

- Stress and pain are highly subjective, circular, tautologic concepts whose meanings vary for each of us. Neither can be adequately defined, much less measured, to a scientist's satisfaction. In addition, mechanisms of action and physiologic responses involving acute pain or acute stress differ considerably from responses to more chronic situations. Similarly, there are significant differences in stress or pain of emotional, as opposed to physical, origin, and frequently these are intertwined. It is important to keep such distinctions in mind when reviewing the literature on stress and pain, since the same terms may be used to signify different phenomena, thus complicating the interpretation, transposition, and application of various research findings.

Despite such limitations, research discoveries in these areas of stress, pain, and the stress-pain connection have contributed greatly to our understanding of both subjects and their intricate interrelationships. In fact, the knowledge gained over the past two decades has transformed our appreciation of the nature of endocrine and humoral activities, as well as the physiology and pharmacology of central nervous system functions responsible for mood, behavior, and basic human drives, including responses to pain and stress. Such information has also provided some fascinating teleologic insights into our extraordinary and exquisite evolutionary development.

Despite the semantic problems of defining pain and stress, it is apparent that pain is exceedingly stressful and that stress can be exceedingly painful. Furthermore, no matter how these phenomena are described, both stress and pain are unavoidable, inescapable components of life and the human condition. As the 19th century English poet, Francis Thompson wrote,

Nothing begins, and nothing ends
That is not paid with moan;
For we are born in other's pain
And perish in our own.

(*"The Dread of Height"*)

Although pain can be extremely distressful, some individuals, under conditions of acute stress, demonstrate extraordinary resistance to discomfort. Of the numerous anecdotal observations to support this paradox, one of the most compelling was provided by the African explorer Livingston, who recounted in the 1850s his response to an attack by a lion some 20 years previously:

I heard a shout, starting and looking half around, I saw the lion just in the act of springing upon me. I was upon a little height. He caught my shoulder as he sprang, we both came to the ground below together. Growling horribly, close to my ear, he shook me as a terrier does a rat. The shock produced a stupor similar to that which seems to be felt by a mouse after the first shake of the cat. It caused a sort of dreaminess in which there was no sense of pain or feeling of terror though quite conscious of all that was happening. It was like what patients partially under the influence of chloroform describe, who see all the operation but feel not the knife. This singular condition was not the result of any mental process. The shake annihilated fear and allowed no sense of horror in looking around at the beast. This peculiar state is probably produced in all animals killed by the carnivore, and if so, is a merciful provision by our benevolent Creator for lessening the pain of death.¹

In order to understand how acute stress can obliterate pain, it is necessary to have some understanding of the various

mechanisms involved in the perception of pain. The first stop appears to involve an elaborate network throughout the skin surface of nerve endings, which respond to tissue damage by secreting a neuropeptide known as *substance P*. Released into surrounding areas, this substance activates nerve fibers that then conduct the pain message at varying speeds. Some fibers transmit the signal almost immediately, enabling us to instantaneously remove our fingers from a hot stove. Fibers that conduct messages at slower rates are responsible for the more chronic sensations of pain that persist after such an experience. Pain signals are also transmitted via pathways in the spinal cord. Some of these fibers end in the thalamus, but a tiny area in the mesencephalic central gray matter in the brain stem appears to be the terminal for most pain fibers. Electrical stimulation at this highly selective site enables laboratory animals to be operated on without anesthesia. However, only pain is eliminated, and pressure and temperature sensations are preserved. Surprisingly, destruction or electrical stimulation of other areas of the brain rarely produces or reduces pain.

What fascinated neuroscientists 10 or 15 years ago was how morphine sulfate could reduce pain. Why should minute amounts of opiates obtained from the Mesopotamian poppy produce such an effect? What portions of the pain pathway were involved? Were there specific receptor sites for such compounds, and if so, did that mean that perhaps the body produces its own morphine?

The various research investigations that provided the answers to that question make a fascinating detective story. In the early 1960s, C. H. Li, the brilliant neurochemist who identified such human hormones as adrenocorticotrophic hormone (ACTH) and somatotrophin, also isolated a large pituitary polypeptide consisting of 91 amino acid chains. He named

it β -lipoprotein because it appeared somehow to be involved in the metabolism of fat, but he was unable to obtain sufficient quantities to evaluate its activities. However, Li reasoned that the pituitaries of camels, lean animals with low body fat and high resistance to pain, might be rich in β -lipoproteins. He was able to obtain a large number of camel pituitary glands, but applying the extraction technique used for human pituitaries, he could find no β -lipoprotein. Instead, he isolated what appeared to correspond to the peptide's tail end, since it was made up of the identical amino acid linkage from positions 61 through 91. Li named this new compound β -endorphin but did not study it further.

In 1973, three research teams independently demonstrated that morphine exerted its pain-reducing effects by acting at specific receptor sites in the brain. Studies of other opiates, using radioactive techniques, quickly determined that those with the strongest binding properties to these receptor sites produced the greatest analgesia, although they also had the greatest potential for addiction. Now that the presence of specific receptors for pain relief had been demonstrated, the search focused on finding the body's own natural morphine. Two years later, Scottish investigators isolated a five-amino-acid molecule from pig brain that did seem to be similar to morphine in many of its effects. They labeled it *enkephalin*, meaning "in the head." Although its pain-reducing properties were poor and its addiction potential high, Li recognized that the enkephalin molecule was actually a smaller fragment of that same β -endorphin he had previously isolated from the camel pituitaries in his attempt to obtain β -lipoprotein. To his delight, animal testing confirmed that β -endorphin was about 50 times more potent than morphine, although it proved to be quite addictive.

The pieces of the puzzle appeared to

be coming together. It was postulated that under normal circumstances, the majority of the body's morphine receptors are occupied by natural opiates. Morphine relieves pain by binding to unfilled opiate receptor sites, reducing the amount of such natural substances produced in the brain. Eventually, as more receptors become vacant, there is increased craving for additional narcotics. As these are supplied, receptor sites become occupied by and increasingly dependent upon externally administered narcotics. If they are not available, a severe withdrawal reaction results. Of particular interest is the notation of dense concentrations of enkephalins in the limbic system, which plays an important role in determining mood and behavior. Quite likely, these findings explain the "high" that narcotics produce by binding to such limbic receptor sites.

What has any of this to do with stress? A variety of studies show that under physical as well as mental stress, the pituitary releases large amounts of β -lipoprotein-like hormone. This is subsequently broken down into smaller molecules such as endorphins and enkephalins that reduce pain perception. Additional enkephalin-producing neurons in the spinal cord appear to block the action of the neurons that produce *substance P*, which transmits pain signals from the body. Similar interference comes from fibers originating in the mesencephalic gray matter. These fibers travel down the spinal cord, stimulating other neurons to produce enkephalins. The effect of all these activities is to diminish the sensation of pain during acute stress.

More importantly, both ACTH and endorphins seem to be secreted simultaneously and in proportion to the magnitude of the stressful stimulus. The responses to removing the pituitary or adrenals or to administering dexamethasone confirm that the production and

release of endorphins are regulated by the same adrenal steroid feedback mechanism that controls secretion of ACTH, the premier stress hormone.

However, injection of ACTH increases sensitivity to pain in laboratory animals in a manner similar to that produced by naloxone hydrochloride, a compound that blocks the pain reducing effects of endorphins. When humans are injected with naloxone, their ACTH levels go up while their endorphin levels go down, and their sensitivity to pain increases. Thus, it appears that ACTH and endorphins have opposing and complementary effects, despite their regulation by similar mechanisms. Thus, we have some insight into how acute stress can prevent pain.

Another striking feature of endorphin activity is that it apparently diminishes ability to concentrate, one of the characteristics of schizophrenia. In fact, injection of large amounts of β -endorphin can induce a catatonic-like schizophrenic state. It had been previously noted that schizophrenic patients seem to have increased resistance to pain. Further studies have shown that administering naloxone, an endorphin antagonist, significantly improves concentration abilities in schizophrenic patients. In some patients, behavior reverts to normal, and their resistance to pain seems to decrease as concentration improves, suggesting that these two attributes are somehow linked. Computer-averaging brain signal studies have indeed confirmed that those brain sites that are most active during concentration overlap those with the greatest activity during pain perception. And when naloxone is given to schizophrenic patients, it appears to exert its greatest effects in these areas, particularly the frontal lobe.

Other studies suggest that endorphins may directly suppress attention and concentration by activities at the locus ceruleus, a small noradrenergic nucleus

with projections extending throughout the brain and spinal cord. The locus ceruleus produces most of the norepinephrine in the brain. When the locus ceruleus is stimulated electrically in primates, they display the same behaviors exhibited in situations evoking extreme fear. If the locus ceruleus' firing rate is increased pharmacologically with yohimbine, fearful, anxiety-like activity increases. Conversely, when the firing rate is suppressed with clonidine, such behavior decreases. It is now thought that increased activity of this center and the subsequent release of large amounts of norepinephrine as well as catecholamines from the adrenal medulla produce an augmentation of the fear-anxiety "fight or flight" response.

Our understanding of the physiology of stress has been further expanded by research designed to determine how diazepam [Valium] and similar drugs reduce anxiety and fear. It appears that all psychoactive medications act by mimicking or suppressing the activities of endogenous compounds at the locus ceruleus and similar sites. Although no natural Valium has yet been identified in the body, it is clear that there are benzodiazepine-receptor sites that appear to be functionally and structurally linked to the protein complex containing the recognition site for γ -aminobutyric acid. Natural compounds, such as β -carboline, with an affinity for such receptor sites eight to ten times more powerful than Valium have been identified. However, such substances are benzodiazepine-receptor antagonists that act in monkeys much like stress-inducing hormones, producing extreme behavioral arousal as well as increased discharge of epinephrine and norepinephrine. When closely related compounds are administered to humans, these substances cause feelings of tension and uneasiness and increase heart rate and blood pressure. Such responses can be blocked

by Valium. β -carboline like compounds have now been identified in the urine in increased amounts in subjects who are extremely anxious or who are experiencing stress produced by withdrawal from alcohol or Valium.

We have seen how the analgesic properties of morphine and the anti-anxiety properties of benzodiazepines led to the postulation and ultimate discovery in the body of receptor sites that mediate such effects. Obviously, such receptor sites exist because of the natural presence of endogenous substances with similar properties related to stimulation or suppression. Over 60 different chemical neurotransmitters, all of which appear to affect mood, behavior, or pain, have been extracted from brain tissue. Labeled opioids, some of these naturally occurring peptides, such as dynorphin, are considerably more potent than morphine and β -endorphin. However, electrical stimulation of certain areas of the pain pathway has also been observed to produce analgesia. Could this possibly imply that the brain or central nervous system has receptor sites for weak electrical signals as well as for chemical stimuli that influence pain or stress responsivity?

Electrical stimulation of highly specific areas in the pain pathway produces analgesia, and micro injections of morphine in these precise sites have an identical effect. Yet, injection or stimulation a few millimeters away is worthless. What is intriguing is that combining amounts of morphine or electrical stimulation that by itself is too weak to effect pain relief produces a synergistic effect that does provide analgesia. This suggests that electrical stimulation and morphine relieve pain via the same mechanisms. Furthermore, the pathways whereby morphine or electrical stimulation produce freedom from pain are precisely the sites of action of the endorphins.

Our understanding of the role of electrical energies in modifying pain, behavior, and mood, while long acknowledged, is in its infancy. Almost 2000 years ago, Scribonius Largus reported that the discharge from an electric eel could relieve certain types of headache. There is a vast literature on the influence of positive ions in the atmosphere on mood and behavior. Almost every language or culture has a word for special sorts of winds or meteorologic events that affect behavior or health: In Italy, there is the *sirocco*, the "father of depression," in Spain, the *leveccio*. Egypt has the *chamsin*, Argentina the *zonda*, Hawaii the *kona*, Norway the *bora*, and in France, the *mistral*. In the western United States, we are told of the effects of the *chinook* and California's *Santa Ana*. In some curious way, the weather and its ionizing influences appear to have profound effects on our health and energy. The most well known of these events are the Alpine *foehn* and the Israeli *sharav*, both of which leave hangovers, strokes, coronary thromboses, suicides, and traffic accidents in their wake.

In clinical practice, the application of minute amounts of electrical energy to appropriate anatomic sites, such as in transcutaneous electrical nerve stimulation (TENS), can provide impressive pain relief. Furthermore, such analgesia is potentiated by simultaneous transcranial application. The Russians have for some years been experimenting with a device that apparently produces tranquilizing effects by transcranial application of small amounts of electrical energy. In clinical practice, the effect of TENS analgesia can be enhanced by the simultaneous application of transcranial electrodes. A Swiss research and development firm has now developed a device that achieves similar effects by means of an electrode applied to the soft palate. Clinical trials suggest that after

only 10 or 15 minutes' application of an athermic harmless current in the citizens band range, there is significant relief of insomnia, anxiety, jet lag, and other complaints, with concomitant improvement in objective parameters, including reversal of abnormal electroencephalographic patterns.

The links between stress and pain are thus coming closer together. The processes that affect one appear to influence the other. The efficacy of TENS and acupuncture appears to be blocked in many instances by administration of endorphin antagonists, such as naloxone, which also block analgesia as seen in the placebo response. The discovery on white cells of the immune system of receptor sites for endorphins and, more recently, for Valium raises other exciting implications. Together with other advances in the rapidly growing discipline of psychoneuroimmunology, such observations are tightening the links between the mind, central nervous system, and immune system. Ader's laboratory observations that immune system responses can be conditioned have now been confirmed in a variety of other studies.² Recently it was reported that an experienced meditator could control skin responses to smallpox vaccine. It seems clear that the hypothalamus, which regulates body temperature, hunger, thirst, and a variety of basic drives, also helps to regulate the immune system. Russian experiments have demonstrated that destroying parts of the hypothalamus in animals can prevent severe allergic reactions such as anaphylactic shock. Conversely, when the immune system is busy fighting infection, there is demonstrable alteration of activity in nerve cells in the hypothalamus.

It seems likely, therefore, that the brain and the immune system speak the same language and use the same polypeptide messengers. Administering endogenous opiates such as metenkephalin has

recently been shown to improve immune function in acquired immunodeficiency syndrome and cancer. Such observations offer intriguing explanations for such phenomena as faith healing, the placebo response, and visualization techniques.

Thus, our interest in the connective pathways between stress and pain suggests many other intersecting routes. More important, we are now able to embark on the study of the mind as we realize that the body provides its own best pharmacopeia and that we all possess a vast potential for self-healing, the boundaries of which cannot be defined.

As John Milton wisely noted over 300 years ago,

The mind is its own place, and in
it self
Can make a Heav'n of Hell, a Hell
of Heav'n.

("Paradise Lost")

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REFERENCES

1. Restak R: *The Brain*. New York, Bantam Books, 1984, p 161.
2. Ader R (ed): *Psychoneuroimmunology*. New York, Academic Press, 1981.