viruses produce a secretory protein known as interferon, which, as the name implies, "interferes" with the ability of viruses to produce diseases. Basically, interferon works by producing an antiviral state within the host that prevents viruses from replicating in cells. Interferon has also been associated with the modulation of immune responses.

Inflammation, or the inflammatory response, is also considered part of the body's second line of defense and characterizes the complex manner in which tissues and cells react to an insult or microbial invasion. Immediately after an injury, there is a brief constriction, followed by dilation, of blood vessels. Injured tissues then release a number of chemical mediators, such as histamine, kinins, and prostaglandins (Abbas & Lichtman, 2011; Thibodeau & Patton, 1993). The factors involved in the inflammatory response characteristically results in redness, warmth,

swelling, and pain. Although the inflammatory response is considered beneficial, it can be detrimental if it permanently injures the host tissues and/or impedes normal functioning.

Acquired Immunity

Contrary to nonspecific immunity described earlier, acquired or specific immune mechanisms attack certain agents that the body recognizes as *not self*. Therefore, specific immunity may be considered the body's *third line of defense* (Thibodeau & Patton, 1993). Acquired immunity develops in late fetal and neonatal life and is part of the body's lymphatic system. The lymphatic system, a part of the circulatory system, consists of a vast network of vessels and organs that drains excess fluid and provides a defense for the body (Moore, 1992). Lymphocytes, which circulate in the body's fluids, are the major cells controlling the immune response. They are found most extensively in the lymph nodes, which are glands composed of composites of lymphoid tissues, but are also located in special lymphoid tissues such as the spleen, bone marrow, and gastrointestinal tract (Moore). Lymphoid tissue is strategically disseminated throughout the body and allows for rapid interception and filtering of invading organisms and toxins. Two major types of lymphocytes involved in acquired immunity are T (thymus-derived) cells that form activated lymphocytes and are primarily involved in the slower acting cell-mediated immunity, and B (bone-marrow derived) cells that form circulating antibodies and are primarily involved in the more rapidly responding humoral immunity. Although these two types of lymphocytes are structurally similar, T and B cells are functionally distinct in their reaction to antigens (Abbas & Lichtman, 2011).

Cell-Mediated Processes

In cell-mediated immunity, each T lymphocyte, or T cell, operates by having a precisely distinctive surface receptor that allows it to recognize and bind to only one invading antigen. Thus, a T cell may have numerous receptor sites; however, all of them will be specific for only a certain antigen. T cells, which account for 70–80% of disseminated lymphocytes, circulate in the blood in an inactive form and are incapable of recognizing antigens without assistance. Therefore, when an antigen invades the body, it is typically first identified and then ingested by macrophages, which initiate the process of digestion. The T cells, whose surface receptors match the antigens, then travel to the now inflamed tissues and bind to the antigen.

Once in contact with the antigen, the sensitized T cell begins to divide repeatedly to form a clone of identical, activated T cells (Abbas & Lichtman, 2011; Guyton & Hall, 2006; Thibodeau & Patton, 1993). The antigen-bound, sensitized T cells then release lymphocyte-derived chemical messengers, commonly called cytokines, into

the inflamed tissue to facilitate the immune response (Dunn, 1989). Several variations of T lymphocytes, or T cells, include, for example, helper cells (T-4). The T-helper cell, once activated by the cytokine interleukin-1 (IL-1), releases interleukin-2 (IL-2), which fosters the maturation and marshals the subsequent immune response, including the promotion and multiplication of cytotoxic cells used to combat the invading antigen. There are also suppressor cells (T-8), which inhibit the immune response in order to regulate it, memory T cells, which initiate a rapid response if the antigen is encountered again, and cytotoxic or killer cells, which release a powerfully destructive cytokine called lymphotoxin (Borysenko, 1987).

A distinguishing characteristic of cell-mediated immunity is that specifically sensitized or activated lymphocytes are employed to pursue and contact the invading antigen. Typically, these antigen cells are foreign to the body, malignant, or have been transplanted into the tissue. Therefore, cell-mediated immunity, which requires a localized response that may require several days to detect the invader and to employ the necessary cells to battle it, not only defends us from viruses and cancer but also is directly involved in the rejection of organ and tissue transplants.

Humoral Responses

Comparable to T lymphocytes, B lymphocytes, or B cells, are also initiated by macrophage stimulation. In humoral immunity, an encounter with an antigen activates the B lymphocytes, which, after being released from the bone marrow, circulate to the lymph nodes, spleen, and other lymphoid tissues. Whereas cytotoxic T cells, as described earlier, exit lymphoid tissue to encounter an antigen directly, B cells produce their effects indirectly (McDaniel, 1992). When an antigen binds to antigen receptors on the B cell, the activated B cell divides to form a clone or group of identical B cells. Some of the offspring of these B cells become differentiated to form plasma cells known as antibodies that circulate in the lymph and the blood, and combine selectively with the triggering antigen (Abbas & Lichtman, 2011; Guyton & Hall, 2006). Thus, antibodies are produced within a species to fit part of the antigen (Abbas & Lichtman; Guyton & Hall; Kendall, 1998). The binding of the antigen to the antibodies forms a complex that may (1) render the toxic antigens innocuous, (2) facilitate a bundling of antigens that allows phagocytes and macrophages to dispose of them rapidly, or (3) slightly alter the contour of the antibody, allowing the destruction of the foreign cells.

Antibodies belong to a group of proteins called globulins and are, therefore, referred to as immunoglobulins. The five different classes of antibodies or immunoglobulins known to exist in humans are designated as IgG, IgA, IgM, IgD, and IgE. Each immunoglobulin has a unique structure and function, and as mentioned earlier, generally defends the host by neutralizing toxins, blocking attachment of viruses to cells, or inducing phagocytosis of bacteria or other microorganisms. IgG is the most common immunoglobulin, accounting for around 70% of the circulating antibodies (Goldsby, Kindt, & Osborne, 2000). Therefore, immunoglobulins “not only serve as surface

receptors for foreign substances but also can be released to search out and bind their targets at a considerable distance from the cell" (Parslow, 1994, p. 26).

Activated B cells that do not differentiate into plasma cells are known as memory B cells. Memory B cells do not produce or secrete antibodies. However, if they are exposed at some later time to the antigen responsible for their initial formation, then memory B cells convert into plasma cells that secrete antibodies (Guyton & Hall, 2006). Because there are many more memory cells than the initial B lymphocyte that was cloned, subsequent exposure to the same antigen will produce a more rapid and formidable antibody response (Abbas & Lichtman, 2011; Guyton & Hall).

Different antigens stimulate distinct B cells to develop into plasma cells and memory B cells. Most antigens activate both T and B lymphocytes concurrently, and there is in fact a cooperative relationship between the two (Guyton & Hall, 2006). The primary difference between the T and B cells is that B cells release antibodies, whereas whole T cells are activated and released into the lymph. Therefore, these latter cells may last for months to years in the body fluid (Abbas & Lichtman, 2011; Guyton & Hall).

Also of note, the effects of circulating antibodies and cellular immunity are influenced by a component of blood plasma enzymes known as the complement system, which entails different protein compounds. This system can be initiated by specific or nonspecific immune mechanisms and is closely involved in destroying various foreign tissues in a process known as cytolysis.

Because there is no easy access to the organs containing immune cells, and given that components of the immune system circulate in blood, it is not surprising that psychoneuroimmunological research often involves assessing the immune processes occurring in circulating peripheral blood. However, although peripheral blood is a key factor in immune responses and relatively easy to access (Herbert & Cohen, 1993), some researchers have questioned whether quantifying the typically variable and minute changes in the number or percentages of various white blood cells (neutrophils, monocytes, and lymphocytes) allows for a consistently reliable and completely valid detection of altered immune functioning (Cohen & Herbert, 1996).

Immune functioning has also been assessed by stimulating lymphocytes through incubation with mitogens, which produce nonspecific divergence of T or B cells. In this type of research, greater propagation of cells is usually equated with more effectiveness. Phytohemagglutinin (PHA), pokeweed mitogen (PWM), and concanavalin A (ConA) are the most commonly investigated mitogens. The procedures just described utilize what are known as in vitro tests, in which cells are removed from an organism and their function is then studied in a lab. There are also in vivo tests that study cellular function in living organisms. The quantification of antibodies to herpes viruses is an in vivo test frequently used in psychoneuroimmunology research. Basically, herpes viruses are common viruses that we have all been exposed to at some time in our lives. What makes them unique, however, is that after exposure, they usually remain present yet inactive in the body. When the immune system is threatened or challenged, this inactive virus may begin to replicate. Therefore, assessing and quantifying the level of antibodies to the herpes viruses provides evidence of immune function. More specifically, greater levels of herpes virus antibodies indicate suppressed cellular immune function (Herbert & Cohen, 1993).

Stress and Immune Functioning: Animal Studies

There has been an evolution from animal and human research investigating the link between biogenic and psychosocial stressors, immune functioning, and disease processes. The effects of humoral and cell-mediated immunity, as well as tumor growth and survival, have been used as outcome variables (Bohus & Koolhaas, 1991). In the animal literature, myriad stressors have been used to investigate the impact on immunological functioning. For example, Hans Selye's original description of the GAS was in response to exposing laboratory rats to diverse, nocuous agents, such as cold temperatures, severed spinal cords, excessive exercise, or drug injections. Following exposure to these stimuli, Selye (1936) documented decreased circulating lymphocytes; rapid decreased size of the thymus, spleen, lymph glands, and liver; formation of erosions in the stomach; and loss of muscle tone. He further noted that the animals often developed "resistance" with continued exposure to the stressors that mimicked normal functioning; however, with additional exposure of 1–3 months, the animals became "exhausted" and developed the symptoms described earlier.

The impact of environmental stressors on infectious disease processes has been reviewed extensively in the literature (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004). Laboratory animals have been exposed to electric foot shocks, cold temperatures, loud noises, restraints, crowding, handling, and isolation. For example, restraint models that place rats or mice in narrow tubes or use adhesive substances placed on boards to maintain immobilization often prohibit their movement. These types of studies have often resulted in cellular and humoral suppression, as well as impaired NK-cell activity (Koolhaas & Bohus, 1995; Steplewski & Vogel, 1986). Studies examining the effects of handling, picking up, and holding laboratory animals for various lengths of time have shown a decrease in IgG antibody production and decreased T-cell function (Moynihan et al., 1994). However, additional data have shown that adding another stressor, such as an intraperitoneal injection, resulted in attenuated corticosterone and catecholamine responses in previously handled mice compared to unhandled mice. Thus, Moynihan and colleagues suggested that the psychosocial stressor of handling may result in habituation to the effects of the stress response.

The general immune responses of decreased IgG-antibody production, NK-cell activity, and lymphocyte generation have been fairly well established in response to electric shocks (Cunnick, Lysle, Armfield, & Rabin, 1988; Laudenslager et al., 1988). Other researchers have expanded these findings to include an investigation of psychosocial stressors such as decreased predictability and control. Despite equivocal data, evidence suggests that laboratory rats provided an opportunity to perform a response to avoid or eliminate electric shock developed less severe gastric ulceration and less rapid tumor growth formation than those exposed to the same amount of electric shocks without controllability (Sklar & Anisman, 1979; Weiss, 1968). Foot shock as a physical stressor causes release of pheromones that are an important aspect of rodent communication. Moynihan and colleagues (1994) reported on the results of an investigation in which pheromones produced by foot-shocked mice changed immune functioning in those mice receiving the odor.

Interestingly, they reported suppression in cell-mediated responses and enhanced humoral responses in the odor-exposed mice. Other data have suggested that learning and memory circuits may be conditioned at the CNS level following acute exposure to electric shock, and that these conditioned responses may have both immunosuppressive and immunoenhancement effects (Koolhaas & Bohus, 1995).

Psychosocial stressors induced by crowding and isolation have also been widely studied for their modulating effects on immunity. The results of numerous studies of high-density crowding have generally demonstrated increased disease susceptibility and decreased survival. In one of the original studies of this phenomenon, Vessey (1964) reported that placing typically isolated male mice in a group setting for 4 h a day resulted in lower antibody responses to a mitogen. Of particular interest, the dominant male mouse in the group had the highest antibody production. Other studies have shown that physically dominant or aggressive male rats in a social colony have higher antibody generation, whereas submissive or defeated rats and mice have demonstrated increased immunosuppression (Bohus & Koolhaas, 1991; Koolhaas & Bohus, 1989). Fleshner, Laudenslager, Simons, and Maier (1989) have also shown that engaging in submissive behaviors, as compared to continuing to react aggressively and receiving multiple bites, correlated with reduced antibody formation to an injected antigen. These data suggest that animals may evidence individual differences in coping styles to given stressors. The active coping style has been associated with high SNS reactivity, whereas passive coping has been considered to be affiliated with increased reactivity of the pituitary–adrenocortical axis. As noted by Koolhaas and Bohus (1995), "This interaction between environment and individual is… crucial to understanding the relationship between stress and immunity" (p. 78).

Stress and Immune Function: Human Studies

While the bulk of early empirical data on the effects of "psychological factors" on the immune system was derived from animal studies, in the past 35 years there has been a proliferation of studies conducted with human participants. Since human research is more focused on whether psychological factors or mood states alter immunity and health outcomes, we will briefly review some of the more salient findings that have recently occurred. This in no way is meant to minimize the relevance or impact of animal research, but for sake of space, and consistent with the purpose of this text, we will focus briefly on human studies.

In preface, we should note that investigators need to consider the subtle, selective, multifaceted nature of the precipitants (e.g., age, gender, emotional status, and genetic factors) and physical consequences of stress, in addition to the complex and often lengthy duration of immune responses before generating broadly conclusive causal statements about how stress directly alters immune function (Zeller, McCain, McCann, Swanson, & Colletti, 1996; see Maier et al., 1994, for a detailed discussion on this topic). As the eminent Paul Rosch (1995) noted, "These and other caveats must be considered when evaluating sweeping statements and conclusions

about the effect of "stress" on "immune function" or therapeutic triumphs based on psychoneuroimmunological approaches" (p. 214).

These precautionary notes are not intended to diminish the outstanding advancements and notable influence of stress-induced immunomodulation research or the unequivocal impact that emotions such as stress have on immunity. Instead, they are intended to inform the reader that exploring, uncovering, and externally validating generally accepted tenets between psychological variables such as stress and immunity involve a complex process that continues to evolve. For example, it is worth considering that many of the proposed relations between psychosocial stressors (e.g., loss of a spouse) and disease (e.g., depression) that are often credited to immune changes may be strongly affected by behavioral health changes such as alcohol or drug consumption, noncompliance with medications, decreased sleep, and poorer diets that occur following the stressor (Cohen & Herbert, 1996). That having been said, let us briefly review the putative impact of selected "psychological factors" upon the immune system.

Bereavement

The preponderance of early evidence relating psychological components of human health and disease has been anecdotal, and, of course, ethical considerations have usually precluded the type of controlled experimental research conducted on animals. Correlational designs have primarily been used to examine the impact of stressors such as negative life events on illness and immune function. For example, bereavement studies have consistently demonstrated differences between unmarried and married individuals in terms of physical health. Immune functioning in the form of lymphocyte production was shown to be decreased in several prospective studies of bereaved and nonbereaved men and women who had lost a spouse due to illnesses such as breast and lung cancer (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977; Irwin, Daniels, Smith, Bloom, & Weiner, 1987; Schleifer, Keller, Camerino, Thornton, & Stein, 1983). In a separate but related study, Linn, Linn, and Jensen, (1984) suggested that reduction in lymphocytes was more influenced by level of depression than by bereavement. A meta-analysis demonstrated that clinically depressed individuals have a poorer response to mitogens PHA, ConA, and PWM, and lowered NK- and helper T-cell activity (Herbert & Cohen, 1993). Irwin, Lacher, and Caldwell (1992) have provided longitudinal data suggesting that with successful treatment of depression, decreased NK activity is abrogated. However, the data on immune correlates of depression are not universally supportive (Ravindran, Griffiths, Merali, & Anisman, 1995), and discrepant findings have led researchers to suggest that compromised immune functioning may be more evident in elderly, severely depressed, and hospitalized patients (Houldin, Lev, Prystowsky, Redei, & Lowery, 1991). In a 10-year follow-up of the long-term impact of bereavement on spousal health in a sample of 152 participants, Jones, Bartrop, Forcier, and Penny (2010) reported an overall increase in morbidity of 10–20% compared with a control sample. The information in this chapter is limited to bereavement and immune function. For a comprehensive overview of grief, loss, and stress, see Chap. 20.

Depression

Major depressive disorder (MDD) has been associated with various changes in levels of the neurotransmitters serotonin, norepinephrine, and dopamine, There has been growing theoretical and empirical evidence to suggest, however, that the inflammatory response of the immune system (which is thought to affect neuroendocrine and central nervous system neurotransmitter processes synergistically), more specifically the release of cytokines (substances secreted by specific cells of the immune system that serve to foster communication or cross-talk between the CNS and immune system) might be associated with how neurochemical changes induced by stressors may contribute to MDD (Anisman, 2009). It is thought that the current or past stressful experiences may impact the neurochemical actions of the inflammatory immune system and lead to a MDD diathesis. Human studies, both correlational and case control, have shown an association between elevated levels of circulating proinflammatory cytokines (which indicate a disruption of cell replication and function and are associated with earlier onset and faster progression of disease) and MDD. In addition, several studies have demonstrated how the use of immunotherapy, such as interferon-α to treat certain types of cancer and hepatitis C may result in depressive symptoms (Bonaccorso et al., 2002; Capuron, Ravaud, & Dantzer, 2000; Capuron et al., 2002; Maes & Bonaccorso, 2004; Scalori et al., 2005). Interferon-α also alters levels of serotonin (5-HT), which is involved in depression, but as Anisman (2009) notes, interferon-α is also associated with other nonspecific symptoms not related to depression.

Schizophrenia

With regard to another major psychiatric disorder, researchers have also long noted the heterogenous pathophysiology of schizophrenia. Although not conclusive, studies examining immunoglobulin (IgG) (the most common of the antibodies produced by the body to fight bacterial and viral infections) in cerebrospinal fluid (CSF) in some patients have shown raised levels that may be due to impaired permeability of the blood–brain barrier (Muller & Ackenheil, 1995). Other studies in a subgroup of schizophrenic patients have revealed additional immunological abnormalities such as increased occurrence of autoimmune diseases and decreased lymphocyte (IL-2) production, a cytokine released by T-helper cells to combat an invading antigen, among other immune changes. Muller and Ackenheil have proposed that schizophrenic patients should be classified as those with and without immune alterations. Moreover, preliminary epidemiological evidence utilizing maternal recall has demonstrated an association between second-trimester gestational influenza infections, obstetrical complications (e.g., anemia, emergency cesarean section, breech presentation), and low birth weights in newborns who later developed schizophrenia (Wright, Takei, Rifkin, & Murray, 1995). A meta-analysis of 62 in vivo and in vitro studies with a total sample size of 2,298 schizophrenic and 1,858 healthy participants showed significant increases in certain cytokines in vivo (circulating cytokine levels with

plasma samples) (IL-1RA, sIL-2R, and IL-6), and a decrease in vitro (secretion by peripheral white blood cells (leukocytes) stimulated or not by mitogens (potent stimulators of T cell activation), which collectively provides evidence of an ongoing inflammatory process (Potvin et al., 2008).

Personal Relationships

Studies examining the link between personal relationships (e.g., marital conflict, divorce, and separation) and immune function have provided some notable findings. In a study of 32 women, the 16 women who had been separated 1 year or less showed poorer immune function on immunological blood assays compared to matched controls (Kiecolt-Glaser et al., 1987). In a recent study of 1,211 sexual minority male patients in a community-based health center in Massachusetts 12 months after the legalization of same-sex marriage, participants had decreased medical and mental health care visits and mental health care costs compared to the 12 months before the law change (Hatzenbuehler et al., 2011). Of note, these results were similar for partnered as well as nonpartnered men.

In a study of 64 men, Kiecolt-Glaser and associates (1988) found that the 32 men who had been separated or divorced reported feeling more lonely and described more recent illnesses. Evidence suggests, however, that participants who initiate the separation and those who have less preoccupation with their ex-spouse may experience less distress and have better immune functioning (Keicolt-Glaser et al; Weiss, 1975). In a study of 42 married couples, Kiecolt-Glaser and colleagues (2005) found that those who evinced hostile behavioral exchanges or interactions during a monitored conflict resolution task in a laboratory setting showed poorer wound healing and higher levels of circulating proinflammatory cytokines levels (including interleukin-6 (IL-6) 24 h after a baseline observation, when compared to low-hostile couples.

In general, however, there has been data to suggest that there may be some benefits of emotional disclosure, particularly if expressing negative emotions about stressful experiences occurs in writing (Pennebaker & Beall, 1986; Pennebaker, Kiecolt-Glaser, & Glaser, 1988; Petrie, Fontanilla, Thomas, Booth, & Pennebaker, 2004). There is some suggestion that the benefits may be induced by alterations in cognitive processing, or how participants think about and then express their negative emotions. A method used to assess cognitive processing is the amount of words used related to expressions of insight (e.g., realize, see, understand) and causation (e.g., because, infer, thus), and the use of these words has been shown to predict greater total circulating lymphocyte counts over 3 days of writing in a sample of 65 first-year medical students (Pennebaker, Mayne, & Francis, 1997; Pennebaker, Mehl, & Niederhoffer, 2003; Petrie, Booth, & Pennebaker, 1998)

Graham and colleagues (2009) in a study of 42 married couples involved first in a "nonconflictive" and then in a "conflictive" discussion task, showed that individuals who engaged in the greater use of cognitive processing [words indicative of causal reasoning (e.g., because), insight (e.g., understand), and thinking (e.g.,

ought)], showed less increases in cytokine production over 24 h when in the conflictive task. This attenuation, even when cognitive processing words were used, did not occur in the nonconflicted discussion task.

Academic Stress

Keicolt-Glaser and her colleagues have also been responsible for some of the most methodologically sound, large-scale human stress studies investigating the immunological effects of the predictable acute stressor of academic examinations on medical students (Kiecolt-Glaser et al., 1984). These data have shown a decay in NK-cell activity when compared to baseline blood samples obtained 1 month prior to the exams. Additionally, in main effects noted for stressful life events in self-report inventories of the Holmes–Rahe Social Readjustment Scale and the UCLA Loneliness Scale, high scorers had lower NK activity than low scorers. The use of protein markers ruled out the possibility that the differences in NK-cell response were due to nutritional deficiencies. Also of note, there was no difference in received grades between students who did and did not participate. Other data (Glaser et al., 1992) have suggested that academic stress could negatively impact the ability of hepatitis vaccines to evoke antibody responses in a sample of medical students. Kang, Coe, and McCarthy (1996) recently expanded this line of research when they investigated whether differences in immune responses between healthy and asthmatic adolescents in response to academic examinations. Results revealed alterations in immune functioning, for example, decreased NK-cytolytic activity in both groups, without concurrent changes in lung function for the well-managing asthmatics.

Chronic Stress

Researchers have also investigated the effects of chronic stressors on immune functioning, and Glaser and Kiecolt-Glaser (2005) note, “chronic stressors might accelerate the risk of developing many age-related diseases by “premature ageing” of the immune response” (p. 249). Specifically, the health of family members who provide long-term care of loved ones with Alzheimer’s disease, often considered a form of living bereavement, has been examined over time. Results suggest that caregiving may produce more depression in family members (Crook & Miller, 1985; Kiecolt-Glaser et al., 2003), in addition to impaired immune responses compared to a matched-control sample when exposed to ConA, PHA, and latent Epstein–Barr virus (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Moreover, caregivers experienced significantly more days ill from upper respiratory tract infections, and the poorest immune functioning was observed in caregivers who had institutionalized their spouse within the previous year after caring for them for an average of 5 years. Esterling, Kiecolt-Glaser, Bodnar, and Glaser (1994) expanded these findings by including a group of former Alzheimer’s disease caregivers

(those whose spouse had died at least 2 years earlier) along with current caregivers and a control group. Results revealed no difference in symptoms of depression or perceived distress between the continuing and former caregivers, and both groups were significantly more depressed than the control group. Similarly, the continuing and former caregivers did not differ in the functional responsiveness of NK-cell cytotoxicity to cytokine incubation, and both groups had a significantly poorer immune response than controls. A study has manipulated NK-cell composition at a cellular level to investigate the mechanisms of immune effects on caregivers (Esterling, Kiecolt-Glaser, & Glaser, 1996). Considering how the population is aging, this area of research will be increasingly valuable in the future.

Psychological Factors and HIV/AIDS

First recognized in the early 1980s, human immunodeficiency virus (HIV) is the virus that causes acquired immune deficiency syndrome (AIDS). The virus weakens an infected person's ability to fight infections and cancer, and AIDS is the final stage of HIV infection. The myriad implications associated with the course of HIV and AIDS) have provided a prototypical illness to study from a psychoneuroimmunological perspective (McCain & Zeller, 1996). For example, Kemeny and her colleagues (1995), who reported that HIV-positive men who recently lost an intimate partner to AIDS evidence decreased immune functioning, have also suggested that grief and depression may have different immunological correlates in HIV.

The hallmark of AIDS is a quantitative pattern of depletion of a subset of T-lymphocyte cells, the T-helper or CD4 cells (CD = cluster designation) to a level below 200 (a healthy person's CD4 count can vary from 500 to more than 100) (McCain & Zeller, 1996; US Department of Health and Human Services, 2009). This is the result of HIV disease leading to CD4 cells becoming continually infected, destroyed, and regenerated, and the decline in CD4 cell number is the result of the proportional rate of cell destruction exceeding cell regeneration (Ho et al., 1995; Wei et al., 1995). As the aggregate of CD4 cells continues to decline, the signaling required for normal cellular and humoral responsivity is negatively impacted, leading to the development of opportunistic infections and various diseases that are pathognomonic of AIDS (Kemeny, 1994). The steady immunological decline noted in the beginning stages of HIV-seropositive individuals suggests that early psychosocial interventions may be particularly beneficial in helping patients to enhance their functioning (Antoni et al., 1990).

Estimates are that rates of depression may range from 21% to as high as 42% in HIV+ patients (Gaynes, Pence, Eron, & Miller, 2008; Horberg et al., 2008). Intervention studies of individuals with HIV have often involved exercise training and cognitive-behavioral approaches such as guided imagery and active neuromuscular relaxation (see Chaps. 10, 12, 15, and Appendix B for detailed discussions of these topics). Compared to a group of HIV-seropositive men who improved their aerobic capacity by riding a stationary bicycle for 45 min, three times per week, HIV-seropositive men who did not exercise demonstrated significant increases in anxiety

and depression, and decreases in immune functioning (LaPerriere et al., 1990, 1991). In a randomized control study of 60 HIV-infected adults, those who participated in a 12-week supervised aerobic exercise training program for 3 h per week, consisting of treadmill use, stationary biking, and walking, showed improvements in depressive mood and depressive symptoms compared to the control group (Neidig, Smith, & Brashers, 2003). In a randomized control trial testing whether the effectiveness of three different 10-week stress management approaches (i.e., cognitive-behavioral relaxation training, focused tai chi training, and spiritual growth groups) would improve and then sustain improvements 6 months later in areas of psychosocial functioning, quality of life, and physical health in a sample of 252 individuals with HIV infection, McCain and her colleagues (2008) reported that, in comparison to the control group, both the cognitive-behavioral relaxation training and tai chi training groups showed an enhancement in coping strategies (less emotion focused) and all three intervention groups had higher lymphocyte proliferation function. Guided imagery as a therapeutic intervention gained notoriety in the area of psychoneuroimmunology when researchers claimed that cancer patients who used the technique to most likely envision their body attacking and destroying invading infections were able almost to double their mean survival time (Hall & O'Grady, 1991; Hall, Anderson, & O'Grady, 1994; Holland & Tross, 1987; Simonton, Matthews-Simonton, & Sparks, 1980). Eller (1996) reported that 6 weeks of training in guided imagery and progressive relaxation training (PRT) were associated with less depression and fatigue and increased CD4 cells in a group of individuals with HIV.

Humor

Norman Cousins, the noted essayist and editor of the *Saturday Review*, addressed the potential therapeutic impact of humor on the immune system when he described in detail his use of laughter during his treatment for ankylosing spondylitis, a very uncomfortable inflammation of the vertebrae. Cousins dedicated more than a decade to amassing empirical evidence for his postulate that "laughter is the best medicine," and established the Humor Research Task Force (Wooten, 1996). Controlled studies have shown that laughter lowers cortisol levels and increases lymphocytes, NK cells, and concentration of salivary IgA (Berk, 1989a, b; Dillon & Baker, 1985; McClelland & Cheriff, 1997). Therefore, through the use of what may be considered cathartic liberation, humor and laughter seem to serve a protective immune function. Some hospitals have recognized the positive emotions engendered by humor and have introduced "Laugh Mobiles" that sell humorous novelties (Erdman, 1993).

Traumas

Investigators have also focused on acute and chronic immune system alterations following natural and man-made traumas, as well as technological disasters. One of the first instances of this type of exploration occurred following the nuclear

accident at Three Mile Island (Hatch, Wallenstein, Beyea, Nieves, & Susser, 1991). Compared to control participants, residents near the event had greater numbers of neutrophils (a type of white blood cell that is the first to arrive at an infection site), and fewer B, T, and NK cells (types of lymphocytes or small white blood cells that realize antibodies as part of the immune response) 6 years later, suggesting chronic immune changes. In the Canadian Community Health Survey Cycle ($n = 36{,}984$), participants with a diagnosis of PTSD had significantly higher rates of cancer, chronic pain, cardiovascular diseases, gastrointestinal illnesses, and respiratory diseases, and after adjusting for the effects of other mental disorders and medical morbidity, PTSD was also associated with suicide attempts, poor quality of life, and disability (Sareen et al., 2007). In a longitudinal study of 896 participants following a fireworks depot explosion in a residential area in the Netherlands that killed 23 people and injured about 1,000 others, Dirkzwager, van der Velden, Grievink, and Yzermans (2007) reported that after adjusting for smoking, demographics, and previous health problems, a diagnosis of PTSD was associated with increased vascular (e.g., peripheral vascular disease, artherosclerosis, varicose veins, and edema), musculoskeletal, and dermatological difficulties. In comparison of 14 patients with PTSD, who were otherwise healthy, and 14 matched controls (age and gender) without PTSD, von Kanel and colleagues (2006) reported that more severe PTSD, as assessed by the German version of the Clinician-Administered PTSD Scale (CAPS) was associated with higher levels of plasma clotting factors (e.g., fibrinogen, which is a soluble protein that aids in clotting and high levels are associated with CVD and FVIII:C, a coagulant that is deficient in hemophilia). The authors concluded that even at subthreshold levels PTSD might produce hypercoagulability that may increase the risk of cardiovascular disease by speeding up platelet aggregation and thrombus formation.

Studies have also examined immune effects following the North Ridge earthquake in Southern California and Hurricane Andrew in South Florida (Ironson et al., 1997; Solomon, Segerstrom, Grohr, Kemeny, & Fahey, 1997). In both studies, NK cell cytotoxicity (NKCC) was lower over time. In the latter study, severity of symptoms (particularly perceived loss and intrusive thoughts) was negatively related to NKCC and positively related to white blood cell counts. Of special interest for therapeutic interventions was the evidence of new-onset sleep difficulties as possibly mediating the PTSD symptom–NKCC relationship.

Psychological Manifestations of the Stress Response

The final category of disease to be discussed in this chapter is the diverse psychological manifestations of the stress response. Although we have noted implications for depression, bereavement, trauma, and schizophrenia above; and we shall be examining trauma in far greater detail later in the text, here we shall briefly review the "psyche" as a target organ.

Acute and chronic stress episodes are implicated in the development of both diffuse anxiety and manic behavior patterns that are without defined direction or purpose.

Gellhorn (1969) argues that high levels of sympathetic activity can result in anxiety reactions. This anxiety may occur as a result of SNS and proprioceptive discharges at the cerebral cortical level. Thus, generalized ergotropic tone may then lead to conditions of chronic and diffuse anxiety. Guyton (1982), in apparent agreement with Gellhorn, notes that general sympathetic discharge and proprioceptive feedback may contribute to arousal states such as mania, anxiety, and insomnia. Greden (1974) and Stephenson (1977) have both found that the consumption of methylated xanthines (primarily caffeine) can create signs of diffuse anxiety as well as insomnia and may lead to a diagnosis of anxiety neurosis. The action of the methylated xanthines rests on their ability to stimulate a psychophysiological stress response primarily through sympathetic activation. Finally, Jacobson (1938, 1978) has argued that proprioceptive impulses as such would be found in conditions of high musculoskeletal tension and can contribute to anxiety reactions (see also Everly, 1985b).

Physiologically, in each of the cases just cited, it may be suggested that an ascending neural overload via the reticular activating system to the limbic and neocortical areas may be responsible for creating unorganized and dysfunctional discharges of neural activity that are manifested in clients' presenting symptoms of insomnia, undefined anxiety, and in some cases manic behavior patterns lacking direction or apparent purpose (see Everly, 1985b; Guyton & Hall, 2006).

In each of the three examples, activation of the psychophysiological stress response preceded the manifestation of diffuse, undefined anxiety, often diagnosed as generalized anxiety disorder or atypical anxiety disorder.

It is interesting to note that one link between anxiety and sympathetic stress arousal, specifically, striate muscle tension (Gellhorn, 1969; Jacobson, 1938, 1978), has prompted the development of techniques designed to reduce anxiety through the reduction of muscle tension. We review such techniques later in this text.

Another psychological manifestation of excessive stress is thought to be depressive reactions. Stressor events that lead the patient to the interpretation that his or her efforts are useless, that is, that he or she is in a helpless situation, are clearly associated with arousal of the psychophysiological stress response (Henry & Stephens, 1977). The affective manifestation that typically follows is depression. Henry and Stephens have compiled an impressive review that points to the reactivity of the anterior pituitary–adrenocortical axes during depressive episodes.

In addition to physiological evidence, there is psychological evidence to support the notion that excessive stress can precipitate a depressive reaction. Sociobehavioral research with depressed patients (see Brown, 1972; Paykel et al., 1969) produced somewhat similar evidence that social stressors can lead to major affective syndromes. Rabkin (1982), in her review of stress and affective disorders, states, "Overall, it seems justifiable to conclude that life events do play a role in the genesis of depressive disorders" (p. 578). Indeed, depressed patients report more stressful life events than do normal controls. This was especially true for a 3-week period immediately preceding the onset of the depression (Rabkin).

As noted, evidence supports a link between stress and schizophrenia as well. One behavioral interpretation of schizophrenia views the illness as a maladaptive avoidance

Table 4.2 Psychological disorders and excessive stress

Brief reactive psychosis
Posttraumatic stress disorder
Adjustment disorders
Various anxiety disorders
Various affective disorders
Some forms of schizophrenia

mechanism in the face of an anxiety-producing environment (Epstein & Coleman, 1970). Serban (1975) found in a study of 125 acute and 516 chronic schizophrenics that excessive stress did play a role in the precipitation of hospital readmission. A more far-reaching view of psychopathology and stress is presented by Eisler and Polak (1971). In a study of 172 psychiatric patients, they concluded that excessive stress could contribute to a wide range of psychiatric disorders, including depression and schizophrenia, as well as personality disturbance—depending on the predisposing characteristics of the individual (see Millon & Everly, 1985). Rabkin (1982) concludes that stress may well be associated with schizophrenic relapse and subsequent hospitalization.

Most important, however, with the advent of the multiaxial DSM, came the identification of psychiatric disorders that were, by definition, a result of stressful life events. Thus, for such categories, mental status, that is, the mind, need no longer be seen as a viable target organ only by inference. Both the diagnoses of *brief reactive psychosis* and *posttraumatic stress disorder* are viewed diagnostically as being a *direct* consequence of a "recognizable stressor." So, too, would be the diagnostic categories of *adjustment disorders*. Diagnoses such as adjustment disorder with anxious mood, adjustment disorder with depressed mood, and adjustment disorder with mixed emotional features demonstrate an official nosological acceptance of the wide spectrum of psychiatric manifestations that can result directly from stress (Everly & Lating, 2004).

Thus, we see that in the last several years, the "mind" has been officially recognized as a potential target organ for pathogenic stress arousal. Table 4.2 summarizes diagnostic categories that serve as psychological target-organ manifestations of excessive stress.

Summary

The purpose of this chapter has been to briefly review some of the more common disorders seen in clinical practice that potentially possess a significant stress-related component. Let us review some of the main points addressed in this chapter:

1. There is a well-established literature linking the GI system to the stress response. The most commonly encountered stress-related GI disorders are peptic ulcers (gastric and duodenal), ulcerative colitis, irritable bowel syndrome, and esophageal

reflux. There appear to be two major pathogenic mechanisms in these disorders: vagus-induced hypersecretion of digestive acids and glucocorticoid (cortisol)-induced diminution of the protective mucosal lining of the GI system. Gastric acid hypersecretion has been shown to be related to anger and rage (Wolfe & Glass, 1950), whereas alterations in mucosal integrity have been shown to be related to depression and feelings of deprivation (Backus & Dudley, 1977).

2. The cardiovascular system is believed by many to be the prime target organ of the stress response, especially in males (Humphrey & Everly, 1980). The cardiovascular disorders most commonly associated with excessive stress are essential hypertension, migraine headaches, and Raynaud's disease. Essential hypertension is clearly a multifactorial phenomenon. Although stress may not be the solitary etiological factor in the majority of cases of essential hypertension, it appears to be a contributory factor in the majority of cases in a nonobese population. Mechanisms within the stress response that may contribute to the acute and chronic elevation of blood pressure include SNS activity and adrenomedullary activity, as well as cortisol and aldosterone hyperactivity (refer to Chap. 2).
3. Vasospastic phenomena such as migraine headaches and Raynaud's disease seem to be primarily a function of excessive SNS activity, as are myocardial ischemia and coronary endothelial injury.
4. There is evidence that the respiratory system can also be a target organ for the stress response. Bronchial asthma, hyperventilation syndrome, and even some forms of allergies may be stress related. Mechanisms of mediation may include excessive parasympathetic activation, excessive sympathetic activation, and extraordinary adrenomedullary activity, respectively.
5. According to Jacobson (1938, 1970), Gellhorn (1967), and Tomita (1975), the striated neuromuscular system is an underestimated yet prime target for excessive stress arousal. Stress-response efferent mechanisms of mediation include alpha-motoneuron innervation, adrenomedullary activity, and perhaps even SNS activity.
6. The skin serves as a target for excessive stress. Disorders such as eczema, acne, psoriasis, and alopecia areata have been implicated as stress-related disorders. Specific mechanisms of mediation are unclear.
7. Animal studies have demonstrated the connection between biogenic and psychosocial stressors and immune function. Hans Selye's seminal work investigating the General Adaptation Syndrome (GAS) is an early example of how biogenic stressors adversely affect immune function.
8. The impact of stress on immune function in humans has explored areas such as bereavement, marital conflict, and effects of taking exams, and providing long-term care to loved ones with Alzheimer's disease and AIDS. It is important to keep in mind, however, that individual variables and modifying factors need to be considered before coming to general conclusions about stress and immune function.
9. The impact of humor on immune function, most often credited to Norman Cousins, is an example of a positive and potential therapeutic intervention that may enhance immune functioning.

10. A final yet important target organ for the stress response must be the "mind," that is, psychological status. Mental disorders such as brief reactive psychosis, posttraumatic stress disorder, adjustment disorders, certain anxiety and affective disorders, and even some forms of schizophrenia may possess significant stress-related components.
11. In summary, this rather ambitious chapter has attempted to review the vast field of psychosomatics. There would appear to be considerable professional opinion and scientific data to support the widely held view that disease is a multifactorial, biopsychosocial phenomenon in terms of onset, course, and intervention. That is certainly the view supported by the volume, in general.
12. In closing this chapter, it should be noted that the concept of stress-related psychosomatic diseases has been far broadened with the advent of the multiaxial DSM. Now, via such diagnostic perspectives, the clinician can indicate the degree to which stress may have contributed to the primary Axis I diagnosis through the use of Axis III, Axis IV, and Axis V. Finally, data from the field of psychosomatics cogently suggest that even infectious and degenerative diseases may have significant stress-related components in their initiation or exacerbation.

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