HEALTH AND STRESS

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STRESS AND PAIN

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Since stress and pain are highly personalized phenomena that differ for each of us, they are difficult to define. They also have intricate interrelationships that can be difficult to dissect. Stress can cause pain and pain is usually stressful, so that **pain and stress sometimes seem synonymous.**

Stress is particularly hard to characterize. It is most often used to refer to disturbing threats and challenges, although these would more properly be described as stressors. Stress can also refer to psychophysiologic and biochemical changes in the body in response to such stimuli, as well as symptoms, signs, and disorders believed to result from these reactions.

Things that are distressful for some individuals may be pleasurable for others, or have little impact, as illustrated by the varied reactions of passengers on a steep roller coaster ride. We also respond to stress differently and sometimes in opposite ways. Some people blush while others grow pale, have constipation or diarrhea, and experience either a rise or fall in blood pressure depending on inherited and acquired influences. Other reactions to stress can range from palpitations, hives, back and neck pain, to panic attacks and depression.

Stress is not always necessarily harmful or unpleasant. Increased stress increases productivity - up to a point, and this also differs for each of us. Winning a race or election can be just as stressful as losing, or more so. A passionate kiss and contemplating what might follow is stressful, but does not evoke the same responses as having root canal work. As Hans Selye was fond of noting, stress can be the spice of life or the kiss of death. While stress cannot be defined to a scientist's satisfaction, all of our clinical and laboratory research confirm that **the perception of not having any control is always distressful.**

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The Toll Of Chronic Pain

Pain is an unavoidable consequence of life. As the nineteenth 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."

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." From an evolutionary perspective, acute **pain is often purposeful since it may provide a warning that prevents more serious damage.** If your finger accidentally comes into contact with something that is very hot or very sharp, acute and severe pain causes an immediate and automatic reflex withdrawal from the offending object. You also learn to avoid touching anything that might reproduce this experience.

Most acute pain due to trauma diminishes in a day or two and disappears within two weeks. However, that's not true for the many millions of Americans who live with chronic pain due to arthritis, headaches, back complaints, cancer, and nerve injuries that are relatively resistant to treatment.

Pain that comes on gradually and is persistent is quite different and can be much more pernicious. Differentiating between acute and chronic pain can sometimes be difficult, since time is not the only criterion. **Chronic pain often becomes an autonomous, independent clinical entity** that transcends readily identifiable causes. It can be diagnosed if four or more of the following eight "D's" are present:

- **Duration** - pain extends far beyond the time it normally takes for injured tissues to heal.
- **Dramatization** - exaggerated verbal and non-verbal behaviors.
- **Diagnostic dilemma** - patients often report having seen multiple physicians for their problem because of the inability to obtain a definitive diagnosis or effective treatment.
- **Drug history** - multiple medications have usually been tried alone or in combination.
- **Dependence** - chronic pain patients tend to be withdrawn, introverted, and dependent on families, friends or health care systems.
- **Depression** - low grade depression that occasionally includes suicidal ideation and even attempts in many patients.
- **Disuse** - efforts are made to avoid any activity that might result in pain, resulting in a sedentary lifestyle that leads to musculoskeletal disabilities.
- **Dysfunction**- chronic pain patients may find it difficult to make decisions, and often develop antisocial behaviors that can lead to rejection by friends and family.

Chronic pain is the leading cause of disability, at an estimated cost of $150 billion annually. Back pain results in over 1300 million days of lost productivity for some 36 million workers, and 40 million headache sufferers lose over 600 million days. Another 20 million who suffer from neck problems and 24 million with other types of musculoskeletal complaints are also apt to be absent or unable to work to their full potential because of incapacitating pain. Stress is the major cause of tension headaches, and is also an established trigger for migraine and low back distress.

Stress And Pain - A Vicious Cycle

Pain causes stress, which in turn can cause physical and physiologic responses that worsen pain. This may result in a self-perpetuating chain of events that persists until either stress or pain is abolished or one of the links in the chain is broken. Much like the chicken and the egg, it can sometimes be difficult to decide which came first.

For example, back pain can result from stress induced muscle spasm that causes pressure on a nerve. This pain can lead to more stress and muscle spasm that further impinges on the nerve. The increased pain causes more stress and the cycle of pain → stress → pain is repeated over and over. Alternatively, the process might have started with a pinched nerve due to arthritis or a herniated disk causing pain and subsequently stress-related muscle spasm. This could worsen the original problem leading to the same sequence of events. In either situation, analgesics to relieve pain, tranquilizers to reduce stress, or muscle relaxants to prevent spasm could interrupt this vicious cycle to provide relief.

The same scenario may take place in patients with painful peptic ulcers. Emotional stress increases the secretion of acid and enzymes that produce ulcerations in the stomach and duodenum. The resultant pain causes stress and more ulcerogenic chemicals are released, resulting in increased pain and the pain → stress → pain → stress sequence of events becomes established. Other examples involving the cardiovascular and immune systems could also be cited as illustrations of how stress can cause symptoms that in turn create more stress that intensifies the complaints.

However, **we all respond to stress differently and some reactions can be exactly opposite to what would normally be expected.** Severe stress can reduce or even completely stop pain, especially when the problem is due to a sudden traumatic injury. This well known paradoxical phenomenon has provided important insights into the complex interrelationships between stress and pain, and the intriguing role of endorphin-like compounds.

Stress, Pain, And Suffering

Suffering connotes experiencing or having to endure something that is either unpleasant or inconvenient. Since suffering is a common consequence of pain and stress, it is often viewed as being synonymous with both. However, some stresses can provide pleasure and relief rather than discomfort. In addition, suffering and pain are distinct phenomena because suffering encompasses more dimensions, has many sources other than pain, nor does pain cause suffering in every patient.

As an old French saying goes, the purpose of the physician is "to cure sometimes, to relieve often, and to comfort always." We treat pain to reduce suffering, but in order to accomplish this, it is essential to understand that each patient represents a different biopsychosocial entity . **To comprehend what suffering represents, it is necessary to appreciate the patient as a person.** This is a talent that has steadily been suppressed and superseded by the high-tech, low-touch attitude that characterizes contemporary medical practice.

Suffering results when there is a threat of loss of some essential part of what each of us perceives as "self". Although "self" is somewhat difficult to define, characterize, or even explain, it is essential to understand what it signifies for each individual. It is also crucial for determining which treatment modalities or approaches are likely to be most effective for any given patient.

A few with masochistic tendencies may actually enjoy what would be severe discomfort for most of us. Pain that persists despite treatment can also provide a source of secondary gain because of monetary rewards, especially in patients disabled due to accidents or work-related injuries. Pain may also serve as an excuse for not performing certain duties or attracting attention from sympathetic friends and family members. Many patients may be unaware that such behaviors can contribute to their failure to improve. The important lesson to learn is that to be successful **we need to treat the patient as a person, rather than simply prescribing something for pain .**

Endorphins, Pain, And Addiction

In order to understand how acute stress can obliterate pain, it is necessary to review some of the basic mechanisms and pathways that might be involved. The initial step appears to involve an elaborate network of nerve endings throughout the skin. These respond to injury by secreting a chemical called *Substance P*. When released into surrounding tissues, this powerful neuropeptide activates nerve fibers that conduct the pain message at varying speeds. Some transmit the signal immediately, so that there is instantaneous removal of a finger from a hot stove. Fibers with slower rates of transmission are responsible for the persistent perception of chronic pain that follow such experiences.

Pain signals are also transmitted via spinal cord pathways. Some of these end in the thalamus but the terminus for most pain signals is in a tiny area of the mesencephalic central grey matter in the brain stem. Electrical stimulation at this precise location makes it possible to operate on laboratory animals without anesthesia. Perception of pressure and temperature are preserved and only pain is eliminated at this precise site. Electrical stimulation or destruction of other areas of the brain rarely produce or reduce pain.

Physicians had always wondered about morphine's amazing effects and how it worked. **Why should minute amounts of a chemical derived from a poppy found in Mesopotamia provide consistent relief for so many different types of severe pain?** What portions of the pain pathway were involved? Were there specific receptor sites for such substances? If so, did it mean that the body produced its own morphine-like chemicals? The search for answers to these questions could have been the basis for a fascinating detective story or movie.

In the early 1960's, C.H. Li, the brilliant biochemist who identified ACTH and growth hormone, also isolated another large peptide hormone from human pituitaries. He called it beta-lipoprotein because it seemed to have something to do with fat metabolism. However, he was unable to obtain enough of the compound to study its biologic effects.

One of his post-graduate students from Egypt told him that camels had large pituitary glands and he could arrange to obtain a good supply of these glands during his next visit home. Li reasoned that these lean animals with low body fat might have pituitaries rich in this beta-lipoprotein hormone, and gladly accepted the offer. The student returned a few months later with a pocket full of camel pituitary glands to avoid Customs problems. Li was unable to find any beta-lipoprotein using the extraction technique he developed for human pituitaries. Instead, he isolated what appeared to be the tail end of this peptide, since it was made up of the identical amino acid linkages from position 61 to 91 of beta-lipoprotein. He therefore decided to call it beta-endorphin but did not study it any further. In 1973, three research teams independently found that morphine exerted its analgesic effects by acting at specific receptor sites in the brain. Studies of other opiates using recently developed radioactive techniques quickly confirmed that those with the strongest binding properties to these receptors were also provided the greatest pain relief as well as the most potential for addiction.

Now that the presence of specific receptor sites for pain relief had been identified, the search shifted to finding the body's own natural morphine. Two years later, Scottish scientists isolated a five-amino-acid peptide from pig brain that seemed to mimic many of morphine's effects and called it *enkephalin*, ("in the head"). Compared to morphine, its pain reducing properties were poor and addiction potential was high. Li immediately recognized that enkephalin amino acid sequence was actually a smaller fragment of the same beta-endorphin he had previously isolated from camel pituitaries. He also recalled that camels were notoriously resistant to pain.

Li was able to retrieve the supply of material he had stored away with numerous other compounds for possible future study. To his delight, animal testing confirmed that **beta-endorphin was about fifty times more potent than morphine with respect to its ability to relieve pain.** Unfortunately, it also proved to be more addictive. (*Continued on Page 5*)

The pieces of the puzzle appeared to be coming together. It was postulated that under normal circumstances, the body's morphine receptors were occupied by natural opiates. Morphine reduced pain by binding to unfilled receptors, thus reducing the amount of natural pain relievers produced by the brain. As more receptors became vacant, craving for opiates increased. This could only be immediately satisfied by injections of narcotics, eventualy resulting in more receptor sites being occupied pied by and dependent on externally administered narcotics. If these were not available a severe withdrawal reaction would result.

In addition to pain relief, narcotics also produce an emotional "high", which is one of the reasons they can be so addictive. In that regard, the concentration of enkephalin and endorphin-like compounds is particularly dense in the limbic system of the brain, which plays an important role in determining mood and behavior. This may explain the "runner's high' experienced by some elite marathoners. Others may continue to run despite broken bones and other injuries because they are oblivious to any pain, discomfort, or disability that would normally curtail their activities.

Increased resistance to pain is often seen in schizophrenia and injection of large amounts of beta-endorphin can induce a catatonic-like schizophrenic state in experimental animals. Another feature of endorphin activity is interference with concentration, which is another characteristic of schizophrenia. Naloxone, an endorphin antagonist, can significantly improve concentration in schizophrenics and along with their resistance to pain also seems to decrease. This suggests some link between the two, and sophisticated studies confirm that those brain sites most active during concentration overlap those with the greatest activity when pain is perceived. When naloxone is given to schizophrenic patients, it also appears to exert its greatest activity in these areas of the brain. Other studies suggest that endorphins may suppress attention and concentration by effects at the locus ceruleus, a nor-adrenergic structure that plays an important role in the "fight or flight" response to acute stress.

Genes And The Immune System

Why should a medication relieve pain for one person but have no effect in another? Is it nature or nurture? Do conditioning factors or coping capabilities determine sensitivity to pain? Some studies demonstrate a relationship between initial sensitivity to pain and subsequent responses to analgesic drugs. Strains of mice that are more sensitive to painful stimuli are also more resistant to opiates. Do men and women differ in their responses? The "weaker sex" has generally been considered to be more sensitive to pain or to react in a more emotional and dramatic manner. Some animal studies do confirm that females have lower pain thresholds to heat than males and may require higher doses of analgesics to obtain relief. However, these differences are not very great, and there can be significant individual variation due to genes that have not yet been identified.

The brain and the immune system have a common origin and are the only parts of the body that can "remember". They are closely connected with hardwired and humoral messengers that are in constant communication. One carefully studied pathway involves brain cytokines and neuropeptides like ACTH and beta-endorphin that are secreted by immune system lymphocytes involved in mediating inflammatory responses. Researchers have found that T lymphocytes migrate to inflamed tissues where they deliver beta-endorphin. The pituitary also releases beta-endorphin into the general circulation in response to stress and pain, but it is rapidly degraded by proteases.

The ability to deliver beta-endorphin directly into inflamed tissue maximize its analgesic and anti-inflammatory effects. Corticotropin-releasing hormone (CRH) from the hypothalamus signals the pituitary to secrete ACTH during stress, but CRH is also manufactured in immune system cells. It also produces potent analgesia when injected into inflammed areas by potentiating the effects of beta-endorphin. These activities have provided new insights into how the immune system can modulate responses to stress and pain.

Stress Induced Analgesia

It has long been known that **severe stress may be associated with almost complete freedom from pain or fear, a heightened sense of awareness, and other unusual powers.** Anecdotal tales abound, such as the ability of a frail, elderly grandmother being suddenly able to lift a log several times her weight to free her grandchild from being run over by an oncoming train. World War II soldiers who had lost a limb or suffered severe injuries in battle frequently experienced no pain until many hours later after they reached the safety of a hospital This was in sharp contrast to civilians who sustained similar injuries as the result of accidents but rarely exhibited this unusual freedom from pain.

Perhaps the best description of this was provided by the African explorer Livingston, of Stanley and Livingston fame (" Dr. Livingston, I presume"). In the 1850's, Livingston recounted his response to an attack by a lion some 20 years previously.

> "I heard a shout, starting and looking 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."

During severe stress, the large beta-lipo protein polypeptide secreted by the pituitary i broken down into smaller endorphin and en kephalin compounds. These block the brain' perception of pain and enkephalin producin neurons in the spinal cord can prevent th production of substance P. Fibers from th mesencephalic gray matter also appear to trave down the spinal cord to stimulate other neu rons to produce similar pain reducing chemi cals as part of the response to acute stress.

Both ACTH and beta endorphin seem t be secreted simultaneously and in proportio to the magnitude of stressful stimuli. Response following removal of the pituitary or adminis tering adrenal steroids that inhibit ACTH pro duction confirm that **the manufacture and re lease of endorphins are regulated by the sam feedback mechanism that controls ACTH secretion**. However, when injected into ani mals, ACTH increases sensitivity to pain, pos sibly by blocking endorphins, since the effect are similar to those seen with naloxone. I humans, naloxone causes ACTH levels to rise endorphins fall, and pain sensitivity increases

ACTH and endorphins appear to hav opposing actions that are called into play whe stress disrupts homeostasis. This is reminis cent of the complementary concept of *yin* an *yang*, and the equilibrium achieved by sympa thetic and parasympathetic balancing effects At least four groups of endorphins have bee identified (alpha, beta, gamma, and sigma) an it is believed that they play a role in the pai relief associated with acupuncture, laughte and deep meditation, as well as exercise.

There is also evidence that increase amounts of beta-endorphin may contribute t autism: naloxone has been reported to improv socialization, eye contact, and mood and t reduce self-injury as pain sensitivity is normal ized in autistic patients. Numerous other opioi neurotransmitters that affect mood, behavio and pain have been isolated, and one of these dynorphin, is perhaps 60 times more potent fo abolishing pain than either morphine or beta endorphin. We have only scratched the surfac with respect to realizing the full potential o these multifaceted agents.

"Electroceuticals" For Pain And Stress

It has been shown that injections of minute amounts of morphine at very specific sites in the pain pathway produce analgesia. Electrical stimulation at these precise locations has an identical effect. Neither injecting morphine or electrical stimulation just a few millimeters away from these sites provides any pain relief or any reduction in sensitivity to painful stimuli. Researchers were intrigued when they discovered that amounts of morphine or electrical stimulation that were too weak to be effective when administered separately, could produce analgesia when they were applied simultaneously.

This synergism strongly suggests that morphine and electrical stimulation provide pain relief via the same mechanism. The combination of these two modalities is effective only at highly specific locations, which correspond exactly with the sites of action of beta-endorphin. Endorphins and other neurotransmitters, and opiates like morphine seem to fit into special receptor sites like keys that open certain locks. But how are weak electrical signals able to achieve similar effects on pain, mood, and behavior? **Is it possible that these receptor sites also respond to weak energy signals from the external environment, as well as others generated internally?**

Lodestones have been used to treat pain for four thousand years, permanent magnets were popular in the nineteenth century, and there has been a recent resurgence of interest in this as a result of more powerful products that are allegedly effective in disorders ranging from diabetic neuropathy to osteoarthritis. Electrical stimulation dates back to the Roman physician Scribonius Largus, who reported that the discharge from an electrical eel could relieve severe headache. Transcutaneous electrical nerve stimulation (TENS) has been popular for over 50 years, and cranioelectrical stimulation was subsequently found to enhance the ability of TENS to relieve pain. More recently, as repeatedly demonstrated at our annual Congresses, electromagnetic energies and particularly Pulsed Signal Therapy (PST) have provided impressive results in a variety of painful disorders. Although other mechanisms may be responsible, in some instances, endorphin effects may also be involved.

As with morphine and naloxone, it would appear that **all psychoactive drugs exert their effects by simulating or antagonizing the actions of natural compounds at specific receptor sites**. One very important location is the locus ceruleus which produces most of the norepinephrine in the brain. When this area is stimulated electrically, primates display the same behaviors seen in response to extreme fear. Yohimbine-like drugs that increase the locus ceruleus firing rate also elicit feelings of fear and anxiety. Conversely, clonidine which suppresses the firing rate decreases this type of behavior.

Although no natural equivalent of Valium has yet been identified, receptors for this and other benzodiazepines abound. These appear to be functionally and structurally linked to the protein complex containing the recognition site for gamma-aminobutyric acid. Beta-carboline is a natural compound with an affinity for such sites that is ten times stronger than Valium. However, this is a receptor antagonists or blocker that mimics the activities of stress induced hormones. In monkeys, it produces marked behavioral arousal and increased secretion of adrenaline and similar compounds cause feelings of tension and a rise in heart rate and blood pressure in humans. Increased amounts of beta-carboline-like compounds have been found in the urine of extremely anxious patients and others experiencing stress due to withdrawal from alcohol or tranquilizers.

In addition to pain relief, weak electromagnetic energies can also provide benefits for a variety of stress related complaints. Cranioelectrical stimulation and repetitive transcranial magnetic stimulation can provide rapid improvement in drug resistant depression, and electroconvulsive therapy is still used for severe cases. Low energy emission therapy is probably the most effective treatment for insomnia, and double blind studies also confirm its efficacy and safety in anxiety disorders. We have only scratched the surface of realizing the full potential of electroceutical therapies.

Chronic Pain: Irrespective Of The Cause, What Can You Do About It?

The wide variety of medications and other modalities currently used to treat pain provide some appreciation of its complex causes as well as its multifaceted characteristics. They include:

Nonsteroidal Anti-inflammatory Drugs (NSAID's) - These can have serious side effects including gastrointestinal bleeding, ulcers, and liver disease. The newest class of these, the COX-2 inhibitors have fewer complications but are not entirely safe and are much more expensive.

Antidepressants – Depression, stress, and pain often coexist and contribute to each other, and it may sometimes be difficult to determine which came first. Depressed patients have elevated levels of cortisol that are not suppressed by dexamethasone suggesting a disturbance in hypothalamic-pituitary–adrenal axis feedback mechanisms. Decades ago, it was found that tricyclic antidepressants facilitated the body's natural pain relieving properties and were particularly effective for relieving headache and neuropathic pain. The explanation for this was not clear since there was no relation to their antidepressant effects. The newer selective serotonin reuptake inhibitors may also be useful for reducing the depression that accompanies chronic pain and contributes to its perpetuation.

Anticonvulsants – These drugs prevent seizures by suppressing the sensitivity of different areas of the brain to various stimuli. In some pain syndromes, nerve fibers exhibit hyperexcitability by producing what might be viewed as "mini-seizures" of pain wave signals to the brain. Anticonvulsants, and particularly gabapentin, can slow down and suppress these stimuli. Anticonvulsants tend to stabilize the electrical activity of cells, and it would seem logical that the application of specific electromagnetic forces could achieve the same effect in a more predictable and precise fashion.

Opiates –These are medications like morphine and its derivatives that are often the only drugs that can provide effective and sustained relief for patients suffering from chronic pain. Unfortunately, there is a stigma attached to their use, and many patients are deprived of the benefits of these medications because of unwarranted fears of addiction by the public as well as physicians. When carefully supervised, the likelihood of addiction for patients with chronic pain is probably less than one percent. When used correctly, opiates liberate rather than stupefy.

Behavioral Therapies - These include meditation, psychological counseling, biofeedback, and cognitive restructuring procedures to decrease anxiety and improve coping skills and resilience.

Nerve Block -Injections of local anesthetics into specific nerve bundles or even regionally can temporarily suppress pain and relieve anxiety, so that the pain is less severe when the drug wears off.

Implantable Approaches - These include devices that deliver a low voltage current to the spinal cord, and pumps that provide opiates systemically or to specific sites to suppress pain signals.

Electroceuticals - as previously indicated, weak electromagnetic stimuli offer great potential because they are safe, very cost effective, and non-addictive. Moreover, insights into how they work may help us to learn how to tap into the body's own vast potential for pain relief and self-healing; Stay Tuned!

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

John Milton, *Paradise Lost* (1668)

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