11 Endocrinology of the Stress-Response

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We all know that life can be difficult, but evolution has provided mechanisms to protect the body during crises. Such protection requires many different changes in many different parts of the body, and, as usual, hormones coordinate these widespread and diverse efforts. When the crisis is past, ebbing hormone levels signal the all-clear, and the body resumes other interests such as eating, body repair, and reproduction. But if the crisis persists, or if the individual's perception of crisis persists, hormones continue to drive the body to take desperate measures, sometimes with disastrous consequences. Stress and the interaction between stress and the immune system are the focus of this chapter.

What are the hormonal responses to stress and how do they normally provide help for the immediate future? What are the physiological consequences of long-term stress and why does stress seem to affect some individuals more than others?

Introduction

Ours is not an ideal world. If it were, nations would beat their swords into plowshares, there would always be enough parking spaces, and we'd always have exact change for pay phones. But it is not an ideal world, and our bodies are constantly challenged by this imperfection. We can get a serious illness or an injury. The rains may fail, locusts may swarm, and as a result we spend a season malnourished, walking miles daily to forage. We may be menaced by predators, or by the aggressiveness of members of our own species. Our hearts may be broken by loss. We are even smart enough to fear these things. In fact, we sometimes anxiously anticipate them before they happen.

Normally, our bodies are in a state of physiological balance, but so pervasive are the challenges and imperfections of the world that we have evolved an entire physiological system to buffer us from those perturbations. Stress physiology is the study of the response of our bodies to the perturbations that upset our physiological balance. Stress pathophysiology is the study of how, when we are knocked out of balance severely enough, disease emerges.

Some Definitions and Some History

It is an obligation of all stress physiologists to begin by reviewing some of the confusion of terms. The word stress was borrowed by biologists from engineers in a fairly imprecise way. Stress can mean the thing that creates an imbalance, or the response of your body to it, or both. Two terms have since

been adopted to distinguish between the two. A **stressor** is anything that disrupts physiological balance. It can be a physical insult—famine, for example—or a psychological insult—the expectation of famine. The **stress-response** is the body's adaptations designed to reestablish the balance. Stress will be used informally to refer to the general state of stressors that provoke a stress-response (Mason 1975; Selye 1976).

While these terms are recent, the ideas underlying them go back millennia. Hippocrates, in 400 B.C., postulated that disease did not represent divine will but rather arose from logical antecedents. This rationalist view is the foundation of modern medicine. He emphasized that health consisted of a harmonious balance with the surrounding world, while disease arose from challenges to that balance. This notion of balance ran through the works of many subsequent investigators. For example, Claude Bernard coined the phrase "internal milieu." He emphasized that organisms have evolved to become more independent of the outside environment, and that a goal of physiological systems was to buffer the internal environment or milieu from environmental perturbations. By our century, this stability of the internal milieu was termed **homeostasis**.

Stress physiology emerged as a real discipline primarily owing to the work of Walter Cannon (1871–1945), who coined the term homeostasis, and Hans Selye (1907–1982). By the beginning of this century, it was clear that maintaining homeostasis was indeed a high priority of the body, but there was little understanding of how our bodies accomplished this balance.

Two endocrine systems dominate the stress-response. Both involve the **adrenal gland**. The core, or medulla, of the adrenal gland secretes the most famous hormone of the stress-response, adrenaline, also known as epinephrine. Cannon demonstrated the role of epinephrine in stress physiology. The outer layer of the adrenal, the cortex, secretes a class of hormones called **glucocorticoids**. Selye was the first to discover their role. Cannon and Selye also made critical contributions to the theoretical framework of stress physiology. They both emphasized the nonspecificity of the stress-response. In other words, the magnitude of a stress-response is determined by the magnitude of the imbalance, not by the direction of the homeostatic imbalance.

To give a concrete example, imagine a scenario from the savanna. A zebra is mauled by a lion. The lion has not hunted successfully in days and is near starvation. The zebra's stomach is ripped open, yet for the next few hours, it has just enough strength to evade the lion. The body of the lion, near starvation, and of the zebra, terrified and in pain, are having very similar stress-responses. Somewhat similar responses would be triggered whether someone is too hot, too cold, about to make a first terrifying parachute jump, or about to go to a first terrifying high school dance. Cannon termed this nonspecific reaction the flight or fight response because such very different situations trigger the same response; he found that various stressors trigger the secretion of epinephrine. Cannon thought that he was studying how the body successfully coped with a stressful situation. To some extent, he was right.

Selye noted that stressors also provoked glucocorticoid secretion, and he termed this nonspecific response the **general adaptation syndrome**. Both terms are basically synonymous with the stress-response. Selye frequently recounted the story of how he came to think about the nonspecificity of the stress-response. As a young scientist, he was investigating the physiological effects of a potential new hormone (which turned out not to really exist). Every day rats received injections of ovarian extracts containing this putative compound. He found that the rats developed peptic ulcers, enlarged adrenal glands, and shrunken tissues of the immune system.

His tremendous excitement collapsed when he found that the same symptoms were occurring in his control rats. Rats receiving extracts from other organs or with saline alone had the same symptoms. Clearly, the changes could not have been caused by his putative hormone. Selye intuited that the experience common to all the rats, experimentals and controls alike, was the unpleasantry of daily injections. Perhaps, he thought, he was observing the nonspecific response to unpleasantry itself. He tested this by subjecting rats to other unpleasantries—cold, heat, hemorrhage, illness, and so on. The rats showed the same changes. The stress-response appeared to be nonspecific; it did not matter what the emergency, only that there was an emergency.

Selye had initially thought that the stress-response was beneficial, as reflected in his use of the word "adaptive" as to describe the stress-response. Yet his rats were getting sick—they had peptic ulcers and their immune systems were collapsing. If the stress-response is adaptive, why were Seyle's rats getting sick? The answer was clear: Under some circumstances, the body's adaptations in the face of stressors are not perfect. The field of stress pathophysiology had been founded.

In the first half of this chapter, we will review the complex physiology of the stress-response. Which hormonal and neural systems are stimulated by stressors and which are inhibited? What physiological adaptations do these bring about and why do they make sense? Why do these adaptations fail at times and bring about a variety of diseases? In the second half of the chapter, we will consider why psychological stressors are stressful and why individuals differ in the quality of their stress-response and their vulnerability to stress-related disease.

The Neural and Endocrine Mediators of the Stress-Response

To understand how the body adapts to stressors, we must begin by cataloging the mediators of such adaptations. This is, in effect, an introduction to the actors (Reichlin 1998).

Systems Stimulated by Stressors

As noted, glucocorticoids and adrenaline (hereafter called epinephrine) are the two most critical hormones released during the stress-response (figure 11.1). Glucocorticoid secretion by the adrenal cortex is just the final step in a cascade of events that begin in the brain.

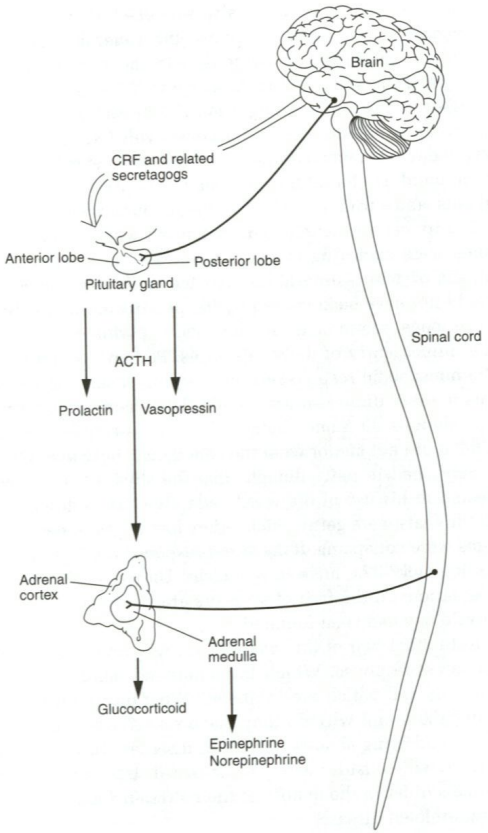

Figure 11.1 The endocrine and neural systems stimulated by stress. Stress causes the hypothalamus to release CRH and related secretagogs, which enter the hypothalamic-pituitary portal circulations. This triggers anterior pituitary release of ACTH which, in turn, stimulates glucocorticoid release from the adrenal cortex. Prolactin is also released by the anterior pituitary during stress; as with ACTH, its secretion is ultimately under complex hypothalamic control, but those hormones are deleted here for simplicity. Vasopressin is released by the posterior pituitary; in this case, hypothalamic control is neural, rather than hormonal, in that the cell bodies for the vasopressin-releasing neurons are actually located in the hypothalamus. In addition, the sympathetic nervous system is activated, releasing norepinephrine (NE) from most of its nerve endings; the sole exception is the release of epinephrine (EPI) from the sympathetic projection that terminates in the adrenal medulla. For simplicity, pancreateic release of glucagon has not been portrayed.

A stressor is perceived by the brain. The hormone corticotropin-releasing hormone (CRH) is released from the base of the brain, the hypothalamus. CRH stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH), which stimulates the adrenal to release glucocorticoids. Glucocorticoids are steroid hormones, and a number of different forms occur. In humans and primates, the dominant form released is **cortisol** (also known as hydrocortisone), whereas in rodents it is **corticosterone**. During stress, there is an increase in the secretion of CRH within a few seconds, of ACTH within perhaps 15 seconds, and of glucocorticoids within a few minutes. Predictably, the picture is actually far more complicated than this. CRH, which was isolated in the 1980s after decades of work, is only one of probably a half-dozen hypothalamic hormones that modulate ACTH release from the pituitary. Recent work shows that different stressors cause different patterns of these hormones to be released by the hypothalamus.

The other main component of the stress-response is the **sympathetic nervous system**. Neural control of peripheral bodily functions is generally divided into voluntary and involuntary (or autonomic) control. The former allows you to make intentional muscle movements: You sign checks, make silly faces, tap dance, and so on. The latter mediates responses like blushing, gooseflesh, orgasms, and getting breathless. This involuntary **autonomic nervous system** has two components with opposing roles (figure 11.2). The **parasympathetic nervous system** mediates calm vegetative functions such as growth and digestion, slow heart rate, and breathing. It is typically stimulated during sleep or after a large meal. In contrast, the sympathetic nervous system is stimulated by arousal, vigilance, or an emergency. When something scares us, the sympathetic response triggers the "adrenaline" surge that we feel. Sympathetic relays originating in the spinal cord terminate in the adrenal medulla and stimulate the release of epinephrine within seconds. Other projections go to essentially every organ in the body and release the closely related hormone **norepinephrine**. Epinephrine and norepinephrine both belong to the class of compounds known as **catecholamines**. As will be seen, glucocorticoids and catecholamines together mediate most of the changes that form the stress-response.

Other hormones are typically secreted during stress as well. **Endorphin**, which is secreted by the pituitary gland, is part of a class of opiate compounds that regulate pain perception and reproductive physiology during stress. Reproductive physiology is also affected during stress by the pituitary hormone prolactin. Vasopressin (also known as antidiuretic hormone), is a posterior pituitary hormone involved in the regulation of renal function and water volume. Finally, glucagon, a pancreatic hormone, helps to regulate carbohydrate trafficking. This does not represent a complete list of the endocrine systems stimulated by stress, but these are the ones that will be referred to most frequently in this chapter. All these systems help to marshal and conserve body resources in preparation for a crisis.

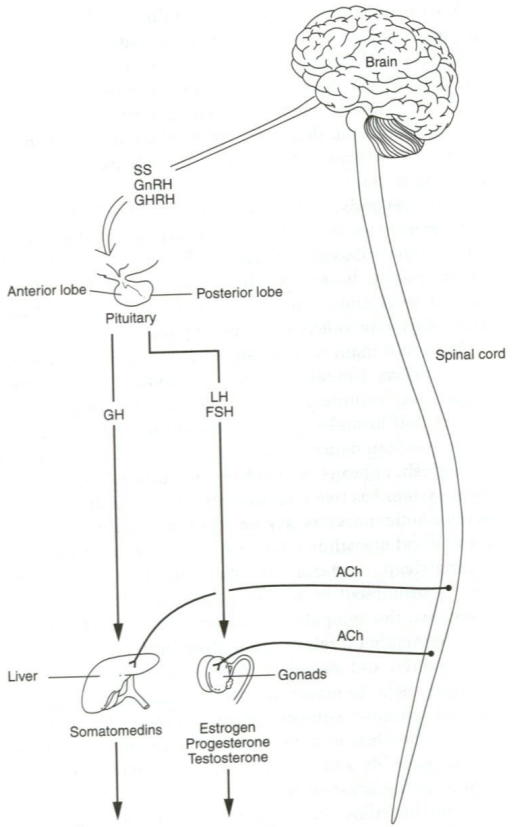

Figure 11.2 Outline of some of the effects of sympathetic and parasympathetic nervous systems on various organs and glands.

Systems Inhibited by Stressors

As noted, the sympathetic and parasympathetic branches of the autonomic nervous system usually work in opposition (figure 11.3). Thus, the parasympathetic system is inhibited promptly by stress. There is also inhibition of the numerous hormones involved in reproductive physiology and behavior. The secretion of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and the gonadal steroids is inhibited by stress. Finally, the secretion of insulin, the pancreatic hormone concerned with glucose storage, is typically inhibited.

A more confusing picture is seen with **growth hormone** (GH). Its secretion by the pituitary is under regulation by the brain, in that the hypothalamus secretes both **growth hormone–releasing hormone** (GHRH), which stimulates GH release, and **somatostatin**, which inhibits it. These work like an accelerator and a brake, respectively. GH, in turn, exerts many of its effects by stimulating the secretion of **somatomedins** by the liver. In rodents, the secretion of GH, and consequently of somatomedins, is promptly inhibited by stressors. In contrast, in humans, most short-term stressors stimulate GH release transiently, whereas more sustained stressors tend to inhibit release.

The Logic of the Stress-Response: What Good Is It?

It seems particularly reasonable to ask this in the context of the variety of stressors that elicit this relatively consistent set of responses. As physiologists, we are trained to understand what the body does when it is too hot and when it is too cold. Intuitively, it seems that the responses to each should be fairly different, if not opposite. Similarly, it seems that being frightened and injured (like the zebra) should be a different physiologic state from being hungry and predatory (like the lion). Why, then, should there be a whole set of physiologic changes that is elicited whether you are too hot or too cold, whether you are the zebra or the lion? Is there a logical explanation for these changes?

Much of biology has a logical structure that can be discerned. The disparate endocrine and neural changes that comprise the stress-response actually make a fair amount of sense. Such differing states as being too hot or too cold, injured or hungry, can all elicit similar responses because there is a common thread to all of them. Even though the different stressors throw the body out of homeostasis in different directions, the task of reestablishing the balance, however disrupted, is still fairly similar (Sapolsky et al. 2000; Sapolsky 1998).

First and foremost, both the zebra and the lion have an immediate need for energy. The metabolic hallmark of the stress-response is the need to mobilize energy for immediate use. Therefore energy storage is inhibited, and preexisting stores of energy are broken down into simpler, more readily utilized forms in the bloodstream. (This is the metabolic equivalent of going to the bank in a time of financial crisis and emptying your savings account in order to have cash in your pocket.) The net result is increased concentrations of

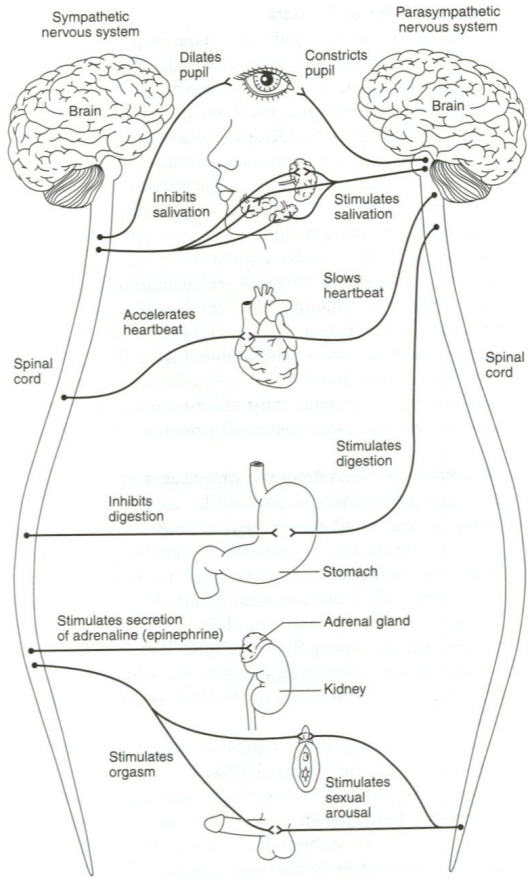

Figure 11.3 The endocrine and neural systems inhibited by stress. Hormones for which secretion is inhibited are underlined. Normally, hypothalamic GnRH stimulates the pituitary release of LH and FSH which, in turn, stimulate gonadal secretion of steroid hormones. During stress, all secretion is inhibited. Pituitary release of GH is stimulated by GHRH and inhibited by somatostatin (SS). During stress, GHRH release is inhibited, whereas there is no clear evidence that secretion of SS is changed, The result is decreased GH release and, in turn, decreased somtaomedin release. As discussed in the text, the inhibition of this growth axis is somewhat species-specific. Finally, parasympathetic nervous system activity (as represented by the release of acetylcholine [ACh]) is inhibited. For simplicity, the inhibition of pancreateic release of insulin is not included.

glucose in the bloodstream. The glucose, along with oxygen, must be delivered rapidly to the muscles that are being worked heavily in the zebra and lion. Thus, the breathing rate increases to facilitate the exchange of oxygen in the lungs. Cardiovascular tone also increases. Blood pressure and heart rate rise. Water is retained in the circulation to increase the blood volume. In addition, parts of the circulatory system are shut down to ensure that blood is preferentially shunted to the organs and muscles that need it most.

This pattern of curtailing nonessentials is seen in many other ways. If a hurricane appears to be heading for your town, this is not the afternoon to decide to paint the kitchen or to finally replant the tulip bulbs in the garden. It is an emergency, and long-term building projects can wait for tomorrow. By this logic, numerous anabolic processes are inhibited by the stress-response. For example, digestion is curtailed. While the digestive process will eventually provide the body with needed nutrients, it will not do so rapidly enough to help that lion or zebra in the coming minutes, and it is an unnecessary expense in the meantime.

By the same logic, reproductive physiology and behavior are usually inhibited by stressors. Reproduction is certainly one of the most expensive, optimistic things you can do with your body, especially if you are female, and it simply cannot be a high priority when you are sprinting for your life. Similarly, growth and tissue repair are typically inhibited. The former is dramatically the case in young, growing organisms.

Another feature of the stress-response is the suppression of inflammation and pain perception. Suppose in the initial attack on the zebra, its knee was injured. In most circumstances, the logical next step would be an inflammatory response. Capillaries dilate to allow fluid to rush into the extracellular space, leukocytes migrate into the region to scavenge damaged tissue. The knee swells and becomes painful and difficult to use. This is a way to convince the organism to rest the knee and allow it to repair. But this is a luxury that the zebra cannot afford. True, the knee joint may become even more injured if the zebra continues to use it, but the consequences will be far worse if the animal stops. Thus, inhibition of the inflammatory response makes a fair amount of sense. Pain perception can be blunted as well. For example, at the height of battle, soldiers are occasionally grievously injured and do not even notice the pain at the time. Such "stress-induced analgesia" has been documented in many circumstances and appears to be mediated by the release of endorphins.

Thus, when subjected to a physical stressor, it is adaptive for an organism to mobilize energy and deliver it to the parts of the body that need it, to curtail nonessential physiological processes, and to blunt pain and inflammation. As will be detailed in later sections, these are precisely the consequences of the various endocrine and neural responses.

Some investigators have begun to view these hormonal shifts not only as a way to understand how the organism initiates its response to the emergency but also how it eventually terminates the response. This could explain some

puzzling features of the stress-response. For example, many metabolic consequences of the shifts in glucocorticoids, catecholamines, glucagon, growth hormone, and insulin appear to be contradictory, because opposing responses are triggered. The resolution of this puzzle is that the various hormones work at different speeds. Catecholamines, for example, produce their effects upon target tissues within seconds, whereas most of the effects of glucocorticoids or growth hormone take hours. Thus, two opposing endocrine signals may be given simultaneously, yet they may exert their effects at different times. The slower responses may not be mediators of the stress-response as much as counterregulatory signals that prepare the organism for eventually recovering from that stress-response. As we will see in some detail, considering *time course* in this way is relevant to understanding the complex effects of stress on the immune system.

The Illogic of the Stress-Response: The Emergence of Stress-Related Disease

The stress-response seems ideal for aiding the zebra or the lion in its stressful encounter. Energy is mobilized and delivered where it is needed, pain is blunted, costly anabolism is deferred until a more auspicious time. In some ways, their bodies are already gambling that the stressor will be survived and are preparing for a return to normal. From this perspective, the system seems quite adaptive. Yet, from the first day of Selye's work, it was apparent that the stress-response is not perfect; his rats had peptic ulcers and atrophied immune systems. We now know that Selye had discovered the tip of the iceberg of stress-related disease. If the stress-response is so logical and adaptive, why do such diseases emerge?

The answer lies in the sorts of disclaimers that one gets with the instructions for a new appliance: The stress-response, just like a new microwave oven, must be used properly. It is an ideal system for allowing an organism to deal with short-term physical stress, and that is exactly the sort of stressor that most organisms face most of the time. Stress-related disease appears most likely to emerge when the stress-response is activated for too long, or too frequently (i.e., chronic stressors), and when it is not activated for a physiological reason (i.e., psychological and social stressors).

Selye noted the seeming paradox that the physiological system he had discovered, so logical and adaptive under some circumstances, could cause disease. He was among the first to guess that prolonged stressors could cause disease. His explanation for the phenomenon, however, was mostly incorrect. Selye conceptualized the stress-response as coming in three stages. The first, alarm, involved noting the challenge to homeostasis, the stressor. The second, resistance, consisted of successfully dealing with the short-term physical insult. The third stage was when disease started, when the stressor went on for too long. Selye termed this stage exhaustion. In his view, at some point the capacity to mount a stress-response fails and the adrenal runs out of glucocorticoids to secrete. The sympathetic nerve endings become depleted of catecholamines, and so on. In effect, the army defending the body from the

external stressor runs out of ammunition, and the stressor can now assault the body unhindered. In actuality, this scenario of exhaustion does not really occur very often. With sustained stressors, for example, the adrenal increases its capacity to secrete catecholamines by increasing the concentrations of the rate-limiting enzyme for catecholamine synthesis, **tyrosine hydroxylase**. In addition, the adrenal cortex, the zone in which glucocorticoids are synthesized, increases in size (explaining why Selye's original rats had hyperplastic—enlarged—adrenals). In some circumstances of sustained stress, the hormonal output decreases over time, but this is because the organism has become habituated to the stressor (i.e., it views the event as less stressful) rather than because it has become depleted of the hormones. This can be proved by showing that when the catecholamine response to a sustained stressor decreases, a novel stressor still elicits a large catecholamine response.

Thus, there is little evidence that sustained stressors deplete the system of the hormones it needs for the stress-response. The army does not run out of ammunition. The problem is that with sustained stress, the stress-response can eventually be as damaging as the stressor. To extend the military metaphor, if you keep spending your budget on bullets instead of on bread or education, you can ultimately destroy your country just as effectively as an invading enemy. Most features of the stress-response are damaging, inefficient, and even dangerous. Yet that zebra and that lion must activate the stress-response; it is an emergency. If the body constantly decides it is an emergency and activates the stress-response, disease eventually emerges.

It is not the stress that makes you sick. As a first qualification, stress makes you more *likely* to become sick—it is a statistical relationship, and some individuals are more prone to stress-related disease than others, a point that will be explored in detail towards the end of this chapter. As a second qualification, the statement that stress makes you more likely to become sick is more accurately stated as stress makes you more likely to get diseases that make you sick. In other words, stress interacts with the ways in which bacteria, viruses, toxins, and rogue genes make you sick—as will be seen, in many cases, what stress does is impair the body's defenses against those sources of disease.

In subsequent sections, we will review how the hormones of the stress-response bring about helpful adaptations to acute physical stressors and how the same hormones, secreted over time, endanger health.

THE METABOLIC STRESS-RESPONSE

When faced with an acute physical stressor, there are two adaptive metabolic responses. First, the body makes sure that none of the energy substrates in the bloodstream are stored away. Second, it gets access to previously stored energy and converts it back to circulating energy substrates (Goodman 1980). The first task is accomplished quite readily. In times of plenty, when there are surplus energy substrates in circulation, the body stores them in complex

storage forms. Circulating fats maintained in the form of fatty acids and glycerol are stored in adipose tissue as triglycerides. Amino acids are stored throughout the body as proteins, and glucose is stored as glycogen.

The critical hormone in this storage process is insulin, which is secreted by the pancreas in response to increased circulating glucose concentrations. At fat cells, insulin promotes glucose uptake and fatty acid synthesis, and blocks the breakdown of triglycerides. All these steps promote the formation and maintenance of triglyceride stores. In muscles, insulin promotes glucose and amino acid transport and glycogen and protein synthesis, and blocks the breakdown of proteins and glycogen. Finally, in the liver, insulin promotes the formation of glycogen and blocks the breakdown of preexisting glycogen. Insulin is the prototypical hormone that signals that there is no metabolic crisis looming on the horizon.

With the onset of a stressor, insulin secretion is typically inhibited, and the storage of substrates is halted. The process of gaining access to substrates already stored is more complex, principally involving glucocorticoids, catecholamines, and glucagon. Collectively, they reverse all the effects of insulin. In fat cells, glucose uptake, protein synthesis, and fatty acid synthesis are halted. Preexisting triglycerides are broken down (lipolysis), and free fatty acids are flushed into the circulation. In muscle, the uptake of glucose and amino acids and the synthesis of glycogen and proteins are halted. Preexisting glycogen and proteins are degraded (glycogenolysis and proteolysis), and glucose and amino acids are again flushed into the circulation. This is the picture in nonexercising muscle. Things are quite different in the muscles that are working to save you from the stressor, in that all the energy substrates being mobilized are being shuttled towards such muscle. How your body differentiates between exercising and nonexercising muscle is not completely understood.

Stored energy has now been turned into cash—circulating glucose, amino acids, and fatty acids. As a final step, glucocorticoids, catecholamines, and glucagon stimulate the liver to convert fatty acids and amino acids to glucose, a process called "gluconeogensis." Thus, in the face of an acute stressor, there are increased concentrations of glucose available to whichever tissue needs it.

How do these metabolic adaptations cause disease when activated chronically? Quite simply, if you constantly mobilize energy at the cost of energy storage, it will ultimately prove disastrous. Constantly breaking down stored proteins in order to flux amino acids into the circulation produces myopathy, the wasting away of muscles, a prime storage site for protein. This causes weakness and fatigue. Fatigue will also arise from the fact that, collectively, the processes of lipolysis, proteolysis, glycogenolysis, and gluconeogenesis are inefficient. One can use a surprisingly apt metaphor from the economic world. If you open a long-term savings account in which money is put away for a stipulated period, you receive a lot of interest for keeping the money in the account and a penalty if you break the agreement and withdraw the money early. Similarly, the body is penalized for constantly mobilizing energy from storage sites and transforming it; each biochemical step is inefficient, and altogether, approximately 30% of potential energy is lost.

THE CARDIOVASCULAR STRESS-RESPONSE

In the presence of a physical stressor, it is logical to increase cardiovascular tone in order to deliver more of the mobilized glucose and oxygen to the tissues that need it. This is mostly accomplished through the sympathetic nervous system, which stimulates the heart to beat faster. Blood pressure is increased through vasoconstriction, which indirectly increases the force of cardiac contractions. Blood flow to some organs (for example, the digestive tract) is decreased; this is part of the strategy of shutting down nonessentials. Blood volume is also increased by vasopressin, which increases water resorption by the kidneys. If you are sprinting across a field with a lion on your heels and your blood pressure is 160/95, this is extremely helpful. If you have the same blood pressure whenever you have to stand in a line, you are putting yourself at risk. The danger is rarely of the "guy gets bad news, clutches his chest, and collapses dead" variety. Stress-induced sudden cardiac arrest is actually quite rare. Instead, chronic activation of the cardiovascular stress-response gradually damages heart muscle, weakens vessel walls, and promotes the deposition of cholesterol and the formation of atherosclerotic plaques.

THE GASTROINTESTINAL STRESS-RESPONSE

As discussed, it makes sense to inhibit the gastrointestinal (GI) tract during an acute physical stressor; digestion can wait for later. These changes are principally mediated by the autonomic nervous system through its shift from parasympathetic to sympathetic tone. Normally the former stimulates digestion. In the mouth, saliva is secreted, while in the stomach, acid, pepsinogen, mucus, and gastrin are secreted. In the intestines, secretion of a large array of digestive enzymes and hormones is stimulated, including lipase, trypsinogen, chymotrypsin, enterokinase, cholesystokinin (CCK), and vasoactive intestinal polypeptide (VIP). Furthermore, stomach churning and the relaxation and tightening of sphincters are all coordinated to promote digestion. With stress, all of these processes are inhibited, due both to the decreased parasympathetic tone and to the increased sympathetic outflow. We are all familiar with the first sign of the shutdown—our mouths become dry when we are nervous because we have stopped secreting saliva. In addition, the sympathetic nervous system decreases blood flow to the GI tract.

There have been major changes of opinion recently about the gastrointestinal consequences of prolonged stress. Since Selye and others in the 1930s, it was recognized that stress can cause stomach ulcers—holes in the stomach wall—and the lay public probably considers peptic ulcers to be the definitive stress-related disease. There is indeed a kind of ulcer that emerges rapidly and is tightly linked to catastrophic stress; such "stress ulcers" can develop

over the course of a few days following massive stressors such as a whole body burn, and involve sufficient bleeding to be life-threatening. But most gastroenterologists now question whether the classic slowly emerging type of ulcer, the type that gives months of nonspecific gut pain until finally being diagnosed, has anything at all to do with stress. The reason for this revisionism is a revolution in the field, namely the recognition that a bacteria called *Helicobacter pylori* is implicated in the vast majority of ulcers in the Western world. No one expected this, because the dogma was that bacteria could not survive the acid bath of stomach juices; however, *H. pylori* turns out to have evolved some sophisticated defenses against the acidity. Once infecting a stomach, it causes inflammation (gastritis) which, through poorly understood mechanisms, compromises the ability of cells lining the stomach wall to defend themselves against stomach acids, and an ulcer quickly ensues. The definitive bit of evidence in favor of this *H. pylori* scenario was the enormously important clinical finding that antimicrobial drugs that kill bacteria can have miraculous effects on ulcers, far better than the traditional medications given for ulcers (such as antacids).

These findings have ushered in what has been termed the "Helicobacterization" of ulcer research. What this has meant is that most gastroenterologists reject the idea that stress is relevant to ulcers. The number of papers related to stress and ulcers has plummeted in recent years, in contrast to the increase in the number of papers related to stress and other gastrointestinal disorders. In effect, most in the field have concluded, "It's not a psychosomatic disorder after all. It's been bacterial all along."

Despite this shift, a number of stress physiologists, including myself, continue to view stress as highly relevant to understanding ulcer formation. Why should this be? For one thing, an *H. pylori* infection is neither necessary nor sufficient for a person to develop a stomach ulcer. Moreover, experimental stressors remain a very reliable means of giving a rat an ulcer, and ulcer formation is more likely to occur among people who are anxious, depressed, or undergoing severe life stressors. Careful studies have shown an interaction between stress and *H. pylori*. Specifically, ulcers are observed in individuals with mild amounts of stress yet heavy bacterial loads, or mild bacterial loads with massive amounts of stress. This is a prime example of a classic feature of stress-related disease—it is rare that stress causes you to be sick. Instead, it is more likely to worsen a preexisting disease, or to impair your defenses against some other pathogenic risk factor (Melmed and Gelpin 1996; Levenstein et al. 1995).

How might stress make the *H. pylori* more damaging? A number of possible routes exist: (1) Because blood flow to the GI tract is inhibited during stress, the delivery of oxygen and nutrients is curtailed. If this situation is prolonged, the stomach walls become weak and necrotic, making them more vulnerable to the bacteria. (2) Normally, the stomach expends considerable energy in building and thickening stomach walls and secreting mucus. Both protect the stomach walls from the potentially ulcerative effects of the powerful gastric acids. When the stress-response is prolonged (and acid secretion is inhibited chronically), the stomach curtails both of these housekeeping activities. In effect, the stomach decides that it is a waste of energy to thicken walls and make mucus if there is only minimal exposure to gastric acids anyway. Then, when the stressors abate and acid secretion resumes at its normal heavy rate, the stomach walls are vulnerable to erosions and ulcers. If that is coupled with the presence of the bacteria that impair acid defenses, the likelihood of an ulcer increases. (3) Ulcer repair is aided by a class of compounds called prostaglandins. However, glucocorticoids are powerful inhibitors of prostaglandin synthesis. The relative contributions of each of these mechanisms to ulcer formation remains controversial.

THE REPRODUCTIVE STRESS-RESPONSE

While virtually any adult organism may seek to reproduce at some point, a prolonged stressor will wreak havoc with reproductive physiology and behavior (Warren 1983; Rabin, Gold, Margioris, and Chrousos 1989). In many species, increased population density or decreased food resources are stressors that inhibit ovulation in females. This forms an elegant means by which populations self-regulate their growth rate. In some species (notably, some New World primates), reproduction is often inhibited not so much by the stressor of food shortages as by the stressor of social subordination. A high-ranking monkey ensures that she is the only member of her group to reproduce by physically harassing subordinates into anovulation. Male reproductive physiology is also vulnerable to chronic stress in varied species. Stressors such as surgical incisions, drought, sustained exercise, or defeat in social competition will suppress testosterone secretion. And among humans, there are endless psychological stressors that disrupt reproduction. To give some sense of the magnitude of our sensitivity to stress, it has been estimated that the majority of complaints of reproductive dysfunction by men in this country turn out to be psychogenic rather than organic in origin.

Much is known about how stressors disrupt reproduction in both sexes (Warren 1983; Sapolsky 1991). The summary presented here represents a consensus from studies of various mammalian species; there is, of course, phylogenetic variability. Among females, the points of inhibition are numerous. At the hypothalamus, the secretion of GnRH is inhibited by stress-induced secretion of beta-endorphin and CRH. One step below that, pituitary responsiveness to GnRH is diminished, decreasing LH and FSH secretion. This is due to the inhibitory actions of glucocorticoids or prolactin. Glucocorticoids also inhibit ovarian sensitivity to LH. The net result of these steps is to make the secretion of estrogen and progesterone and the release of a viable egg less likely.

The diminished levels of progesterone and the increased levels of prolactin, in turn, disrupt the normal maturation of the uterine wall. Thus, if an egg is fertilized against these considerable odds, it is less likely that proper implantation into the uterine wall will occur. And if that is not enough, certain

stressors disrupt reproduction in another way. Females of numerous species secrete androgens (male sex hormones) from their adrenal glands. Although the amounts are small, they would normally be enough to impair reproduction. However, they are typically converted to estrogen by an enzyme (aromatase) in fat cells. When stressors involve loss of body fat in females (from famine, wasting illnesses, extreme degrees of exercise, or anorexia nervosa), this conversion step is diminished. The result is a smaller amount of circulating estrogen and a buildup of circulating androgens, which can be disruptive to reproduction.

Among males, the regulatory steps are nearly as numerous. Similarly, CRH and beta-endorphin inhibit GnRH release. As with the female, prolactin inhibits pituitary sensitivity to GnRH, and glucocorticoids inhibit testicular sensitivity to LH. The net result is decreased testosterone secretion and, under more extreme circumstances, decreased sperm production. Cell biologists have uncovered some of the ways in which beta-endorphin, prolactin, and glucocorticoids exert their inhibitory effects in both sexes. In some cases, they decrease the numbers of LH receptors; in others, they have post-receptor effects, and in still others, they sensitize the brain to the inhibitory effects of other hormones. The body is creative and varied in its means of suppressing reproduction during stress.

Another aspect of male reproduction can be maddeningly vulnerable to stressors: attaining and maintaining an erection. The initial erection requires parasympathetic tone. With continued stimulation and arousal, breathing and heart rate increase, and the physiologic profile becomes more sympathetic rather than parasympathetic in tone. Ejaculation consists of a sudden and major inhibition of the parasympathetic tone and stimulation of the sympathetic tone. With the inhibition of parasympathetic tone during stress, it becomes difficult to have an erection—resulting in impotency. And if the erection has already occurred, the tendency of a stressor to shift autonomic tone from parasympathetic to sympathetic accelerates the normal transition—resulting in premature ejaculation.

Why are there so many mechanisms by which stressors can suppress reproduction? Another way to frame this question is to ask how effective these numerous collective mechanisms are. Surprisingly, the answer is, not very. Humans continue to reproduce under dreadful circumstances; for example, in one frequently cited study, nearly 50% of the women in a Nazi concentration camp were continuing to menstruate despite starvation, slave labor, and unspeakable psychological stressors. If you are asking how readily stress causes reproductive behavior and physiology to grind to a complete halt, the answer is that it takes massive amounts of stress to do so, in virtually any mammal studied. It requires so many mechanisms to suppress reproduction during stress because reproduction is one of the strongest biological imperatives there is. But if you ask how readily stress disrupts the subtleties of sexuality—how appealing sex seems, how readily orgasms or erections occur, or how much pleasure any of this mating business brings—the answer is that it takes remarkably little. And it is this subtle realm that makes stress-induced reproductive dysfunction so common in Western life.

THE CONSEQUENCES OF A PROLONGED STRESS-RESPONSE ON GROWTH

If the stress-response involves postponing **anabolism**, then stressors should be particularly disruptive in young, growing animals, in whom anabolism is nearly continuous (Reichlin 1998). Indeed, in rats, stressors promptly inhibit circulating growth hormone (GH) concentrations, mostly due to increased somatostatin released (rather than to decreased release of growth hormone releasing hormone). If GH secretion is inhibited long enough in a young organism, growth is disrupted profoundly. For example, maternal deprivation in rat pups inhibits growth; the same thing occurs in human children living in a war zone. These examples, however, are difficult to interpret. A rat pup deprived of its mother undergoes nutritional as well as emotional deprivation. A child in a war zone is psychologically stressed but is also likely to suffer from poor nutrition and inadequate medical care. Thus, impaired growth may not be due to the nonspecific stressfulness of the situation but instead to poor nutrition or parasitic infestation.

Syndromes of growth inhibition do occur in children with no obvious organic cause (such as starvation, chronic wasting illness, and so on). Instead, in these children there is a history of major emotional disturbance and deprivation. In such cases of "psychosocial dwarfism" (also known as "stress dwarfism" or "psychogenic dwarfism"), children average half the expected height for their age and secrete little GH, even after stimuli that normally elicit GH secretion. They may even be unresponsive to exogenous GH. Typically, within a few months of being placed in a less stressful environment, GH concentrations and rates of growth become normal, and if the child has not yet reached puberty, there can be sufficient growth for the child to eventually attain normal stature. It should be emphasized that stress dwarfism is a rare disorder seen only in tragically stressful (and often psychopathologic) circumstances (Sapolsky 1998).

Adults, obviously, no longer grow. In such cases, the growth that is inhibited during stress is the repair of existing tissues. For example, calcium is normally removed from bone and replaced with new calcium. Glucocorticoids inhibit this anabolic housekeeping. Thus, with glucocorticoid overexposure, bones become decalcified, thin, and prone to fractures. It used to be thought that such glucocorticoid-induced osteoporosis required far higher glucocorticoid levels than were ever generated by stress, and were instead only seen when people were administered large amounts of synthetic glucocorticoids (to control any of a number of diseases, usually of an autoimmune nature—to be discussed below). Thus, this would be termed a "pharmacologic" effect, rather than a "physiologic" one. Recent work with captive primates indicates, however, that prolonged social stress can lead to osteoporosis in females (Shively et al. 1991). Whether the same applies to humans has yet to be determined.

The Stress-Response and Analgesia

It has long been recognized that pain perception can be blunted during extreme stress and emotional arousal (Terman et al. 1984; Olson et al. 1997). Such stress-induced **analgesia** (pain reduction) was often thought to be purely psychological. However, an understanding of the neurochemical nature of the phenomenon came from an explosion of discoveries in the early 1970s. Considerable interest had focused on opiates such as morphine, heroin, and opium, which had similar chemical structures and were analgesic. It was during that period that opiate receptors were discovered in the brain. This discovery carried a vital implication: The brain could not have evolved receptors for a plant compound. Instead, there must be "endogenous opiates" (or "opioids") somewhere in the body that normally bond to these receptors. This triggered a fevered search for opioids. Soon, three types were discovered: the endorphins, the enkephalins, and the dynorphins. They occur in the pituitary, the brain, and a number of peripheral organs and serve endocrine, paracrine, and neuromodulatory roles. Previous lesion, stimulation, and electrical recording studies had already mapped the neuroanatomy of pain pathways. These included relay sites in the dorsal horn of the spinal cord and, within the brain, the periaqueductal gray area and the raphe complex. These regions were shown to contain opiate receptors; opioids caused analgesia when microinjected at these sites, and opiate receptor antagonists blocked such analgesia.

It was soon shown that various stressors caused the secretion of beta-endorphin from the pituitary. Athletes began to call the analgesia that comes about 30 minutes into exercise the "endorphin high," and the subject appeared solved. Two complications have emerged, however. First, it is not clear whether circulating beta-endorphins, derived from the pituitary, actually cause analgesia. Variations in circulating levels of the hormone do not predict analgesia very well. Moreover, it is not clear how the peptide normally gets past the blood-brain barrier from the circulation in order to bind to these neural opiate receptors. Instead, it is probably the release of opioids from neuron terminals within the brain and spinal cord that mediates the analgesia.

As a second complexity, some aspects of stress-induced analgesia occur independently of opioids. Such analgesia shows no crosstolerance with exogenous opiates and cannot be blocked with opiate receptor blockers. Various neurotransmitters have been implicated, including serotonin and histamine. In general, early phases of stress-induced analgesia appear to be opioid-independent, while slower phases (approximately 30 minutes or more) are opioid-mediated.

Are there pathogenic consequences of analgesia following chronic stress? Seemingly not, because the analgesia wanes over the course of hours to days. This does not represent "exhaustion" of the stress-response as Selye conceptualized it (i.e., the system does not run out of opioids); rather, this represents habituation to the stressor. As proof, imposition of a novel, painful stimulus at the point where the analgesia has waned will reinstate the analgesia.

The Effects of the Stress-Response on the Brain

The hormones of the stress-response have numerous effects on the brain; they can influence learning and memory, vulnerability to depression, feeding behavior, and aggression, to name just a few of their effects. In recent years, data have emerged showing that chronic stress, acting through glucocorticoid hypersecretion, can directly damage the brain. These findings are discussed in chapter 14.

A Detailed Analysis: The Stress-Response and Immune Function

One of the most complex subjects in stress physiology is the interaction between stress and immunity, and it has fascinating potential consequences for health. Moreover, recent findings in this area have overturned some long-held beliefs on this subject, making it worth our while to review this topic in detail.

A Brief Review of the Immune System

The immune system, whose primary job is to defend the body against infectious challenges, is frighteningly complex (Dunn 1989). As discussed in chapter 10, the basic cell types that make up the circulating components of the immune system are **lymphocytes** and **monocytes**. There are two classes of lymphocytes: **T cells** and **B cells**. B cells principally produce antibodies, while there are several kinds of T cells (T helper and T suppressor cells, cytotoxic killer cells, and so on). The T and B cells mediate different forms of attack upon infectious agents. The former bring about **cell-mediated immunity** (figure 11.4). When a pathogen invades the body, it is recognized by macrophages, a type of monocyte, which present the foreign particle to a T helper cell. A metaphorical alarm is sounded, and T cells begin proliferating, ultimately producing activation and proliferation of cytotoxic killer cells, which attack and destroy the pathogen. B cells, in contrast, are central to antibody, or **humoral-mediated, immunity** (figure 11.5). Once the macrophage/T helper cell combination has become alarmed, the latter also stimulates B-cell proliferation. In the process, the B cells generate antibodies, proteins that recognize and specifically bind to some feature of the invading pathogen. This binding immobilizes the pathogen and targets it for destruction.

A challenge for the immune system is that its cells are scattered throughout the circulation, requiring the existence of blood-borne chemical messengers that communicate between different cell types. A variety of such messengers exist, including **cytokines** (chemicals that trigger immune cell proliferation). For example, when macrophages first recognize an infectious agent, they release the cytokine interleukin-1. This triggers the T helper cell to release interleukin-2, which stimulates T-cell proliferation. On the hormonal front, T

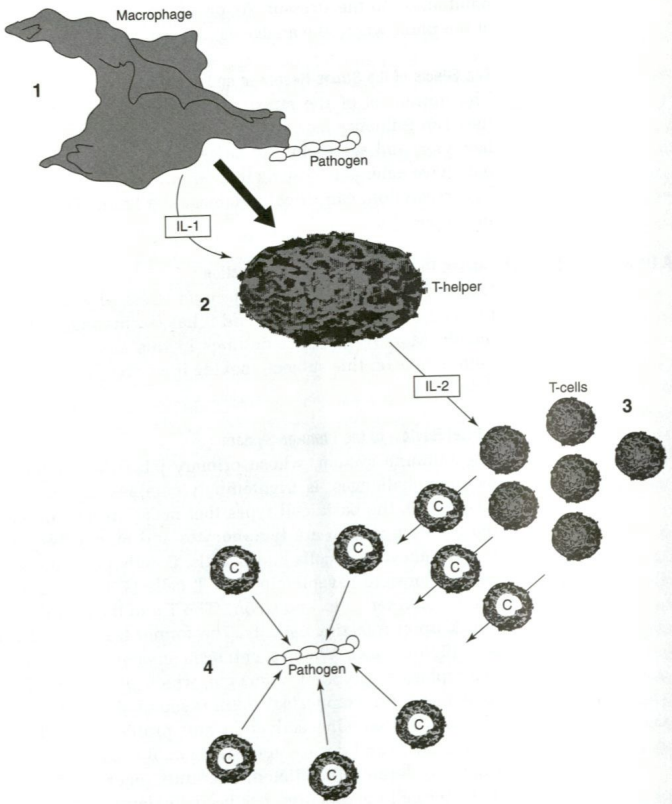

Figure 11.4 The cascade of cell-mediated immunity. (1) A pathogen is encountered by a type of monocyte called a macrophage. (2) This stimulates the macrophage to present the pathogen to a T-helper cell (a type of lymphocyte) and to release interleukin-1 (IL-1), which stimulates T-helper cell activity. (3) The T-helper cell, as a result, releases interleukin-2 (IL-2), which triggers T-cell proliferation. (4) This eventually causes another type of lymphocyte, cytotoxic killer cells, to proliferate and destroy the pathogen.

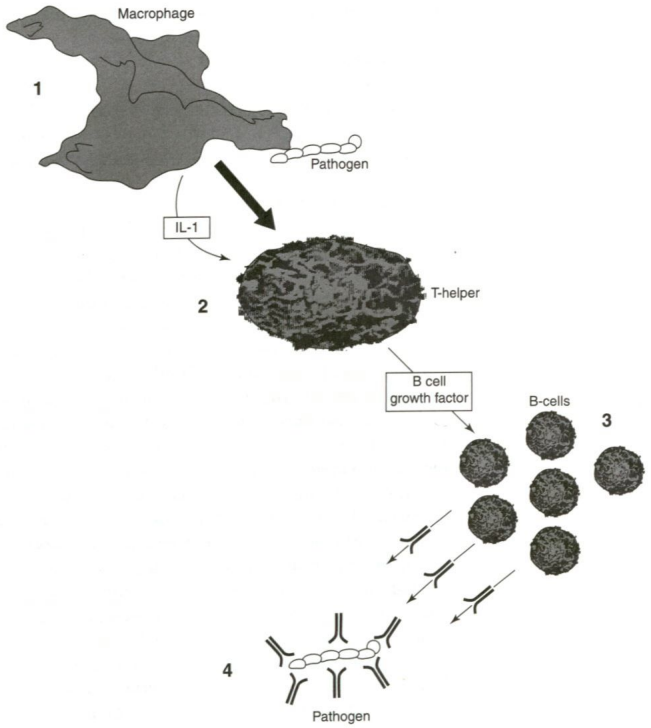

Figure 11.5 The cascade of antibody-mediated immunity. (1) A pathogen is encountered by a macrophage. (2) This stimulates it to present the pathogen to a T-helper cell, and to release interleukin-1 (IL-1), which stimulates T-helper cell activity. (3) The T-helper cell then secretes B-cell growth factor, triggering differentiation and proliferation of another lymphocyte, B-cells. (4) The B-cells make and release specific antibodies which bind to surface proteins on the pathogen, targeting it for destruction by a large group of plasma proteins known as *complement*.

cells also secrete B-cell growth factor, which stimulates B-cell differentiation and proliferation. There is also an additional class of cytokines known as the interferons. These are secreted by T cells and fibroblasts, among other cells, and have broad activating effects on lymphocytes and monocytes. The critical point in this simplistic summary is to appreciate the numerous cell types and messengers involved in immunocompetence. Numerous points in these cascades are subject to the disruptive effects of stress.

Immunosuppression During Stress

Beginning with Selye's observation that his stressed rats had atrophied immune organs, it has been known that prolonged stress can suppress immunity (Ader et al. 1991). If stress can do this, then the brain must be able to influence the immune system, since stressors are, of course, first perceived in the brain. The recognition of neural regulation of immune function arose from two types of studies. First, lesioning or stimulating different brain regions could alter immune function. Second, organisms could be conditioned to change their immune function, and conditioned learning, of course, involves the brain. These studies helped found the field of **psychoneuroimmunology** (Ader et al. 1991) and have paved the way for acceptance of the fact that neuroendocrine systems can influence immune function during stress.

While the sympathetic nervous system and opiates might play some role in suppressing the immune system during stress, the lion's share of that task goes to glucocorticoids. They were also the first hormones to be recognized (by Selye) for that function. The immunosuppressive actions of glucocorticoids are often exploited in clinical medicine. An autoimmune disease occurs when the immune system inadvertently attacks a normal part of the body, as if it is an invasive pathogen. In juvenile diabetes, for example, it is the insulin-secreting cells of the pancreas which are attacked, while multiple sclerosis involves an attack upon a part of the nervous system. Broadly, autoimmunity consists of a pathologically overactive immune system, and a standard treatment is to put the person on "steroids" (i.e., glucocorticoids, also often called "corticosteroids") in order to suppress the immunity back to normal levels (but hopefully, no further).

How do glucocorticoids suppress immunity? For starters, the hormone inhibits release of many cytokines as well as levels of their receptors. By disrupting this network of signaling, glucocorticoids inhibit proliferative responses of the immune system. Glucocorticoids also inhibit B cell-mediated immunity by inhibiting IL-1 release, and also inhibit production of certain components of **complement**, the system needed for the antibody-mediated killing of target cells.

In addition, the steroids can block the maturation of developing lymphocytes; this accounts for the involution of immune tissue first observed by Selye. The steroids also can pull lymphocytes out of the bloodstream. This effect is far more pronounced in some species (for example, humans and guinea pigs) than in others (like rats and mice). Finally, glucocorticoids can

actually destroy lymphocytes, causing them to burst. This "lysis" is due to an active process of programmed cell death ("apoptosis"). Glucocorticoids induce the synthesis of a protein that is either an endonuclease (an enzyme that cleaves DNA), or which activates a preexisting endonuclease. Not surprisingly, once its DNA is fragmented into little pieces, a cell does not last long.

Why Suppress Immune Function During Stress?

Given the large number of ways that stress can suppress immunity, it is reasonable to wonder why this should have evolved. What is the physiologic advantage of suppressing immunity during stress? Investigators have offered theories for decades. A popular one fits into the framework introduced at the beginning of this chapter, namely, that unessentials are suppressed during a stressful emergency—immunity doesn't come cheap, make the antibodies tonight around the campfire, if there is a tonight, don't waste energy now on immunity while sprinting for your life.

The discovery of the glucocorticoid-induced killing of lymphocytes also killed that theory. The notion of immune suppression in order to save energy would make sense if all that happened during stress was that the immune system was stopped in its tracks (i.e., no more cell division, synthesis of cytokines, and so on). Instead, the programmed death of lymphocytes is an active process, requiring energy. The body has to *work* in order to suppress immunity.

Other, less plausible theories have been offered as well (one of which I gleefully advocated in the prior edition of this text). But the answer to this puzzle has recently become clear. This clarification is due to the increased sensitivity of a number of assays of immune function, allowing scientists for the first time to measure immune events within the first few minutes of stress, the period prior to glucocorticoids beginning to have their immunosuppressive actions. These recent studies indicate that there is actually an enhancement of immune function immediately after the onset of all sorts of stressors (Munck, Guyre, and Holbrook 1984; Sapolsky et al. 2000).

Thus, when glucocorticoids begin to have their effects some 30 to 60 minutes into a stressor, they are not suppressing immunity below a baseline. Instead, they are helping the immune system to return to baseline. If you study massive and prolonged stressors (as the stress physiologists had been doing for decades), or give an organism massive amounts of synthetic glucocorticoids, immunity is indeed suppressed far below baseline. But for the typical stressor, the immune system is first transiently activated (possibly through the sympathetic nervous system), which is followed by glucocorticoids mediating its recovery back to normal. This represents a triumph for the physiologist Allan Munck of Dartmouth, who led this revisionism (Munck, Guyre, and Holbrook 1984). His work also provides the answer to what might be the next question—why is it adaptive for the immune system to recover back to its baseline? Why not just have it work at a higher level all the time, presumably providing even better defenses against pathogens? Munck's

answer was that you cannot just have immune activity climb higher and higher, because there is the danger that immunity will eventually spiral out of control into pathologic overactivation. Specifically, he predicted that if glucocorticoids did not damp the immune response back down during stress, immune activation might spill over into autoimmune disease. This turns out to be correct, and various instances of autoimmunity are now understood to involve a failure of the glucocorticoid "brake" during stressors. This also helps explain one of the persistent paradoxes in clinical medicine: synthetic versions of glucocorticoids suppress autoimmunity and help lessen the symptoms of the autoimmune disease. Yet many clinical studies and endless patient reports indicate that periods of stress *worsen* autoimmune symptoms. The resolution is now clear. If there are lots of everyday stressors, there will be bursts of transient immune activation (and thus transient worsening of symptoms in an autoimmune patient); but massive, pharmacologic doses of glucocorticoids will flatten immunity.

Recent work has added an extra subtlety to our understanding of the actions of glucocorticoids during stress. Once again, massive amounts of such steroids suppresses virtually every facet of immunity. However, as the more physiologic stress-induced levels of glucocorticoids begin to have their effects, they preferentially inhibit older constituents of the immune system. This can be seen as sculpting the immune response, bringing the newer and more helpful immune cells to the forefront (Besedovsky and Del Ray 1996). Furthermore, when glucocorticoids cause immune cells to be removed from the circulation, the classical notion was that such cells were stored, inactive, in immune tissues; recent work has shown that the early phase of glucocorticoid actions involves, instead, the diverting of immune cells to injured tissues—rather than being placed in the barracks, soldiers are being rushed to the front lines (Dharbar and McEwen 1996).

Thus, a new picture of immune function during stress has emerged. With the onset of stress, immune defenses are activated, with a number of hormones, including glucocorticoids, working to sharpen immune defenses and mobilize them to where they are needed. Shortly thereafter, glucocorticoids act to return immunity back to baseline, a critical step to avoid autoimmune overshoot. And it is only with massive and prolonged stressors that immunity is suppressed below baseline. The next section considers the controversial question of whether such immune suppression during chronic stress is enough to make you sick.

The Pathogenic Effects of Chronic Stress on the Immune System

If prolonged stress suppresses immunity, more infectious diseases should result. This seems straightforward, but is actually anything but (Booth-Kewley and Friedman 1987; Friedman and Booth-Kewley 1987; Fox 1983; House, Landis, and Umberson 1988; Sapolsky 1998; Shekelle et al. 1981, chapter 8). The stress/infection linkage is built on the following logic: during prolonged stress, there is prolonged glucocorticoid secretion; this suppresses immunity

below baseline, impairing disease defenses and resulting in more illnesses. The first problem with this sequence concerns individual differences and psychological stressors (topics detailed in the next sections of this chapter). If you break someone's leg, they are going to secrete glucocorticoids, no doubt about it. But if you stick someone on a slow line at the supermarket checkout, they might fume and complain and have a robust stress-response, or they may happily daydream. When it comes to most psychological and social stressors, we differ dramatically as to what we perceive as stressful (and thus whether we mobilize glucocorticoid secretion).

Uncertainty comes with the next steps as well. We now know that, depending on the type and duration of a stressor, glucocorticoids can either stimulate or inhibit immunity, and individuals will differ as to where the transition occurs between the stimulatory and inhibitory actions. Thus, it is not even clear whether a particular stress-induced burst of glucocorticoid secretion actually inhibits immunity.

Finally, while massive suppression of immunity causes individuals to fester with infectious diseases, stress-induced immune suppression is subtler and more transient. For example, the extent of immune suppression due to a sleepless week of studying for finals doesn't remotely resemble the extent of immune suppression seen in AIDS. And it is just not clear whether the milder extent of suppression in the former case is enough to actually make a difference in defenses against disease.

When you put these various caveats together, you are left with a lot of confusion. Stress-induced immune suppression is most likely to put you more at risk for the common cold, mononucleosis, or cold-sore flare ups. But the relevance in other areas remains unclear. For example, there appears to be an increased risk of disease or mortality among individuals who are grieving for a lost loved one. Maybe this is because the stressfulness of loss leads to glucocorticoid-induced immune suppression and thus more infectious disease. However, maybe grieving, depressed people simply no longer bother taking their daily medications or eating healthy meals. In studies of such individuals, it is often quite difficult to control for some of these life-style variables. Thus, while stress-induced immune suppression almost certainly is relevant to why everyone gets colds just after finals week, it remains to be seen whether it is relevant to more serious areas of medicine.

One area in which stress-induced immune suppression plays almost no role is with respect to cancer. Many health care professionals have sensed a link between stress and cancer, as have many patients. A rather poorly controlled literature has purported to show that link as well. For example, a number of studies have reported a link between a major depression (a highly stressful state, as will be discussed below) and an increased risk of cancer, even years later. However, the effects in these studies have been tiny, and critical confounds have not been controlled for. For example, the most widely cited of these studies, carried out on a population working in an electric plant, failed to control for the fact that the depressed subpopulation also had

the highest exposure to environmental carcinogens. The more careful studies have failed to show any relationship between stressors of any sort (such as depression or bereavement) and cancer incidence.

Laboratory studies have also focused on this issue. None have shown that stress can increase the rate of spontaneous tumors in a laboratory animal. A number have shown that stress can accelerate the growth of artificially induced tumors and have even uncovered likely mechanisms to explain this observation. However, the types of tumors in these studies (virally derived ones) are very rarely suffered by humans, and there is no convincing evidence that stress can accelerate the growth of the types of tumors that humans get (those that are genetic in nature or due to environmental carcinogens).

Finally, studies have shown that people who have a "fighting spirit" about their cancer (that is, those who approach the cancer as something that can be beaten) or those placed in support groups with other cancer patients are likely to survive cancer longer than cancer patients in a control group. Perhaps this is because such individuals secrete less glucocorticoids and thus have better immune defenses against the tumor. But perhaps these people are simply more compliant with treatment regimes—more likely to subject themselves to the extra chemotherapy sessions, to take their medicine although it makes them nauseous, to eat despite having no appetite, and so on.

Collectively, there is next to no scientific evidence to link stress to human cancer. It strikes me as critical to emphasize this point, given the many health care professionals and patients who believe there is a link. When you teach someone about a legitimate link between stress and disease, you are providing them with a means to improve their health. But when someone suffering from a horrible, often fatal disease is led erroneously to believe that stress had something to do with its cause or progression, you can convince them that it is their own fault that they are dying. This is not good science, good medicine, or good ethics.

Few areas of the life sciences are more exciting these days than psychoimmunology because its potential impact on health and disease is so profound. Nevertheless, it is clearly a nascent discipline, and one should be cautious about overemphasizing its findings. More research is clearly needed.

The preceding pages have reviewed the effects of stress on metabolism, cardiovascular function, and so on, detailing the adaptive features of the short-term stress-response and the pathogenic potential of chronic stress. These are summarized in table 11.1. Amid this mountain of data, two conclusions seem clear: If you are that lion or zebra and you cannot appropriately initiate a stress-response, you are in deep trouble. But just as clearly, if you are unable to terminate a stress-response appropriately, as is so often the case with modern humans, you also pay a considerable pathologic price.

How Generalized Is the Stress-Response?

Figures 11.1 and 11.3 depict the hormones and neural systems thought to be turned on by all stressors and those inhibited by all stressors, respectively

Table 11.1 The Principal Components of the Stress-Response and the Most Common Pathologic Consequences of Prolonged Exposure to Stress

THE STRESS-RESPONSE	ITS PATHOLOGIC CONSEQUENCES, WHEN PROLONGED
Mobilization of energy at the cost of energy storage	Fatigue, myopathy, steroid diabetes
Increased cardiovascular and cardiopulmonary tone	Hypertension
Suppression of digestion	Ulceration
Suppression of growth	Psychogenic dwarfism, bone decalcification
Suppression of reproduction	Anovulation, impotency, loss of libido
Suppression of immunity and the inflammatory response	Impaired disease resistance
Analgesia	
Neural responses, including altered cognition and sensory thresholds	Accelerated neural degeneration during aging

(Frakenhaeuser 1980; Mason 1968; Weiner 1992). For Selye, one of the cornerstones of the stress-response was this nonspecificity—for example, that whether you are too hot or too cold, the stress-response is essentially similar. It was no accident that Selye used the word "general" with "adaptation syndrome." He wrote:

It is difficult to see how such essentially different things as cold, heat, drugs, hormones, sorrow and joy could provoke an identical biochemical reaction in the organism. Yet this is the case; it can now be demonstrated by highly objective quantitative biochemical determinations that certain reactions of the body are totally nonspecific and common to all types of exposure.

As with many grand and sweeping statements in science, this is not entirely true; not all stressors provoke the identical package of responses. In Selye's view, any stressor would provoke norepinephrine release from all the many branches of the system. Yet there is some specificity of response. For example, hypoxia stimulates renal and gastric sympathetic activity, while hypotension stimulates only the former. Furthermore, norepinephrine and epinephrine secretion during stress can dissociate. For example, hypotension affects both renal and adrenal sympathetic activity similarly, whereas hypoglycemia does not. Thus, the entire sympathetic nervous system is not necessarily turned on in a nonspecific way in response to any stressor. This specificity of coding is also observed when comparing different endocrine systems. Some stressors provoke adrenocortical activity far more than adrenomedullary activity, while others do the opposite. Some stressors also influence glucocorticoid secretion without affecting growth hormone secretion. Broadly, you would be on safe ground if you stated that all stressors provoke

some degree of catecholamine and glucocorticoid secretion. However, the exact orchestration of responses of the many hormones discussed will vary depending on the stressor, something now referred to as a "stress signature."

Psychologic Stress

We have summarized the understanding of stress that would satisfy most physiologists. Much of the remainder of this chapter examines individual differences in the stress-response. Why do two individuals differ in how often or how much they activate the stress-response? By thinking purely in terms of the physiology presented in this chapter up until now, it would be easy to approach this question. One would first point out the obvious, that the two organisms might differ in the amount of stressors they are exposed to and then move on to the next and more interesting level of analysis—two organisms that are exposed to the same stressor but differ in the resulting stress-response. We can speculate about interesting mechanisms that might explain the differences. Suppose two monkeys are both deprived of food to the point where metabolic homeostasis is disturbed and to an equal extent in both animals. Both should then secrete glucocorticoids; if there are marked differences in the amount of glucocorticoids secreted, the well-trained physiologist should immediately think of explanations such as differences in ACTH half-lives in the blood, differences in adrenal perfusion rates, numbers of glucocorticoid receptors, and so on. This would be the traditional approach of stress physiologists (Levine, Weiner, and Coe 1989; Miller 1980; Weiss 1970).

One study suffices to show how much more complex the picture really is. In the study cited above, the two monkeys differed in one critical way. While both were deprived of any nutrition, one was fed a flavored placebo. That monkey did not secrete glucocorticoids, whereas the first one had a sizable stress-response. Nothing in the world of Selye and the physiologists could have predicted this outcome because the homeostatic balance was equally disturbed in both monkeys (they were equally hypoglycemic). However, the second monkey did not *perceive* things to be as stressful as the first one did.

This study signaled a major change in the study of stress physiology. The prior view held that if you knew how physiologically disruptive the external insult was, you had a good chance of predicting the magnitude of the stress-response. Suddenly, critical intermediary—psychological factors could modulate the stressfulness of a stressor. Psychological factors could even trigger a stress-response in the absence of homeostatic disruption: Animals and humans were shown to have classic stress-responses during bereavement, difficulty in cognitive tasks, conditioned fear, and so on.

How much can psychological variables modulate the stress-response? Clearly, a great deal. Numerous physical stressors are no longer stressful when the organism is habituated to the situation and is thus accustomed to it. Yet it cannot be true that all physical stressors are stressful only to the extent that they cause emotional arousal. As evidence, an anesthetized person has a stress-response following a surgical incision.

Most scientists now accept the power of psychological variables to modulate stress physiology. The question, of course, is, what are these variables? What is stressful about psychological stress? Elegant studies have shown that the answer includes a lack of control, a lack of predictability, and a lack of outlets for frustration. Other terms and constructs have been used in the field, but these encompass the most important ideas.

Lack of control is critical. In one demonstration of this, rats were subjected to intermittent electric shocks. One rat could control the situation because it was able to press a lever to decrease the rate of shocks. The second rat received a shock whenever the first one did, but without control. The latter had far more glucocorticoid secretion and a greater chance of developing ulcers; this result occurred despite an identical extent of physical perturbation. Similar findings have emerged with dogs and humans. In a subtle elaboration, if a rat is trained to press a lever to avoid a shock and is then prevented from performing that avoidance behavior when it expects a shock, there is glucocorticoid secretion even if no shock is actually delivered. Here, loss of control is a trigger, even in the absence of a physical stressor.

Lack of predictability is also critical. If rats are given a signal indicating the impending delivery of a shock or when the shock period has ended, they have less glucocorticoid secretion than rats given identical shocks with no warning. In the former case, the signal allows the rat to predict when a shock is and is not about to occur and thus when it can relax its vigilance.

Some have noted that loss of control and of predictability share the trait of the outcome being discrepant with expectations (or, in other words, novel). Thus, the simple act of putting a rat in a novel environment—a new cage—activates the stress-response. In men learning to parachute jump, their first jump elicited a robust stress-response. With subsequent jumps, however, the response eventually habituated as the novelty of the situation lessened. Some have also emphasized that the common theme in loss of control and of predictability is the consequent arousal or vigilance, as the animal searches for the new rules of control and prediction.

A number of studies have emphasized the importance of *outlets for frustration*. For example, when rats are shocked, there is less glucocorticoid secretion and fewer ulcers if they can gnaw on a piece of wood or can attack another rat. Eating, drinking, or access to a running wheel can also serve as protective outlets.

One can ask some subtle questions. For example, does novelty stimulate the stress-response in a linear or all-or-none fashion? It appears to be linear. Thus, the more novel an environment for a rat (handled and returned to home cage, or returned to a new but similar cage, to a new type of cage, to a new type of cage illuminated with bright lights, and so on), the higher the level of glucocorticoid secretion. This demonstrates the rigor of current psychoendocrine approaches in stress research.

Thus, the extent to which a physical insult is stressful is modulated dramatically by intervening psychological variables, and psychological factors

can initiate a stress-response even in the absence of a physical insult. Clearly, one vital prerequisite for responding to psychological stressors is a certain level of intelligence. One needs to have a decent memory to perceive a novelty stressor—"I know what is normal, and what's happening now is not normal, and this makes me nervous," or a conditioned stressor—"Uh oh, I remember what occurred last time this happened and it wasn't good." Thus, only the more cognitively sophisticated species can have sustained psychologic stressors (and pay the pathogenic price). And humans excel at this.

Individual Differences in Stress Physiology

Why is it interesting to study individual differences? Most physiologists hate individual variability. Just when you think you have discovered something and can announce that "X causes Y," you have to qualify your observation by saying "X causes Y most of the time, but not in a subset of animals, and don't ask me why not." Individual variability makes data messy and it's harder to know what is really going on. The emphasis in physiology on using inbred strains of animals with identical housing conditions is meant to eliminate individual variability. Why study it?

The answer must be because individual variability is a major chance to understand the prevention of stress-related disease. A mountain of data now demonstrates that stress can increase your chances of becoming sick. It sometimes seems miraculous that any of us manages to survive the lifetime of stressors that we are all subject to. Yet only some of us get stress-related diseases. To study individual differences in stress physiology is to study what some individuals are doing right and to study why some bodies and some psyches deal with stressors better than others. In the next few sections, we will review some examples of stress-responses differing systematically between individuals.