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Chapter 6

Pain and Stress: A New Perspective

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The neuromatrix theory of pain (Melzack, 1989, 1990, 1991, 1992, 1995) proposes that pain is a multidimensional experience produced by characteristic "neurosignature" patterns of nerve impulses generated by a widely distributed neural network—the "body-self neuromatrix"—in the brain. These neurosignature patterns may be triggered by sensory inputs, but they may also be generated independently of them. Pains that are evoked by noxious sensory inputs have been meticulously investigated by neuroscientists, and their sensory transmission mechanisms are generally well understood (see Melzack & Wall, 1996). In contrast, chronic pain syndromes, which are often characterized by severe pain associated with little or no discernible injury or pathology, remain a mystery. The neuromatrix theory of pain, however, provides a new conceptual framework that is consistent with recent clinical evidence. It proposes that the output patterns of the neuromatrix activate perceptual, homeostatic, and behavioral programs after injury or pathology or as a result of multiple other inputs that act on the neuromatrix.

Pain, then, is produced by the output of a widely distributed neural network in the brain rather than directly by sensory input evoked by injury, inflammation, or other pathology. The neuromatrix, which is genetically determined and modified by sensory experience, is the primary mechanism that generates the neural pattern that produces pain. Its output pattern is determined by multiple influences, of which the somatic sensory input is only a part, that converge on the neuromatrix.

We are so accustomed to considering pain as a purely perceptual phenomenon that we have ignored the obvious fact that injury also disrupts the body's homeostatic regulation systems, thereby producing stress and initiating complex programs to restore homeostasis. By recognizing the role of the stress system in pain processes, the scope of the puzzle of pain is greatly expanded, and new pieces of the puzzle provide valuable clues in our quest to understand chronic pain.

THE STRESS SYSTEM

Hans Selye (1950), who founded the field of stress research, studied stress as a biological response to a wide range of stressors. They include physical injury, infection, and other pathology, as well as psychological stressors such as the loss of a job or the death of a friend. Recently, stress has been defined (Chrousos, 1992) as a state of threatened homeostasis—that is, a disruption by stressors of physiological processes such as blood sugar level and body temperature that are normally maintained at a fixed, delicately balanced set point.

The disruption of homeostasis by a stressor, either physical or psychological, activates programs of neural, hormonal, and behavioral activity aimed at restoring homeostasis. The particular programs that are activated are selected from a genetically determined repertoire of programs (which have been modified by events such as earlier exposure to stress) and are influenced by the extent and severity of the perceived stress.

Given the multiplicity of interacting neural and hormonal factors that contribute to homeo-

stasis, it is not surprising that programs to reinstate homeostasis may go awry. The consequence is a variety of stress-related disorders, which include several chronic pain syndromes (Chrousos, 1992; Chrousos & Gold, 1992; Sapolsky, 1992). It is important, therefore, to examine the hypothesis that stress may produce the conditions that give rise to some forms of chronic pain.

When injury occurs, sensory information is projected rapidly to the brain, and, in parallel with the neuromatrix activities that usually lead to pain perception (Melzack, 1991, 1995), the stress system (Figure 6.1) initiates the complex sequence of events to restore biological homeostasis. Activities in the injured tissues produce cytokines, which are complex molecules produced by the interaction of transformed white blood cells known as macrophages and injured tissues. These cytokines are released within seconds after injury and take part in producing a local inflammatory response. Within minutes, cytokines such as gamma-interferon, interleukins 1 and 6, and tumor necrosis factor enter the bloodstream and travel to the brain, where they breach the blood-brain barrier at specific sites and have an immediate effect on hypothalamic cells (Sapolsky, 1992). The cytokines, together with the perception of pain—a stressor—rapidly begin a sequence of activities aimed at the release and utili-

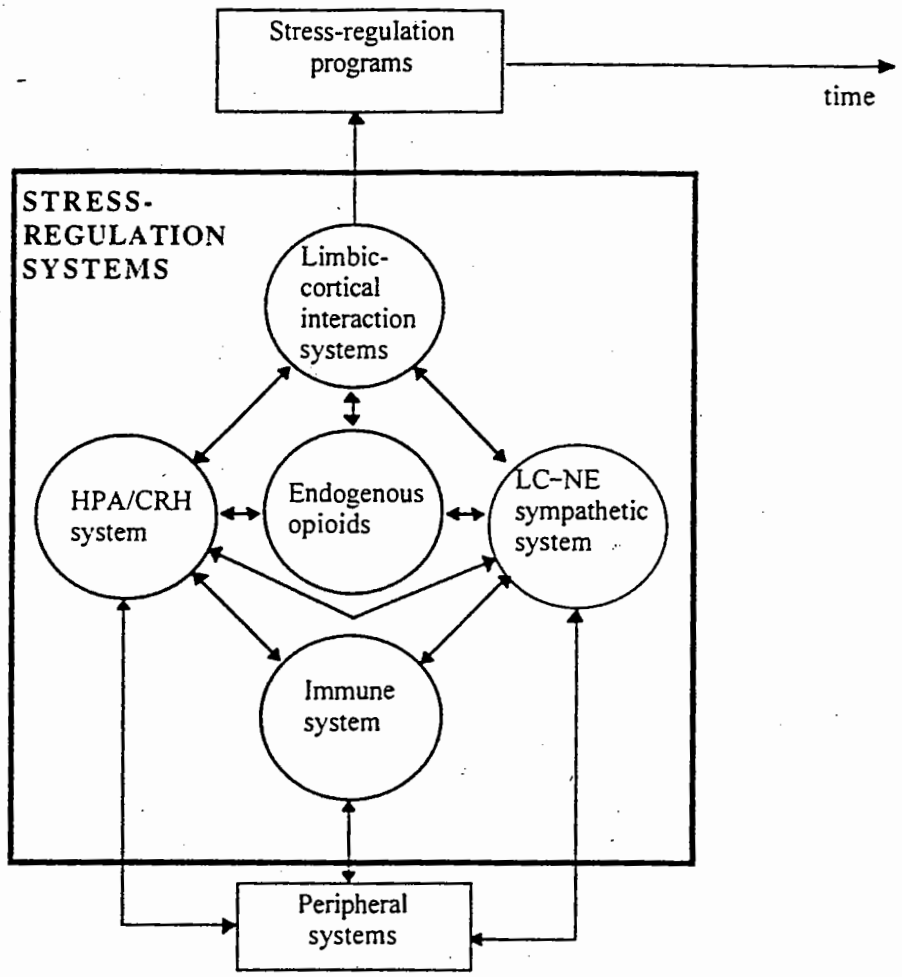

FIGURE 6.1. Components of the stress-regulation systems and their interactions. In the HPA (hypothalamic-pituitary-adrenal) system, the paraventricular nucleus of the hypothalamus, during a stressful event, produces CRH (corticotropin-releasing hormone), which activates the pituitary to produce adrenocorticotropic hormone (ACTH) that, in turn, acts on the adrenal cortex to produce cortisol in humans and corticosterone in animals. The LC-NE (locus coeruleus-norepinephrine)-sympathetic system in the brainstem has descending and ascending projections. Both of these systems interact with the immune, opioid, and limbic-cortical systems. A more detailed schematic figure, which depicts many of the components of the systems and their interactions, is presented by Chrousos and Gold (1992).

zation of glucose for necessary actions such as the repair of tissues and "fight or flight" responses to survive the threat to the body-self.

Cytokines that penetrate the hypothalamus activate the hypothalamic-pituitary-adrenal (HPA) system, in which corticotropin-releasing hormone (CRH) produced in the hypothalamus is released into the local bloodstream that carries it to the pituitary. There, the CRH causes the release of adrenocorticotropic hormone (ACTH) and other substances (Sapolsky, 1992; Chrousos, 1992). The ACTH then activates the adrenal cortex to release cortisol (in humans; corticosterone in animals), which plays a powerful role in the stress response.

At the same time that the HPA system carries out these processes, the autonomic system is activated: The powerful locus coeruleus-norepinephrine (LC-NE)-sympathetic system in the brainstem acts upward on neural mechanisms throughout the brain and, via hypothalamic and other limbic areas, downward through the descending autonomic (sympathetic and parasympathetic) nervous system (Chrousos, 1992). During the stress response, the sympathetic system predominates and produces readiness of the heart, blood vessels, and other viscera for complex action programs to respond appropriately to the stressor and to reinstate homeostasis.

As the stress response continues, it has a powerful impact on multiple additional systems. The immune system is suppressed, and major portions of the limbic system (mesocorticolimbic areas, as well as the amygdala and hippocampus), which play a role in emotional, motivational, homeostatic, and cognitive processes, are activated. Furthermore, the endogenous opioids, such as endorphin, are released within minutes. Their initial function may be primarily to inhibit or modulate the release of cortisol (Chrousos, 1992; Sapolsky, 1992). This highly simplified description does not include multiple other neural and hormonal systems and the complex interactions among them that take part in the stress response (Chrousos, 1992). Figure 6.1 provides a schematic representation of the major components that make up the stress system and their interactions.

The stress and pain-perception systems, therefore, possess overlapping mechanisms. Injury produces information that feeds into the body-self neuromatrix that generates the output patterns that comprise the neurosignature for the perception of the extent and severity of the injury and concurrently activate the appropriate action patterns to be chosen from the available pool (Melzack, 1995). This output, together with information generated by the neuromatrixes that receive inputs from the other sensory and cognitive systems, acts on the stress-regulation mechanisms that are part of the system—the HPA and LC-NE-sympathetic systems—and determines whether or not pain will be experienced or suppressed. It is well known (Melzack, Wall, & Ty, 1982; Melzack & Wall, 1996) that people who undergo severe injury may not feel any pain for as long as hours, even days, afterward. Because the stress system requires about 1-4 minutes to be activated, the endorphin and other opioid substances released by stressors cannot be the determinant of the complete suppression of pain after injury. Rather, the neuromatrixes that generate sensory-discriminative and evaluative information regarding the state of the body and the circumstances of injury (for example, an injury in an automobile accident or a gash made in the leg of a zebra by a hungry lion) determine the initial activation or suppression of the pain, inflammation processes, and immune systems (Sapolsky, 1992).

Prolonged activation of the stress-regulation systems produces breakdown of muscle, bone, and neural tissue. Excessively long or intense activation of these systems, therefore, can have disastrous consequences. They may set the stage for fibromyalgia, osteoporosis, and other chronic pain syndromes (Chrousos & Gold, 1992).

To recapitulate, the HPA and LC-NE-sympathetic systems are activated by perceived pain or other forms of stress on the basis of sensory and cognitive input to the body-self neuromatrix. At the same time, when injury or other pathology occurs, cytokines are released into the bloodstream and are carried to the hypothalamus, where they act directly on the HPA and LC-NE-sympathetic systems, the two major pillars of the stress system. Activation of the stress system also influences several other powerful systems, including the immune system, the endogenous opiates, and major portions of the limbic system (mesocorticolimbic areas, as well as the amygdala and hippocampus). All of these systems interact with each other and are characterized by multiple checks and balances (Chrousos & Gold, 1992; Fuchs & Melzack, 1996, 1997; Fuchs, Kerr, & Melzack, 1996; Harbuz & Lightman, 1992; Lariviere, Fuchs, & Melzack, 1995; Sapolsky, 1992). It is not surprising, then, to find great variability among studies. Nevertheless, particular effects of the stress system are firmly established.

The inhibitory effect of cortisol on the immune system and the serious effects of prolonged immune

suppression are fully documented (Chrousos, 1992; Sapolsky, 1992). The opiates appear to modulate the effects of cortisol, but their full function is not understood. The programs aimed at a return to homeostasis are only partly known; their relation to chronic pain must, because of our lack of knowledge, be surmised.

PROGRAMS INVOLVING THE CORTISOL SYSTEM

Cortisol, together with the activation of the sympathetic system, sets the stage for the stress response. Cortisol plays an essential role because it is responsible for producing and maintaining high levels of glucose for the response. At the same time, cortisol is potentially a highly destructive substance because, to ensure a high level of glucose, it breaks down the protein in muscle and inhibits the ongoing replacement of calcium in bone. It can also have a marked deleterious effect on neurons in the hippocampus (Sapolsky, 1996). As a result, if the output of cortisol is prolonged, excessive, or abnormally patterned, it may produce destruction of muscle, bone, and neural tissue and produce the conditions for many kinds of chronic pain.

The deleterious effect of aging on hippocampal neurons is particularly serious because the hippocampus acts as a natural brake on cortisol release. As aging proceeds, therefore, cortisol is released in larger amounts, producing a cascading destructive effect (Sapolsky, 1992) that could contribute to the increase of chronic pain problems known to occur among older people.

It is possible that any site of increased cytokine activity and inflammation, including sites of strain, sprain, or spasm of muscles and tendons, could become the focus of cortisol action and muscle destruction. This could mark the beginning of trigger zones at sites that tend to become inflamed due to minor injury (Sola, 1994) and may become particularly vulnerable to cortisol's destructive effects. The breakdown of muscle protein could also be the basis for fibromyalgia and other muscle pains. At the same time, calcium replacement in bone is inhibited (Sapolsky, 1992). If the inhibition is prolonged, it may become the basis of osteoporosis, which may produce deformities and fractures, particularly of the vertebrae and hip, that are often extremely painful.

The cortisol output by itself may not be sufficient to cause chronic pain problems but rather provides the background conditions so that other contributing factors may, all together, produce them. Estrogen levels, genetic predispositions, and psychological stresses derived from social competition and the hassles of everyday life may act together to influence the effects of cortisol on the target organs.

A high proportion of cases of chronic back pain may be due to more subtle causes (Jayson & Freemont, 1995). The perpetual stresses and strains on the vertebral column (at discs and facet joints) produce greatly increased vascularization and fibrosis of the area. As a result, there is a release of substances such as bradykinen that are known to produce inflammation and pain into local tissues and bloodstream. As a result, the whole HPA cascade may be triggered repeatedly.

The effect of stress-produced substances—such as cortisol and noradrenalin—at sites of minor lesions and inflammation may, if it occurs often and is prolonged, activate a neuromatrix program that anticipates increasingly severe damage and attempts to counteract it. The program to reduce strain and inflammation could generate the neurosignature for pain, which induces rest, the repair of injured tissues, and the restoration of homeostasis.

This speculation is supported by strong evidence. Chrousos and Gold (1992) and Tsigos and Chrousos (1994) have documented the effects of dysregulation of the cortisol system, to which they attribute fibromyalgia, rheumatoid arthritis, and chronic fatigue syndrome (which is often painful). They propose, on the basis of experimental data, that they are associated with *hypo*cortisolism—that is, reduced release of cortisol during stress. However, hypocortisolism may also reflect a higher level of utilization and metabolism of cortisol, which may appear as a depletion due to prolonged stress. Indeed, an important problem that requires investigation is the effect of a prolonged series of brief stresses—that is, brief spurts of hypo- or hypercortisolism over a long period of time—compared to prolonged, continuous stress. Whatever the mechanism, myopathy, bone decalcification, fatigue, and accelerated neural degeneration during aging are produced by prolonged exposure to stress.

A better understanding of the multiple modulation effects among the components of the stress system, as well as the effects of long durations of abnormal patterns of secretion of cortisol, may reveal the underlying interactional mechanisms (Chrousos & Gold, 1992; Sapolsky, 1992). For example, the endogenous opioids that are released by stress produce a further reduction in cortisol output. Cortisol levels are also decreased by sym-

pathetic activity. The temporal patterns of output of different substances may determine hypo- versus hypercortisolism and, therefore, the resultant painful conditions. Diabetes mellitus, especially with diabetic neuropathy, is associated with *hyper*cortisolism (Tsigos & Chrousos, 1994). Research is therefore especially needed to investigate these deleterious effects on tissues in relation to pain.

PROGRAMS INVOLVING THE IMMUNE SYSTEM

A major effect of stress is the suppression of the immune system, which normally attacks invading bacteria, viruses, and other foreign substances (Steinman, 1993). However, this suppression may induce the immune system to attack the body itself, which would produce autoimmune diseases, many of which are also chronic pain syndromes. A possible mechanism is that prolonged suppression may result in dangerous levels of infection and an accumulation of toxins. Conceivably, the release from suppression may lead to a rebound excessive autoimmune response.

Concurrently with the suppression of the immune response, stress also suppresses the perception of pain and inflammation at the site of injury. The value of suppressing pain is clear: A wounded zebra, for example, needs to run from an attacking lion, and pain, as well as inflammation, would hamper running speed and could lead to death (Sapolsky, 1992). However, this suppression of pain, inflammation, and immune-system activity could also produce increased levels of tissue damage and infection. The suppression of pain may persist for hours, sometimes days, yet the pain returns (Fuchs, Kerr, & Melzack, 1996; Fuchs & Melzack, 1997; Melzack, Wall, & Ty, 1982), indicating that the mechanisms that produce pain and inflammation remain intact. It is possible, therefore, that the immune system may rebound with excessive vigor.

Consequently, the initially protective mechanisms may produce autoimmune diseases that are associated with significant levels of pain (Table 6.1). Some are also categorized as chronic pain syndromes—such as Crohn's disease, multiple sclerosis, rheumatoid arthritis, scleroderma, and lupus (Merskey & Bogduk, 1994).

The mechanisms that relate immune suppression to chronic pain are not understood. One possibility is that immune suppression, which prolongs the presence of dead tissue and invading bacteria and viruses, could produce a greater output of cytokines, with a consequent increase in cortisol release and its destructive effects. Another possibility, as I have already suggested, is that prolonged immune suppression may give way to a rebound excessive immune response that may lead

TABLE 6.1. Autoimmune Diseases with a Prominent Pain Component and Painful Diseases with a Suspected Autoimmune Component

Autoimmune diseases with a prominent pain component	Painful diseases with a suspected autoimmune component
Autoimmune arthropathy: rheumatoid synovitis	Endometriosis
Autoimmune polyneuropathies	Fibromyalgia
Dermatomyositis	Osteoarthritis
Inflammatory bowel diseases (Crohn's disease; ulcerative colitis)	
Inflammatory myopathy	
Insulin-dependent diabetes (diabetic neuropathy and pseudo-tabes lightening pains)	
Interstitial cystitis	
Mixed connective tissue disease (polyarthritis; diffuse scleroderma; trigeminal neuropathy)	
Multiple sclerosis	
Polymyositis	
Rheumatoid arthritis	
Scleroderma	
Sjögren's syndrome	
Systemic lupus erythematosus	
Systemic sclerosis	

to autoimmune disease and chronic pain syndromes. Thorough investigation may provide valuable clues for understanding at least some of the chronic pain syndromes that perplex us and are beyond our control. For example, it is well known that estrogen promotes the release of the cytokine gamma-interferon, which in turn produces increases in cortisol output, as well as autoimmune diseases (Steinman, 1993). This may explain why more females than males suffer from most kinds of chronic pain, as well as painful autoimmune diseases such as multiple sclerosis and lupus.

In general, more women than men have autoimmune diseases and chronic pain syndromes (Table 6.2). Among the 5% of adults who suffer from an autoimmune disease, two out of three are women. Pain syndromes also show sex differences, as Berkley (1997) has argued, with the majority prevalent in women and a much smaller number prevalent in men. Of particular importance are the increases and decreases in chronic pain among women concurrently with changes in estrogen output as a function of age. The relationship between autoimmune diseases and some forms of chronic pain leads to a search for possible causes. It is well known that estrogen produces an increase in cortisol levels for a brief period prior to menstruation. If this happens each month, the repetitive pattern could produce a cumulative destructive effect. Because these differences are small, they tend to be discounted, but they should not be. Abnormal patterns of cortisol release may produce myopathy, osteoporosis, neural dysfunction during aging, and autoimmune diseases (Sapolsky, 1992).

However, the role of estrogen in stress-regulation programs is obviously very complex. Estrogen has been implicated by Steinman (1993) as playing a role in several autoimmune syndromes, whereas Chrousos (1992) and Sapolsky (1992) believe that there is not sufficient free estrogen to have a significant effect on stress-dysregulation syndromes. Estrogen, in fact, presents a paradox: It increases the output of cortisol, which diminishes calcium replacement, yet estrogen replacement therapy after menopause is widely used to prevent osteoporosis. It is possible, though unlikely, that estrogen plays only a minor role in stress-related dysfunctional syndromes. It is more likely that its effects are modulated, inhibited, or facilitated by genetic determinants or other concurrently circulating hormones such as vasopressin, as well as by the levels of estrogen receptors and

TABLE 6.2. Sex Prevalence of Various Painful Disorders

Female prevalence	Male prevalence	No sex prevalence
Atypical facial pain (odontalgia) (F>>M)	Ankylosing spondylitis (9:1)	Acute herpes zoster
Burning tongue syndrome (F>M)	Cluster headache (9:1)	Chronic gastric ulcer
Chronic tension headache (1.5:1)	Hemophilic arthropathy (M>>F)	Cluster-tic syndrome
Fibromyalgia syndrome (7:1)	Postherpetic neuralgia (M>F)	Crohn's disease
Interstitial cystitis (10:1)	Posttraumatic headache (M>F)	Thoracic outlet syndrome
Irritable bowel syndrome (5:1)		
Migraine with aura (2:1)		
Migraine without aura (7:1)		
Multiple sclerosis (2:1)		
Raynaud's disease (5:1)		
Rheumatoid arthritis (F>M)		
Scleroderma (3:1)		
Systemic lupus erythematosus (9:1)		
Temporomandibular joint disorder (F>M)		
Tic douloureux (2:1)		
	Age-dependent sex differences	
Gout (after age 60)	Erythromelalgia (over age 50)	
Livedo reticularis (under age 40)	Gout (before age 60)	
Osteoarthritis (after age 45)	Osteoarthritis (before age 45)	
Reflex sympathetic dystrophy (under age 18 [6:1] and after age 50)		

Note. The ratios shown in parentheses are the best estimates available in Merskey and Bogduk (1994) or Wall and Melzack (1994). The "greater than" sign (> or >>) is used when ratios are not available. Adapted from Berkley (1997). Copyright 1997 by *Behavioral and Brain Sciences*. Adapted by permission. Additional information from Merskey and Bogduk (1994).

even the patterns of change of all of these factors. It is also possible that, under some conditions, estrogen may have an inhibitory effect on the cascade of events that leads to stress-related syndromes. Clearly, this is a potentially important field for research, with many tantalizing clues.

Three additional clues reveal the relationship between stress and chronic pain. First, in addition to a higher incidence of autoimmune diseases and chronic pain syndromes, women also have a disproportionately higher incidence (3:1) of depression, which is strongly influenced by stress. Second, as we have seen, antidepressants are often highly effective for the treatment of chronic pain. Third, antidepressants act on the hippocampus, which acts as a brake on cortisol release during stress. Smith (1991) has made a strong argument that macrophages such as interleukin-1 provoke depression. Because the hippocampus plays a powerful role in the affective dimension of pain and acts as a brake on stress, the effect of antidepressants on the neural activity of the hippocampus would be expected to modify the output neurosignature pattern and influence both pain and depression.

PROGRAMS INVOLVING HOMEOSTATIC REGULATION

Pain and other stressors produce changes in every physiological activity that is under homeostatic control, such as blood pressure, blood sugar level, and body temperature. A major stressor produces marked changes in one or more of these activities, and homeostatic programs are activated to bring about a return to normal set-point levels. The relationship between pain sensitivity and several homeostatic physiological activities provides valuable evidence that the body-self neuromatrix contains programs that exert a continuous influence on pain sensitivity in order to maintain homeostatic equilibrium. At least, this is a reasonable assumption. Consider the following examples.

Hypertension and Pain

It is now well established (France & Ditto, 1996) that chronic hypertension is associated with decreased sensitivity to pain. The current explanation is that baroreceptors are stimulated by increased blood pressure to bring about a reduction in pain sensitivity. However, in place of this stimulus-response interpretation, it is more plausible to propose a genetically determined neuroendocrine program that regulates both hypertension and pain. The decreased sensitivity to pain, I assume, decreases the possibility that severe pain will raise blood pressure to dangerous levels that threaten survival of the body-self. Hypertensive people are less sensitive to pain in a variety of experimental and clinical situations. Remarkably, even the adult children of hypertensive parents who show no signs of hypertension are also less sensitive to pain. This points to a genetically determined program that is influenced by the concurrent genetic predisposition to hypertension and its potential danger to survival. The neuroendocrine program, the evidence suggests, produces a continuously lowered sensitivity to pain.

Further evidence (reviewed by France & Ditto, 1996) supports this concept. Hypertensive people who were placed on antihypertensive medication for 3 months showed significant decreases in blood pressure but no significant change in pain sensitivity. Lowered pain sensitivity, evidently, was maintained by a mechanism independently from the hypertension, although the strong link between the two has been confirmed by a large number of excellent studies. Interestingly, specially bred hypertensive rats also show, as early as 3 weeks of age, a decreased sensitivity to pain that precedes the later development of elevated blood pressure. It is reasonable, then, to propose a genetic mechanism for a neuroendocrine program that anticipates the development of hypertension and maintains a decreased sensitivity to pain in order to prevent bombardment of the brain when injury occurs, thus diminishing pain, stress, and a consequent reflex increase in blood pressure.

Blood Sugar Levels and Pain

Remarkably, lower pain sensitivity is also found in patients with anorexia nervosa and bulimia nervosa and in subjects who restrain their food intake (Lautenbacher, Pauls, Strian, Pirke, & Krieg, 1990; Krieg, Roscher, Strian, Pirke, & Lautenbacher, 1993; Faris et al., 1992). The reduction in sensitivity to heat pain and pressure pain is assumed to be due to an increase in blood sugar and appears to occur after acute rather than persistent episodes of diminished food intake and hypoglycemia (Krieg et al., 1993). Reduced pain sensitivity did not occur after a 3-week diet period, even though the diet resulted in substantial weight loss

(Lautenbacher et al., 1991). In contrast, participants—diabetic or nondiabetic—who receive transfusions of glucose show an increased sensitivity to pain (Morley, Mooradian, Levine, & Morley, 1984). Similar increased pain sensitivity was found in diabetic patients (Morley et al., 1984) and diabetic rats (Lee & McCarthy, 1992). Thye-Rønn et al. (1994) administered transfusions of glucose in a double-blind study and confirmed that there is a significant increase in sensitivity to pressure pain. Interestingly, diabetics who also had high blood pressure showed lower pain sensitivity than diabetics without hypertension, suggesting that the high blood pressure decreases the tendency by diabetics to show increased sensitivity to pain.

Why should there be a relationship between blood sugar levels and sensitivity to pain? It is conceivable that metabolic programs in the homeostatic regulation system have evolved so that, in conditions of low blood sugar availability, the sensory gates to noxious stimuli are relatively closed, decreasing perceived pain, stress, and metabolic demands. However, the programs act rapidly to reinstate normal pain sensitivity when homeostasis is achieved. It is interesting that the neural program permits hyperglycemia to increase pain sensitivity above normal baseline levels, so that after eating, when blood sugar levels are elevated, the organism is more likely to be activated by injury, thereby counteracting the tendency to drowsiness and loss of alertness that often occur after eating.

Brain Temperature and Pain

A major aim of homeostatic programs after moderate to severe injury is to prevent large increases in brain metabolism and the consequent rise in brain temperature produced by injury from reaching dangerous levels. It is a fact that a rise in brain temperature of a few degrees produces convulsions, and a few degrees more results in death. To achieve the goal of maintaining brain temperature within a narrow range, a number of strategies are available to the brain: (1) decrease of brain activity by direct neural inhibition or by the local constriction of blood vessels; (2) dilation of blood vessels in the brain to increase blood flow to remove the heat produced by brain metabolism; (3) decrease of blood flow to sensory nerves (which may destroy them); and (4) the destruction of transmitting nerve cells (apoptosis) by commands from program centers.

Inhibition of activity in widespread areas of the brain, including portions of the visual system, may be induced by cutaneous stimulation (such as rubbing the skin) under particular conditions (light anesthesia) (Melzack & Casey, 1967; Melzack, Konrad, & Dubrovsky, 1968, 1969). The mechanisms that underlie this inhibition are not known. The large decrease (and occasional increase) in metabolic activity reflect both neural metabolic changes and blood flow. The inhibition, moreover, may persist for long durations after brief periods of stimulation. The brain, therefore, possesses a system capable of exerting strong widespread inhibition that is normally held under control but is available as a program to modulate brain metabolism.

Recent evidence using elegant brain imaging techniques supports the concept of inhibition of brain metabolism during pain. Jones and his colleagues (Di Piero et al., 1991) found that patients with severe, persistent pain due to cancer showed a significantly *lower* level of blood flow in the thalamus compared to pain-free control subjects. Even more impressive is the fact that a cordotomy (which cuts the sensory pathways from the cancerous areas to the thalamus) produced relief of pain and a striking *increase* in blood flow to the thalamus until local temperatures reached normal levels. A further recent study (Canavero et al., 1993) found that two patients with central pain syndromes showed a decrease of blood flow in the parietal lobe, with still further decreases after nonpainful stimulation. These results provide powerful evidence that pain is associated with a homeostatic *decrease* in blood flow in a major sensory transmission relay, which returns to normal, higher levels when pain is relieved. This may seem anomalous, but it is consistent with the idea of long-term homeostatic programs that prevent an excessive increase in brain temperature.

The dilation or constriction of blood vessels to the brain is a well-known accompaniment of the sequence of events that occurs during most migraines. Migraines are subjectively undesirable but represent a powerful program by which the brain, because of a perceived threat, can diminish activity in a large part of the brain and, by inducing pain, can force the organism to rest and decrease all inputs to the brain.

The possible strategy of prolonged, reduced blood flow to nerves and apoptosis ("suicide") of neurons in response to the anticipated danger of a rise in brain temperature may seem drastic, but it is a reasonable strategy for coping with a perceived threat of a prolonged rise in brain temperature that could eventually produce convulsions and

incapacitate an animal seeking to escape a deadly predator. Apoptosis of neurons could occur at any level—in the brain itself, in the cord, and in peripheral nerves. It could explain spontaneous neuropathies (as a program gone wrong) or diabetic or other neuropathies related to conditions involving abnormal stimulation of peripheral nerves. For example, because the lower limbs in diabetics may develop circulation problems that would produce massive input and pain, the brain may activate an anticipatory program to destroy the potentially offending nerves by restricting blood flow to them or by apoptosis. Misinformation, misinterpretation of information, or misresponse to information could all lead to inappropriate spontaneous neuropathy. Apoptosis, in this case, is akin to the immune system behaving inappropriately and producing some of the autoimmune diseases.

IMPLICATIONS OF STRESS REGULATION

By unifying the perceptual and stress systems involved in pain, we immediately expand our available knowledge related to pain and open the door to new therapies. Our present understanding of receptor and spinal mechanisms, which is the basis of the gate control theory of pain (see Melzack & Wall, 1996) and its more recent extensions (Melzack, 1971; Melzack & Casey, 1968), is not diminished. Rather, the data and the gate control theory now fit into the broader framework of the neuromatrix theory of pain.

Unity of Perceptual and Stress Mechanisms of Pain

The intimate relationship between the perceptual and stress systems is not surprising. The limbic system, which receives the projections of the medial sensory transmission pathways, is the neural substrate of the affective-motivational dimension of pain (Dennis & Melzack, 1977; Melzack & Casey, 1968), and a portion of the system, including the hypothalamus, is an integral part of the stress system. The two systems are so interdependent that they should be considered as components of a single system (Figure 6.2). This close relationship is further indicated by observations that pain exhibited by rats in the formalin test is abolished by a lesion of the medial projection system at the level of the thalamus but is unaffected by a lesion of the lateral system at the same level (McKenna & Melzack, 1994). The lateral system has the important role of conveying precise information to the body-self neuromatrix and generates the information needed for the localization and evaluation of the input. Both kinds of information are projected to the limbic system, which is prepared to generate the affective-motivational response to perceived injury and stress. We now have a new conceptual model of the brain in which limbic structures, the cerebral cortex, and all major components of the stress system play key roles. The new concept has important implications for the study of pain.

Rationale of Pain Therapies

First, let us look at therapies that make sense within the framework of the new concept. For example, tricyclic antidepressant drugs relieve some forms of chronic pain even though the pain is not caused by depression. However, cytokines, particularly interleukin-1, alpha-interferon, and tumor necrosis factor, have been shown to produce the symptoms of major depression (see Smith, 1991), and they also activate the stress system, which may produce the basis for chronic pain syndromes. Conceivably, antidepressants may act on hormones and neurotransmitters, such as noradrenalin and serotonin, that play a role in both depression and pain. Smith (1991) also notes that major depression is as much as two to three times more common among women than men. Moreover, estrogen increases the production of cytokines, which produce an almost fourfold increase in cortisol production. Rheumatoid arthritis, which is associated with dysregulation of cortisol output, also has a female:male ratio in young adults of 5:1. After age 60, this ratio drops to 2:1, and major depression also drops dramatically in women after age 65 (from 5.8% in women aged 18–44 to 1.6% in women over 65). Because migraine, lupus, and a variety of stress- and immune-system diseases also show female:male ratios that range from 2:1 to 9:1, it is reasonable to assume that a large number of chronic pain syndromes, as well as depression, are linked to the stress regulation systems.

A variety of well-known facts that had no place in the Cartesian paradigm now have plausible, meaningful roles. For example, the high rate of pain relief after lesions of the pituitary in cancer patients now becomes comprehensible (Miles, 1994), because the pituitary is a major link in the HPA system. This dramatic relief is reported by patients

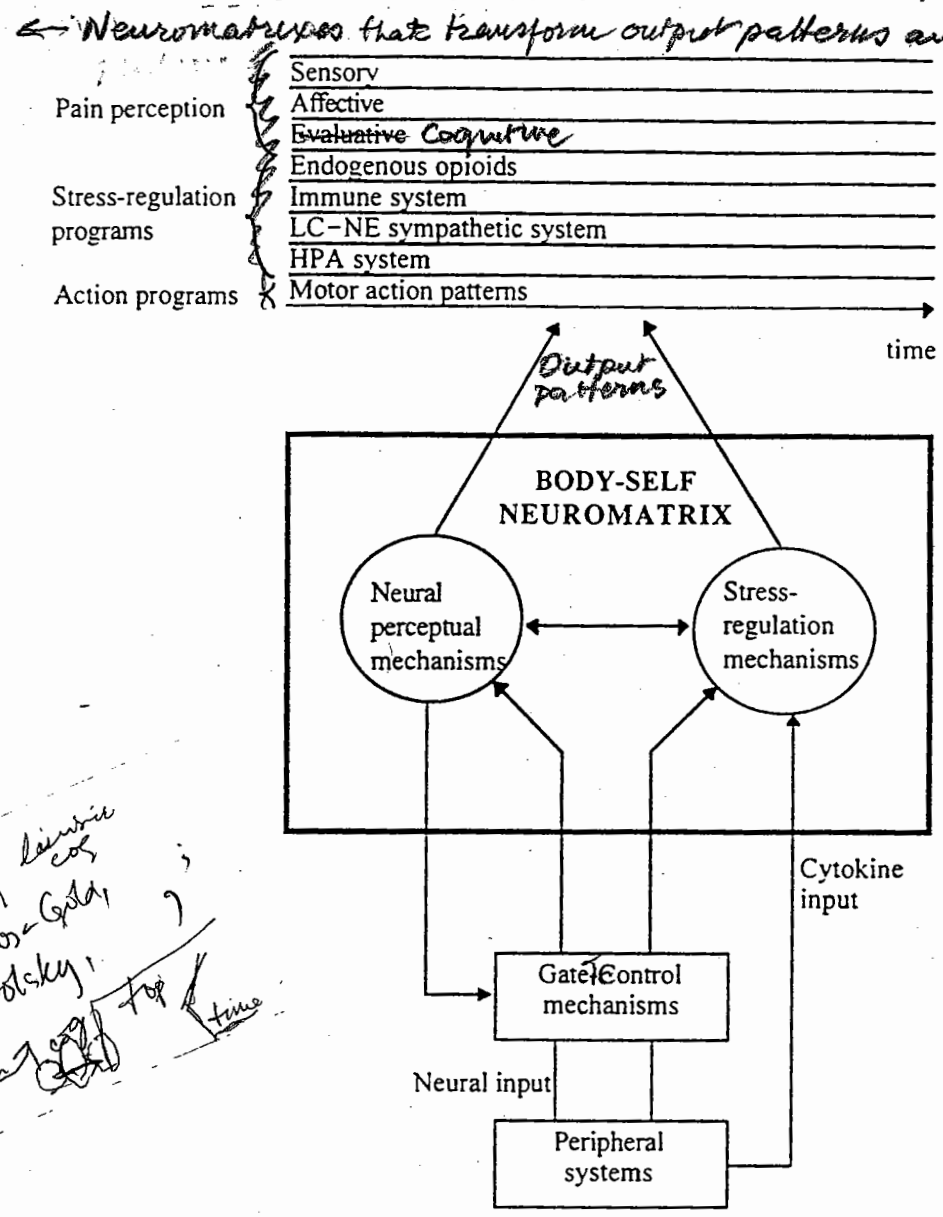

FIGURE 6.2. Components of the neuromatrix theory of pain. The body-self neuromatrix comprises (1) neural perceptual mechanisms and (2) the stress-regulation system. Neural perceptual mechanisms incorporate the mechanisms of the gate control theory (see Melzack & Wall, 1996), as well as the conceptual model of parallel distributed processing systems described by Melzack and Casey (1968). The stress system comprises the component systems and their interactions shown schematically in Figures 6.1 and 6.2. Both parts—perceptual and stress systems—produce actions and perceptions that persist in time and are shown as a vivigram of the components of the action systems. Also shown is the perceptual experience produced concomitantly with the action system activities by the output neurosignature patterns generated by the body-self neuromatrix. The influences of other sensory and cognitive processes on the generation of the neurosignature are not shown.

with hormone-related cancers but also occurs in a variety of non-hormone-related chronic pains. Lesions of the hypothalamus can also produce relief of some kinds of chronic pain (Bouckoms, 1994). Even the excellent pain-relieving effects of lesions of the cingulate cortex and cingulum bundle (Bouckoms, 1994) become comprehensible in view of their strategic location as part of the limbic system and, therefore, of the stress/immune systems.

The neuromatrix theory of pain also fits with observations that a program involving steroid injections can have powerful pain-relieving effects (Kozin, McCarty, Sims, & Genant, 1976; Kozin, Ryan, Carerra, Soin, & Wortmann, 1981). These effects cannot be attributed simply to the local control of inflammation. Steroid injections for reflex sympathetic dystrophy (RSD) can have very dramatic effects, revealing mechanisms that must

involve widespread neural, adrenergic, and hormonal mechanisms. The effects of steroids on rheumatoid arthritis may be explained in terms of the dysfunctional HPA system in these patients. But the excellent effects of steroids on RSD cannot be so easily explained. Steroids are potentially dangerous substances, yet they can dramatically relieve pain. Conceivably, as we learn more about augmenting steroids with other substances that are part of the whole stress system, we will learn to do even better. This approach toward controlling the stress system has, I believe, tremendous potential. There is, to be sure, the complexity of the inhibitory, excitatory, and modulatory interactions. But research will undoubtedly reveal them, and our armamentarium for pain therapy will be greatly enriched.

Genetic Determinants of Chronic Pain

Genetic predisposition may contribute to the development of chronic pain syndromes or other illnesses that have a prominent pain component. In the case of multiple sclerosis, for example, a genetic factor appears to be involved (Steinman, 1993): If one member of a set of monozygotic twins has multiple sclerosis, there is one chance in three that the other twin will also develop it. Table 6.3 lists several pain syndromes which may have a genetic contribution.

Genes and sensory inputs may both play synergistic roles in determining the development of a chronic pain syndrome. Consider the following study: Mayeux et al. (1995) and Mayeux (1996) examined the risk of developing Alzheimer's disease in elderly people who had sustained a head injury and possessed the gene known as apolipoprotein-epsilon 4. They found that a tenfold increase in the risk of Alzheimer's disease was associated with both apolipoprotein-epsilon 4 and a history of traumatic head injury, compared with a twofold increase in risk with apolipoprotein-epsilon 4 alone. Head injury in the absence of an apolipoprotein-epsilon 4 allele did not increase risk. These data imply that the biological effects of head injury may increase the risk of Alzheimer's disease but only through a synergistic relationship with apolipoprotein-epsilon 4. In other words, after a physical head injury, the gene may turn a normal repair process into a step toward disease of far greater complexity.

It is reasonable to suspect a similar synergistic relationship between other genes and physical injuries or illnesses as a causal factor in some chronic pain syndromes. For example, multiple sclerosis—which has a prominent pain component—has been shown to have a genetic contribution and often appears a few weeks after a routine illness. These combinations merit further investigation in the attempt to understand chronic pain syndromes. Many syndromes, such as reflex sympathetic dystrophy, causalgia, postherpetic neuralgia, or diabetic peripheral neuropathy, develop in some people and not others, even though the nerve injury is apparently the same in both groups. Why should two people receive virtually identical gunshot wounds, yet one develops horrible, persistent burning pain and the other heals without any subsequent pain? Or why should two people have the same degree of diabetes, yet one person develops peripheral neuropathy and the other does not? Conceivably, a genetic predisposition exerts a synergistic effect together with sensory input following an injury. This hypothesis is highly speculative but merits consideration.

Psychological Contributions to Pain

The place of psychological factors in producing pain and relieving it is clear. Cortisol is released by either psychological stress or physical injury, and Sapolsky (1992) has proposed that the cumulative release of pulses of cortisol is a major determinant of pathology. All psychological stresses may contribute to the neuroendocrine processes that give rise to pain syndromes, and psychological therapies that control stress ultimately affect cortisol release and, therefore, influence the development of chronic pain. A decrease in cortisol output by psychological therapy may not by itself be sufficient to produce a major reduction in pain, but it should be part of multiple therapies that can have additive effects in decreasing the destructive effects of cortisol.

Each kind of stressor can produce physiological effects that are additive with the effects of other stressors. The patterns of stress responses, moreover, may vary for each (Sapolsky, 1992). It is important, therefore, in the context of injury and pain, to recognize that the stress effects of an injury can vary, in severity and pattern, as a function of other stresses, such as loss of self-esteem, employment, or other security symbols.

Individual variation in response to injury or other stresses may be influenced by the enhancement of a given stress by (1) other concurrent stress, (2) the cumulative effect of prior stresses (determined partly by their pattern of appearance),

TABLE 6.3. Pain Syndromes That May Have a Genetic Contribution

Clinical syndrome	Proposed mechanism
Ankylosing spondylitis (Calin & Elswood, 1989; Strosberg, Allen, Calabro, & Harris, 1975)	Familial genetic predisposition. HLA genotype is implicated, and teenagers develop back pain.
Ankylosing spondylitis and coexisting rheumatoid arthritis (Tan, Caughey, & Jugusch, 1983)	Both diseases were found in a patient who had the associated HLA genes.
Back pain (Bengtsson & Thorson, 1991)	In a monozygotic and dizygotic twin study, twin concordance regarding back pain is considerably higher in MZ than DZ twins.
Congenital insensitivity to pain (Landrieu, Said & Allaire, 1990; Larner, Moss, Rossi, & Anderson, 1994)	Inherited abnormalities of peripheral sensory nerves, autonomic nervous system, and/or central nervous system
Degenerative disk disease (Simmons, Guntupalli, Kovalski, Braun, & Seidel, 1996)	Familial predisposition compared to controls; family history: 44.6% versus 25.4%; spinal surgery: 18.5% versus 4.5%
Diskogenic low back pain (Postacchini, Lami, & Pugliese, 1988)	Strong familial predisposition suggests genetic and environmental factors.
Herniation of a lumbar disk in patients younger than 21 years old (Varlotta, Brown, Kelsey, & Golden, 1991)	32% had a positive family history compared with 7% in the control group.
Familial amyloidotic polyneuropathy (Fujitake, Horii, Tatsuoka, Funauchi, & Saida, 1991)	Familial genetic predisposition
Familial coinciding trigeminal and glossopharyngeal neuralgia (Knuckey & Gubbay, 1979)	Familial genetic predisposition
Familial myalgia and cramps (Gospe et al., 1989; Lazaro, Rollinson, & Fenichel, 1981)	Autosomal dominant inheritance
Familial rheumatoid arthritis (Wolfe, Kleinhekel, & Khan, 1988)	Familial genetic predisposition
Familial spinal canal stenosis (Yasuda et al., 1986)	Autosomal dominant disorder
Familial trigeminal neuralgia (Kirkpatrick, 1989)	Family of three nontwin sisters with middle-age onset of classic, severe trigeminal neuralgia
Familial visceral myopathy (Rodrigues, Shepherd, Lennard-Jones, Hawley, & Thompson, 1989)	Autosomal dominant mode of inheritance
Fibromyalgia (Neeck & Riedel, 1994)	Malfunctioning muscle metabolism; defective absorption of tryptophan from the gut, producing decreased serotonin, thereby dysregulating sleep and sensory neural transmission
Hereditary neuralgic amyotrophy (Arts et al., 1983)	Four-generation family is described.
Hereditary sensory neuropathy with neurotrophic keratitis (Donaghy et al., 1987)	Autosomal recessive disorder; loss of small myelinated fibers
Hereditary sensory radicular neuropathy (Shahriaree, Kotcamp, Sheikh, & Sajadi, 1979)	Autosomal dominant
Hereditary spastic paraplegia (Schady & Sheard, 1990; Serena, Rizzuto, Moretto, & Arrigoni, 1990)	Found in 23 patients in 14 families
Migraine (Stewart, Lipton, & Liberman, 1996)	Prevalence differences in Caucasian, African, and Asian women (20.4%; 16.2%; 9.2%) and men (8.6%; 7.2%; 4.2%). Race-related differences in genetic vulnerability.
Multiple sclerosis (Steinman, 1993)	If multiple sclerosis is diagnosed in one monozygotic twin, the other twin has one chance in three of also developing multiple sclerosis.
Osteoarthritis (Hochberg, 1991)	Hereditary defects in type II collagen predispose to early osteoarthritis.

(cont.)

TABLE 6.3. (cont.)

Clinical syndrome	Proposed mechanism
Osteoarthritis in women (Spector, Cicuttini, Baker, Loughlin, & Hart, 1996)	Twin study: genetic influence ranging from 39–65%
Primary dysmenorrhea (Silberg, Martin, & Heath, 1987)	Monozygotic and dizygotic twin study; evidence of genes affecting flow and pain
Reflex sympathetic dystrophy (pilot study) (Mailis & Wade, 1994)	Twofold increase in human lymphocyte antigen; is associated with chromosome 6
Sickle cell disease (Gil et al., 1995)	Genetically determined
Rat model of neuropathic pain, revealing genetic determinants (Devor & Raber, 1990; Inbal, Devor, Tuchendler, & Lieblich, 1980)	Different strains of rat show differences in autotomy after denervation of a paw.

Note. This list is tentative due to the small number of studies and the need for replication. Moreover, the extent of the genetic contribution requires further research. Because this field is relatively new, some of the clinical diagnoses and nomenclature overlap, and some have been found in only a single family or even in a single generation. Nevertheless, the studies listed in the table strongly suggest that there is a genetic contribution to several major chronic pain syndromes or diseases with a prominent pain component.

(3) the kinds of concurrent or prior stresses—that is, psychological or physical, and (4) the severity and duration of the stresses.

It is well known that adaptation to repetitive stressors often occurs, so that chronic or repeated stress is frequently associated with normal circulating levels of ACTH and corticosterone (the rat's equivalent of cortisol). There is convincing evidence, however, that the system may become more sensitive to other types of acute stressors during this period. The pituitaries of chronically stressed animals become hypersensitive to the effects of vasopressin, which is an important regulator of pituitary responsiveness to stress (Harbuz & Lightman, 1992).

Studies with animal subjects throw light on these additive effects. Meaney and his colleagues (1993) demonstrated the effects of prenatal stress on HPA function in the adult. Pregnant female rats were subjected to the stress of physical restraint during the third trimester of pregnancy, and the offspring were studied when they were fully mature adults. Interestingly, the effects of prenatal stress were pronounced in female offspring but not in males. The females showed sharply enhanced responses to stress. Similarly, prenatal alcohol intake by the mothers resulted in increased HPA responses to stress in female offspring but not in males. These investigators also found that handling or "gentling" in early postnatal life produced substantial decreases in the response to stress at maturity—a positive effect that occurred in males as well as females. Meaney and his colleagues (1993, p. 83) conclude that "the early environment is able to 'fine-tune' the sensitivity and efficiency of certain neuroendocrine systems that mediate the animal's response to stimuli that threaten homeostasis."

The neuromatrix theory, therefore, provides a reasonable mechanism whereby psychological stresses may provide the basis for chronic pain. Stressors have destructive effects on muscle, skeletal, and hippocampal neural tissue, which may become the immediate basis of pain or provide a basis for the devastating effects of later minor injuries in which the severity of pain is disproportionately far greater than would be expected from the injury.

It is possible that psychological stress alone can become a cause of chronic pain because it produces substances that have destructive effects on body tissues. Prolonged stressful events, it is now evident, can leave a memory etched into bone, muscle, and nerve tissue, just as an injury sculpts a neuronal pattern into the neuromatrix. Stress, however, is a subjective experience. Threatening sensory or cognitive events may or may not be perceived as stressors, just as the sensory input from an injury may or may not be perceived as pain. Even when pain is experienced, it may be a stressor if it implies danger and threat to survival of the self, physically or psychologically. In contrast, a major injury may evoke little or no stress if it is perceived as a successful escape from danger, such as a battlefield.

Reflex Sympathetic Dystrophy

The neuromatrix theory of pain also has implications for understanding the origins of reflex sympathetic dystrophy (RSD). It has long been

assumed that RSD is primarily a disease of overstimulation of the sympathetic nervous system. However, it is possible that after a period of time the HPA axis takes over and that the destructive signs observed after several months are the result of dysregulation of the cortisol system rather than the noradrenergic system. This could explain the observation (Hannington-Kiff, 1994) that sympathetic blocks may prevent RSD if administered early in the disease but not if given after the signs are well under way.

Hannington-Kiff (1994) has observed that the "early," mainly autonomic, features are usually clinically obvious by about 3–6 weeks after a minor injury. After this time, major dystrophic changes occur in the skin and nails, with muscle and joint stiffness, skin swelling, excessive heat and sweating, abnormal blood flow and skin color, and abnormal skin sensitivity and pain. At this stage, treatment with sympathetic blocks is rarely effective. The reason may be that the HPA axis has superseded the sympathetic system and now dominates the stress response to the injury that initiated the cascade of events. For this reason, it is possible that psychological stress and stressful events at earlier stages in life contributed to the sequence of events. Current stress also aggravates the course of the disease. This does not mean that RSD is due to "psychogenic" causes. Rather, it may be a stress-related disease, in which all types of stress produce cumulative actions and in which the HPA axis and the destructive effects of cortisol predominate.

These considerations suggest lines of therapy for RSD that differ from those now generally in use. Decreases in stress and manipulation of the HPA component of the stress system are likelier to produce pain relief for these people who suffer so terribly. Kozin (1993) has achieved generally excellent results with RSD patients by using steroid injection therapy, and he notes wistfully that "unlike the interruption of sympathetic pathways, no currently known theoretic mechanisms explain the efficacy of corticosteroids in RSD" (1993, p. 1670). The powerful role of the stress system in chronic pain provides a plausible mechanism.

Predictors of Chronic Pain

A further important feature of chronic pain that implicates the stress system is the fact that the severity of pain during an injury or infection is a major predictor of the occurrence of subsequent persistent pain. Dworkin and Portenoy (1996) have identified six factors that predict those patients with shingles (herpes zoster) who are most likely to develop chronic pain (postherpetic neuralgia) that persists long after the infection has healed. The predictors are: more severe pain during the initial acute stage, greater severity of the infection of the nerve and its effects on the adjacent skin, greater sensory dysfunction of the affected dermatome, greater magnitude and duration of the humoral and immune response during the acute stage, pain in the dermatome before the appearance of the rash (painful prodrome), and fever greater than 38°C during the acute stage. Clearly, these factors include signs of activity of the stress system in addition to the greater pain, which is itself a stressor.

Further evidence of acute pain intensity as a predictor of later persistent pain is the observation by Malenfant et al. (1996) that patients with severe burns who suffer the most intense pain in the initial stages of recovery and healing are the ones most likely to have persistent pain that continues for years after full healing has occurred. Finally, Katz, Jackson, Kavanagh, and Sandler (1996) found that patients with intense pain during the first 2 days after a chest operation (thoracotomy) are much more likely to report persistent chest pain 1½ years after the operation than patients who were pain-free after the operation. Katz concludes that aggressive management of early postoperative pain may reduce the likelihood of long-term post-thoracotomy pain. It is evident, then, that severe pain, which is a powerful stressor, is a major determinant of chronic pain that remains after healing has occurred when there are no obvious physical causes of the severe pain suffered by the patients. The initial pain and stress, it is reasonable to assume, produced changes in both the perceptual and stress systems that contributed to the abnormal output patterns of the body-self neuromatrix.

SUMMARY

In summary, the neuromatrix theory of pain proposes that the neurosignature for pain experience is determined by the synaptic architecture of the neuromatrix, which is produced by genetic and sensory influences. The neurosignature pattern is also modulated by sensory inputs and by cognitive events, such as psychological stress. It may also occur because stressors, physical as well as psychological, act on stress-regulation systems, which may produce lesions of muscle, bone, and nerve tissue,

thereby contributing to the neurosignature patterns that give rise to chronic pain. In short, the neuromatrix, as a result of homeostasis-regulation patterns that have failed, produces the destructive conditions that may give rise to many of the chronic pains that so far have been resistant to treatments developed primarily to manage pains that are triggered by sensory inputs. The stress regulation system, with its complex, delicately balanced interactions, is an integral part of the multiple contributions that give rise to chronic pain.

The neuromatrix theory guides us away from the Cartesian concept of pain as a sensation produced by injury, inflammation, or other tissue pathology and toward the concept of pain as a multidimensional experience produced by multiple influences. These influences range from the existing synaptic architecture of the neuromatrix—which is determined by genetic and sensory factors—to influences from within the body and from other areas in the brain. Genetic influences on synaptic architecture may determine—or predispose toward—the development of chronic pain syndromes. Figure 6.3 summarizes the factors that contribute to the output pattern from the neuromatrix that produce the sensory, affective, and cognitive dimensions of pain experience and behavior. We have traveled a long way from the psychophysical concept that seeks a simple one-to-one relationship between injury and pain. We now have a theoreti-

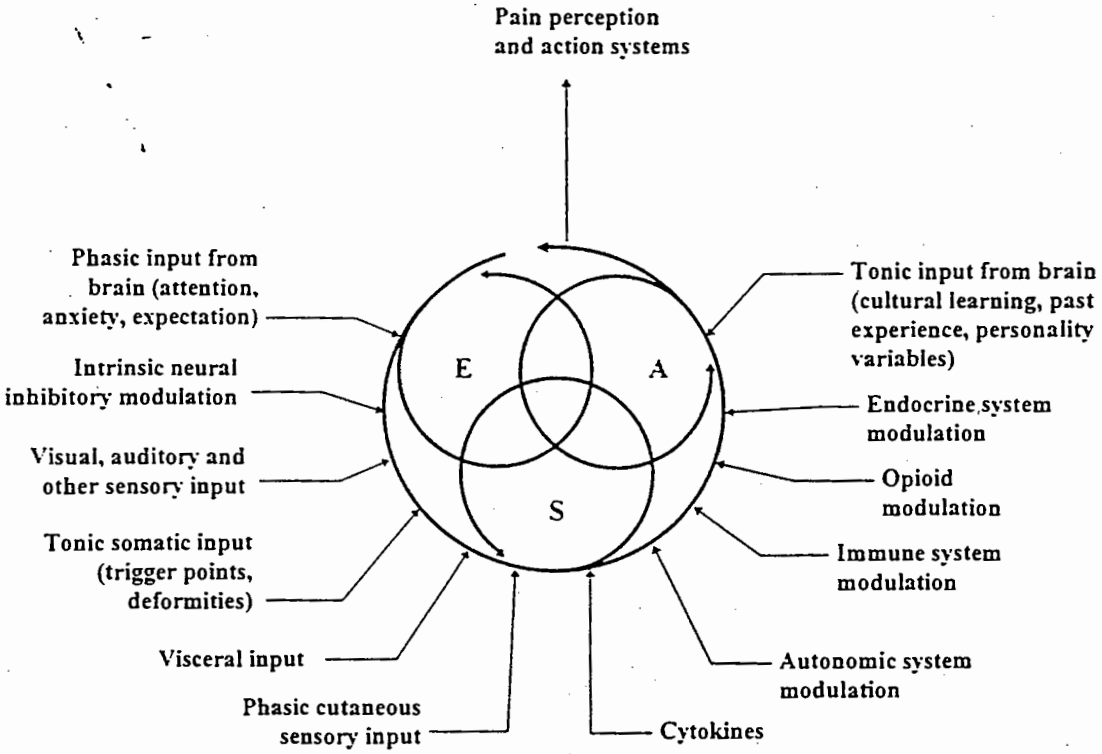

FIGURE 6.3. The body-self neuromatrix. The body-self neuromatrix, which comprises a widely distributed neural network that includes somatosensory, limbic, and thalamocortical components, is schematically depicted as a circle containing smaller parallel networks that contribute to the sensory-discriminative (S), affective-motivational (A), and evaluative-cognitive (E) dimensions of pain experience. The synaptic architecture of the neuromatrix is determined by genetic and sensory influences. The "neurosignature" output of the neuromatrix—patterns of nerve impulses of varying temporal and spatial dimensions—is produced by neural programs genetically built into the neuromatrix and determines the particular qualities and other properties of the pain experience and behavior. Multiple inputs that act on the neuromatrix programs and contribute to the output neurosignature include (1) sensory inputs from somatic receptors (phasic cutaneous, visceral, and tonic somatic inputs); (2) visual and other sensory inputs that influence the cognitive interpretation of the situation; (3) phasic and tonic cognitive and emotional inputs from other areas of the brain; (4) intrinsic neural inhibitory modulation inherent in all brain function; and (5) the activity of the body's stress-regulation systems, including cytokines as well as the endocrine, autonomic, immune, and opioid systems.

cal framework in which a template for the body-self is modulated by the powerful stress system and the cognitive functions of the brain, in addition to the traditional sensory inputs.

The neuromatrix theory of pain—which places genetic contributions and the neural-hormonal mechanisms of stress on a level of equal importance with the neural mechanisms of sensory transmission—has important implications for research and therapy. Some of these have been sketched out here. Others will become evident to endocrinologists and immunologists and, perhaps, to pain specialists with a knowledge of the field of stress. An immediate recommendation is that interdisciplinary pain clinics should expand to include specialists in endocrinology and immunology. Such a collaboration may lead to insights and new research strategies that may reveal the underlying mechanisms of chronic pain and give rise to new therapies to relieve the tragedy of unrelenting suffering.

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