Neurophysiological Underpinnings of Electronic Analgesic Neuromodulation for Dummies

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ABSTRACT

Electronic neuromodulation can be a safe and effective treatment for intractable pain. Unfortunately, many physicians and other healthcare providers know nothing of neuromodulatory techniques. There is little opportunity to learn about them in medical school or during general medical training. Nearly all of the literature about neuromodulation is aimed at specialists who already have a detailed knowledge of the field. This article reviews the pathophysiology of chronic pain from the point of view of a primary care practitioner, with the aim of providing a rationale for the appropriate use of electronic neurostimulators in patients with chronic pain. In order to understand advanced pain management, it is important to first understand that pain management is not about treating pain, but about “reducing hypersensitivity.” Specifically, advanced pain management techniques are aimed at the pathophysiological processes of hyperalgesia, allodynia, neurogenic inflammation, and neural remodeling. Some approaches to electronic analgesic neuromodulation are summarized.

Key Words: Analgesic; Neuromodulation

Introduction

Electronic stimulation of the nervous system has been used to treat pain for thousands of years [1,2] but has developed rapidly only over the past 30 years [3]. Lack of information among physicians nearly killed this modality of treatment in the 1970s and 1980s [4]. Acceptance of neuromodulation by the medical community is still limited to a relatively small number of physicians. It can be difficult for busy practitioners to absorb all the swiftly evolving knowledge about electronic hardware, new surgical techniques, and our growing understanding of chronic pain. As a primary care practitioner—and not an implanter—I thought that it would be useful to take time to review the pathophysiology of chronic pain and perhaps even stick our tongues in our cheeks before we arrange to have our colleagues stick electronic appliances in our patients. The aim of this paper was to set the stage for improving our ability to help some of our most “difficult” patients, those with long-standing pain who so often seem buried beneath an avalanche of complexity and chronicity.

Dumb

Since time immemorial, ever since the first child rubbed the first scraped knee, people have done some pretty dumb things to treat pain. This included a variety of popular techniques to treat pain [5], ranging from moxibustion, burning pieces of fabrics or vegetables on the skin, to trephination, splitting the scalp, drilling a hole in the skull, and filling the hole with dirt and dead leaves for the treatment of headache (although, in all fairness, I think you were supposed to wash your hands before packing in the dirt and leaves). Just because some of these popular techniques were dumb does not necessarily mean that they were wrong, just that they were done without an underlying knowledge of the physiology and pathology that could rationalize their use.
And Dumber
Sad to say, some of the dumbest pain-management techniques throughout history have been promoted by physicians. These have included destructive techniques that could worsen the pain, ranging from amputation of painful limbs to unnecessary removal of internal structures that were thought to somehow "drive" chronic pain such as dessicated intervertebral discs, urinary bladders, and a whole lot of normal uteruses. One of the most frightening aspects of some of these physician-driven techniques is not that they were dumb, but that they violated one of the basic tenets of the profession, motivated more by a drive to provide treatment than the desire to provide relief.

Who Are You Calling a Dummy?
For the time being, nobody but myself. As I have gotten older, I have come to realize that being a dummy might be the thing to be.

Why Be a Dummy?
Because the alternative is so much worse. The farther I get from my medical training, the fewer lectures and labs I remember. Still, there are some lectures that have actually "come back." These days, I can actually remember the first lecture we ever had on the first day of medical school 30 years ago... in its entirety. An old professor got up on stage, looked at every student directly in the eye and, after 15 minutes or 20 minutes, finally spoke to us.

"Welcome to world of medicine," he said, "I hope you will find that your new lives are marvelous. I am sure that you'll all be working hard and learning a lot of important things over the next four years. So today, I've brought just one thing to tell you. More than half of everything your teachers and professors are going to teach you will be wrong... and they don't even know which half! Good luck and try to get in a little fun!" And with that, he shuffled off the stage.

I remember giving some thought to that lecture, especially on those long, cold nights spent on memorizing things that have been so useful to me as a practicing physician, such as the Krebs cycle. I thought I understood what our professor had said. I thought that he was telling us that we could not know everything and that we would have to spend the rest of our lives learning. I could live with that. However, as I got older and dumber, I eventually realized what he was telling us.

He was telling us that much of the things that we had worked hard to learn were "false" and that we ran the risk of carrying many of these falsehoods out into our practices where we could use them to harm our patients. The way to tell when "knowledge" was false was that it did not help our patients get better. Unfortunately, when faced with an "unnecessarily" deteriorating patient, we often find ourselves with a choice of whom to blame. Sadly, that blame sometimes falls on the patient. This can lead to isolation and abandonment of those whose illnesses we do not understand, which can be even a greater burden than the physical illness itself. As I have gotten older and dumber, I have increasing respect for those teachers and colleagues who are just as willing to tell me what they do not know as what they do. These are the physicians who will somehow find a way to treat unbelievable illnesses. These are the most difficult illnesses to treat.

What Are Illnesses?
There are many useful ways of conceptualizing illness. One model holds that illness occurs when the body has been breached by foreign organisms or toxins, as would be the case in an infection or poisoning. Another model of illness holds that localized degeneration or unhealed injury has led to dysfunction or disability, as could be the case in arthritis or cardiomyopathy. A third concept is that we experience illness when the body's counterbalancing regulatory, defensive, and healing mechanisms function out of balance. This model has great relevance to illnesses mediated by the central nervous system (CNS), especially those that involve chronic pain.

Life Is in the Balance
The idea that the body's homeostatic mechanisms function in a delicate, counteractive balance goes back to antiquity. More than 4,000 years ago, Chinese physicians described a balance of vital energy, the ch'i, which flowed through the organs and vital structures through a network of bodily conduits called meridians. Disease and pain were thought to be due to an imbalance of two opposing forces, the yin and yang, that are related to obstructions (deficiencies) or outpourings (excesses) in the circulation of the ch'i. This view of disease as a generalized imbalance linked the pathology of visceral organs with dysfunction of somatic structures and abnormal sensations throughout the body, such as chronic pain. This conceptual model gave rise to medical treatments designed to restore
balance. Among these were the first effective treatments for chronic pain, including the precursors to many of the medications and techniques that we use to this day [6].

**Chronic Pain: Life Gets Out of Balance**

According to this point of view, chronic pain can be seen as a pathological condition in which the natural pain-sensing and pain-relieving systems have gotten out of balance. Because of this, pain persists in spite of having lost its connection to the inciting injury. Once the pain is chronic, fixing the injury will no longer fix the pain. In this situation, the sensation of pain no longer has a purpose and the body is barraged by a torrent of meaningless signals. In the final analysis, it is meaning itself that allows us to endure severe pain. Once the meaning of pain is lost, the urge to survive can be undermined. Neuromodulatory treatments for chronic pain are specifically aimed at restoring balance to an unbalanced system.

**What Is Neuromodulation?**

The neuromodulatory approach to treating chronic pain involves delivering inputs into the CNS that either dampen the abnormal pain signals or reinforce the activity of the body's natural pain-relieving mechanisms. Neuromodulatory treatments do not “kill” pain. After all, we do not want to kill any part of the body. Instead, by restoring balance, neuromodulation safely relieves discomfort while promoting normal function. As we closely examine our patients with chronic pain, we find that their conditions involve more than just the persistent sensation of pain. Through mechanisms that have recently come to light, we now understand that the processes that promote and maintain chronic pain can also damage tissues and destroy organs. It should not be surprising, therefore, to discover that successful neuromodulation can promote the healing of diseased tissue and prolong life [7]. This highlights the essential difference between normal pain, which is a vital bodily function, and chronic pain, which is a dangerous disease. Chronic pain is pain that has lost its purpose.

**What Is the Purpose of Pain?**

The purpose of pain is to keep us alive. There can be no life without pain. People born without the ability to feel normal pain do not survive through childhood [8]. The most important feature of normal pain is that it is linked to injury, both temporally and topographically. Most of the pain that we experience in our lifetimes is acute pain related to minor trauma to skin, muscle, or other connective tissues. Even though the injury may be minor, the concomitant pain can be overwhelming—overwhelming all awareness, controlling emotions, temporarily disrupting relationships, and embedding itself into our memories. In fact, normal pain is not a single physiological event but rather a healing process with different components, any one of which can become disordered, giving rise to illness [9].

**What Are the Different Components of Normal Pain?**

A patient relates a common experience that illustrates some of the different components of normal pain:

I was preparing lunch for my four-year-old daughter. This could be a pretty daunting task. The crusts had to be precisely trimmed from the bread. Her orange had to be sliced into eight exactly equal sections so she'd be able to fit each section into her mouth and make an orange “smiley face” before eating it. But it was worth the effort. My little girl was the perfect little girl—pretty, sociable, so smart, and so artistic. I remember the day in question. She was showing me some of her artwork from school as I was trying to cut her orange just right. Did I mention how artistic she was? It was a moment of pure love. And then I made that awful mistake.

My mother had always warned me to look at what I was doing, but did I listen? I looked at one thing—the picture—as I was doing another, cutting the orange. So, instead of slicing through the orange I sliced right through the palm of my hand.

Suddenly, things changed. Instead of thinking of my daughter and her artwork, all I could think of was my hand. My emotions changed. I suddenly became upset, even angry. For a second I thought I might even “lose control.” My daughter, keenly aware and possessed of incredible emotional sensitivity at the time (she has since deteriorated into a teenager) immediately knew that something terribly wrong had happened. She gently sought to guide me back to reality.

“Daddy,” she said, “you’re bleeding on my orange.” But I was beyond reach. The pain had overtaken me. “Daddy can’t talk right now,” I told her rather sternly, as I gripped my blood-spurting hand.

“But Daddy,” she cooed, “I don’t want to eat that orange.”

The pain in my mind was so intense, I couldn’t contain my emotions. Through clenched teeth I angrily muttered, “sweetheart, I think you’d better leave the room right now because Daddy is about to say some new words that you are not supposed to hear.”

“Why would you say words if I’m not supposed to hear them?” she cried. What an insightful little girl she was! But the pain had become too much.

“Get out!” I yelled. And she ran from the room crying, thinking that my anger was directed at her.
As soon as she was out of the room I ran to the sink, ran cold water on my injured hand and wrapped it as tightly as I could in a towel. It still hurt but it felt much better. I was able to regain control over my emotions and I ran into the living room where my little daughter sat crying on the couch. I reassured her that I was not angry with her and that it was just the pain that had made me crazy. Once she saw that I was OK and that she wasn’t going to have to eat that bloody orange, things quickly went back to normal. My hand still hurt, but not nearly so bad as long as I didn’t try to grip anything for the next few days. My daughter and I were even able to joke about it. And I certainly learned to look at the orange next time I cut it.

A Gripping Narrative . . . But What Does It Mean?

This dramatic real-life story illustrates some of the functional components of normal acute pain. These include the initial “alarm,” which makes us aware of the injury. This initial sensation localizes the pain, obliterates the awareness of other elements in the environment, and kindles an emotionally laden, energized alertness that prepares us to avoid further injury. The second element in the acute pain response is—surprisingly—“pain relief” [10]. Within minutes of an injury, the pain has lost much of its sharp intensity and we can regain composure and resume functioning. If the sensation of pain was dependent entirely on the damage to tissue and the ensuing inflammation, we would expect that the severest components of pain would continue to escalate from the time of injury until healing had taken place. If this were indeed the case, then every stubbed toe and scraped hand would have us cursing and crazy for days, and we would never be able to function normally.

Another neurological response to acute injury is hypersensitivity. For a transient period after an injury, the affected area will be hyperresponsive to painful stimuli. This is called hyperalgesia. In some cases, the sensorium of the affected area will temporarily change so that nonpainful stimuli such as light touch will elicit the sensation of pain. This phenomenon is called allodynia. From the time the painful impulse reaches the spinal cord, a series of neurochemical responses to the pain integrates the pain signal with other incoming sensory signals and memories, investing the pain with meaning to help the person to formulate an adaptive response. The final step is learning. Eventually, the painful event is incorporated into memory—both in the brain and at the level of the spinal cord. This will trigger the formation of new neural circuits designed to prevent further injury. In addition to several components of pain, the aforementioned story also demonstrates some aspects of analgesic neuromodulation.

Where Was the Neuromodulation in This Story?

After cutting his hand, I . . . er, I mean the subject ran cold water on it and wrapped it tightly in a towel. One would expect that putting pressure on a sensitized, injured area would make the pain worse but instead, it conferred relief. Stimulating certain tactile pathways can serve to dampen a pain signal that it is being transmitted to the same area of the spinal cord. Also, by diverting his attention to his daughter, the subject may have activated pain-dampening circuits in his brain and stimulated higher cortical centers that released pain-relieving neurotransmitters [11]. All-in-all, even though our subject was badly hurt, his painful experience was a normal, positive one—assuring future function without protracted suffering. When one of the components of the normal pain response does not fulfill its function, the pain can become disordered . . . and chronic. By examining some of the normal pain functions more closely, we can begin to understand how dysfunctions can occur and how neuromodulation has the potential to correct them.

Normal Pain Is Like a Smoke Alarm

Even a minor disruption of tissue can elicit the release of chemical mediators from lysosomes and cell membranes. These trigger a self-augmenting inflammatory reaction that gives rise to electrical signals in sensory nerves that carry the message of pain to the spinal cord and onto the brain [12]. Because of the cascading nature of the inflammatory reaction, an intense pain signal can be rapidly generated by a minor injury. This causes the initial sensation of pain to be out of proportion to the degree of injury. The analogy I use when describing this to patients is that of smoke alarms, which we program to give off the loudest blare on the first hint of smoke, rather than to wait for a full-fledged fire to start alarming.

Over the years, I have had the opportunity to ask many people about their smoke alarms. Almost everybody has a smoke alarm, but I have never met anybody who has given one for Christmas. This leads me to believe that everybody feels that they need the alarms but that nobody really likes them. I have also asked people if they have ever experienced their smoke alarm alarming. As it turns out, this is a pretty common experience and people describe a stereotype reaction to the alarm. They become aroused, emotionally activated but, at the same time, focused and goal oriented. Nobody
described the experience as pleasant. In many ways, this resembles the initial part of the pain reaction.

The nerves that carry the acute pain signal from somatic tissue to the CNS are lightly myelinated A-delta fibers and unmyelinated C-fibers. The most important chemical activator of these nerves—the “smoke” for our “smoke alarms”—is bradykinin [13]. A smoke alarm will keep alarming as long as there is smoke (and as long as the battery works), but our pain system is more sophisticated than that. Shortly after a normal pain fiber is activated, it loses its sensitivity to bradykinin, turning down the alarm signal even though the injury and inflammation persist [14]. If cell breakdown at the site of injury continues, some of the metabolites of damaged cell membranes, such as prostaglandins and leukotrienes, can restore this sensitivity to bradykinin and promote continued pain [15].

**Smoke Should Trigger the Smoke Alarm, Not the Other Way Around**

As we will see, if severe pain is allowed to persist, the CNS will undergo changes and will start generating signals that will maintain and drive the peripheral inflammatory response. This type of pathological process involves antidromic (backward) transmission through sensory nerve fibers and is called a *dorsal root reflex*. When this happens, tissue inflammation goes from being a transient response tied to healing to a chronic pathological state. This is associated with significant changes in biological components of the inflammatory response, going from neutrophils and macrophages that characterize traumatic inflammation or lymphocytes and other immune cells that characterize immunogenic inflammation, to sprouting nerve cells, degranulating mast cells, and altered vascular endothelial cells that characterize *neurogenic inflammation* [16].

**What Is the Second Thing You Do after the Smoke Alarm Goes Off?**

Of all the people I have met who have gotten alarmed by their smoke alarms, nobody’s house was burning down at the time. All of these people looked for the fire when the alarm went off and they all did the same thing when they found out that there was no fire. They turned off the alarm. They knew that it would not take long before a dysfunctional alarm would make them pretty dysfunctional too. One function of the body’s pain system is to turn down the alarm once the person has been made aware of the injury. Just as pain is a necessary part of life, so is pain relief.

**How Can Our Bodies Relieve Pain?**

Just as there are multiple neural pathways for transmitting and processing pain, there are also multiple neural pathways for mediating pain relief; just about everyone has heard of endorphins. If you ask a nonmedical person-on-the-street how to increase your level of endorphins, you might be told to watch a pretty sunset or listen to soothing music. In fact, a faster route to a higher level of endorphins is to get into your pick-up truck—make sure you have a full tank of gas, get up to high speed and then SLAM into the nearest brick wall! There is nothing like major trauma to elicit the secretion of endorphins. Endorphins and related pain-relieving mediators were first understood as neurotransmitters that were related to the adaptive response to trauma and injury [17].

Within seconds of an injury, pain signals arriving from injured peripheral tissues stimulate the release of endorphins from the periaqueductal gray matter of the brain and enkephalins from the nucleus raphe magnus of the brain stem. Endorphins inhibit the propagation of pain signals by binding to mu-opioid receptors on the presynaptic terminals of nociceptors and postsynaptic surfaces of dorsal horn cells in the spinal cord. Another group of natural pain relievers, the enkephalins, bind to delta-opioid receptors on inhibitory interneurons in the substantia gelatinosa of the dorsal horn of the spinal cord, causing release of gamma-aminobutyric acid (GABA) and other mediators that dampen pain signals in the spinal cord. There are several loci in the brain for the endorphin-mediated pain control system, the center of which appears to be localized in the rostral ventromedial medulla [18].

**Is All Pain Relief So “Chemical”?**

Of course, isn’t everything? (After all we are doctors . . . remember?) The endorphin system not only mediates “chemical” pain relief but also plays an important role in the action of “nonpharmacological” pain relievers, such as exercise and placebos. For example, the relief generated by a placebo can be inhibited by pretreatment with an endorphin antagonist, such as naloxone [19]. Dys-
function of this natural pain-relieving mechanism may give rise to certain illnesses related to chronic pain.

One example of this is the “daily headache” syndrome that can develop in chronic migraineurs. Functional magnetic resonance imaging (MRI) studies in these patients often show iron deposition in the periaqueductal gray matter of the brain, which is thought to be related to fibrosis of endorphin-producing cells [20]. Conversely, overactivity of endorphin-producing cells, such as can occur among certain elite athletes like marathon runners has been associated with hyposensitivity to visceral pain and may be related to the high incidence of “silent” myocardial ischemia among these people [21].

So It All Just Comes Down to Endorphins and Enkephalins?

No, in certain situations, some people can experience a type of profound, natural pain relief that does not appear to be related to the secretion of endorphins. This type of pain relief appears to be related to specific cognitive inputs and has been called “stress-induced” analgesia. This type of natural pain relief has a strong association with certain cognitive inputs. For example, in crisis situations, people have found that they can pick up a car if a friend or a loved one is pinned underneath. For some reason, these same people are unable to lift the car if they are not familiar with the endangered person.

People who have experienced this type of analgesia—many of whom perform heroic acts despite terribly painful injuries—do not report that they “overcame” their pain. They report that they did not feel it. In contrast to endorphin-related analgesia, stress-induced analgesia is not inhibited by opioid antagonists nor can it be replicated by opioid drugs. Pharmacological agonists of stress-induced analgesia include ketamine and phencyclidine, both of which are “dissociative” anesthetics [23]. This highlights the important role of cognitive inputs in the processing of pain-relieving signals or, in other words, explains why the boo-boo will feel better when Mommy kisses it but not when the doctor does.

The Pain Is Not All in Their Heads and Neither Is the Pain Relief

Not all of the body’s natural pain relievers work in the brain. In reaction to acute injury, spinal interneurons release dynorphin, which can activate kappa-opioid receptors and cause closure of N-type calcium channels, inhibiting spinal cord cells that normally relay pain signals to the brain [24]. This may explain some of the pain-relieving effects of calcium-channel blocking medications such as gabapentin and ziconitide [25]. Responding to the release of enkephalins, spinal cord cells...
release other small molecules including norepinephrine, oxytocin, and relaxin that can act as short-range neurotransmitters, inhibiting the transmission of pain signals in the spinal cord [26].

**Does Pain Relief Expose Us to More Injury?**

Enkephalin binds to delta-opioid receptors that are selectively exposed on nociceptors that are actively transmitting pain signals. Because of this, active nociceptors are more sensitive to both endogenous and exogenous pain-relieving opioids than inactive nociceptors. This helps explain how certain analgesics, such as opioid medications, can relieve ongoing persistent pain without compromising the ability to sense the pain caused by new injuries [27].

**It Is Not Just the Drug, It Is Where You Put It**

Natural pain relief extends to the interface of the peripheral nervous system and CNS. Stimulation of opioid receptors and other inhibitory receptors on peripheral neurons or at presynaptic terminals in the spinal cord can slow up or stop the synaptic release of glutamate, the major neurotransmitter for pain in the periphery. This helps explain the unique efficacy of small doses of intrathecal opioids delivered through an implanted pump in selected pain syndromes. This type of therapy can often provide impressive relief in intractable pain syndromes and can work in a complementary fashion with systemically administered opioid medication. Of note, opioids do not have much presynaptic inhibitory activity on normal peripheral pain nerves but do inhibit the release of glutamate from inflamed pain nerves [28].

The natural pain-relieving system is as critical to normal functioning as the pain-sensing system. Because we have the capacity to naturally suppress pain, common minor injuries make us dysfunctional for only a few minutes and not for days, as might be the case if the pain persisted and intensified until the inciting injury was completely healed.

**Are You Really in Pain or Are You Just a Little Too Sensitive?**

A unifying feature of most chronic pain syndromes is the development of persistent hypersensitivity, a disordering change in the normal relationship between a painful stimulus and the neurological response [29]. Transient hypersensitivity to painful stimuli (i.e., hyperalgesia) and allodynia are normal sequelae of trauma that protect the injured area against further trauma and allow healing. Interleukin-1 is important in the initiation of hyperalgesia [30]. Nerve growth factors (NGFs), such as “substance P,” maintain the allodynic state. Sympathetic activation and release of norepinephrine can also produce hyperalgesia but only in the presence of tissue injury. In these cases, norepinephrine may potentiate pain by stimulating the production of prostaglandins and activating phospholipase C [31]. If hyperalgesia and allodynia are allowed to progress uncontrolled, they can develop into self-sustaining chronic pain.

Hypersensitivity to pain can occur in both the peripheral system and CNS. Persistent inflammation can cause nerve endings to sprout in peripheral tissue, making individual pain fibers more responsive to a given stimulus. In certain syndromes, unremitting pain signals may activate a population of mechano-sensitive afferent nerves (“silent afferents”) that are present throughout the viscera and synovial tissue [32]. Once activated, even slight movement or minimal deformity of surrounding tissues can generate pain. This type of allodynia is common in chronic degenerative arthritis, lower back pain, severe irritable bowel syndrome, and other chronically painful conditions.

**Thanks for the Memories ... Not!**

If pain signals are continuously transmitted to the spinal cord, the CNS itself will undergo physiochemical changes, resulting in hypersensitivity to pain, increased pain with unchanging repeated stimuli (“wind-up”), and resistance to antinociceptive (e.g., pain relieving) inputs (e.g., tolerance to pain medications). Ultimately, the pain signal can become embedded in the CNS like a painful memory, without the need for any peripheral input. The analogy to memory is especially fitting as the generation of hypersensitivity in the spinal cord and memory in the brain both share a common chemical pathway involving NMDA (N-methyl-D-aspartate) receptors [33].

The physical changes that accompany this sensitization process are first seen on the cell membranes of dorsal horn cells of the spinal cord that receive signals from nociceptors. The main chemical mediator used by nociceptors
synapsing with the dorsal horn of the spinal cord is glutamate, which can bind to several different types of receptors. AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic-acid) receptors are sodium–potassium channels on postsynaptic afferent nerve terminals in the dorsal horn and mediate the transmission of acute pain. Activation of these receptors triggers a transient activating current that generates a signal to the brain through the spinothalamic tract but that does not cause cellular changes in the pain-transmitting neuron.

**My Nervous System Keeps Going Through Changes**

NMDA receptors are a separate class of receptors for glutamate on dorsal horn cells that, when activated, open a channel for the influx of calcium into the spinal cord afferents. In the resting state, this calcium channel is blocked by a magnesium ion. With persistent or intense release of glutamate, due to persistent or intense pain, activation of AMPA receptors results in a change in the charge of the cell membrane and the magnesium ion is said to “pop out” of the calcium channel like a cork popping out of a champagne bottle. The “unblocked” NMDA receptor can now be activated (Figure 1). In a biochemical sense, this conformational change in the NMDA receptor marks the central transition from acute to chronic pain [34].

**Turn and Face the Change . . . and Breed Tolerance**

Calcium ions flowing into the dorsal horn cell activate protein kinase C, which triggers the production of nitric oxide (NO) by NO synthase. NO, which is in essence a very short-range neurotransmitter, diffuses back across the synaptic cleft and hits the nociceptor, stimulating guanylylsynthetase-induced closure of potassium channels. Many of these potassium channels are opioid receptors, and the nociceptor is thus rendered insensitive (i.e., tolerant or resistant) to opioid-induced suppression of the pain signal by endorphins, enkephalins, and opioid medications [35]. This explains the clinical observation that one of the most important mediators of opioid tolerance is unremittant pain, rather than the use of opioid medications. In clinical studies NMDA inhibitors, such as ketamine or dextromethorphan, can reverse opioid tolerance, demonstrating that opioid tolerance is more a biochemical phenomenon than a characterological disorder.

**Pain as a Teacher**

One of the most important functions of pain is to teach us to avoid hazards. If we do not learn from our painful experiences, we will be bound to repeat them. This may help explain why children with learning disabilities are at an increased risk for repeated traumatic injury [36]. The process of learning involves nerve growth and the establishment of new neural connections. If the learning process gets out of control, the nervous system can “grow” into a chronic pain state.

**Can We Learn Too Well?**

In a word, yes. Everything can be overdone. If the pain signal is allowed to persist, NO eventually stimulates the release of substance P from the nociceptors. By binding to the NK-1 receptors in the dorsal horn membrane, substance P can trigger the expression of c-fos oncogene, promoting neural remodeling and further hypersensitization. It is interesting to note that the one chemical abnormality repeatedly documented in controlled studies of patients with fibromyalgia syndrome (a condition that many clinicians continue to consider factitious) is an elevated level of substance P in the spinal fluid [37].

**Painkiller or Killer Pain?**

Just because we have decided not to kill pain does not mean that the pain would not kill us. Activation of NMDA receptors has many consequences for nerves in the spinal cord, which can ultimately include cell damage and cell death. NMDA receptors are now being implicated in some of the cell damage that occurs in the brain during strokes, where injured presynaptic cells release torrents of glutamate, literally “burning out” and killing postsynaptic cells downstream. One of the most intriguing avenues in current stroke research is the therapeutic use of NMDA receptor inhibitors to limit damage in the setting of an acute stroke [38].

**Stop It Before It Spreads**

Activation of the NK-1 receptor triggers production of c-fos oncogene product, a protein that in many respects can be regarded as a biochemical footprint of chronic pain. In animal models of chronic pain, the c-fos oncogene protein can be detected in afferent spinal cord cells that are receiving pain signals. As chronic pain persists, the
c-fos oncogene protein will become detectable in cells higher up the spinal cord, appearing outside the dermatome in which the original painful stimulus occurred. This protein will eventually become detectable in the thalamus itself and, at this point, the pain will be virtually untreatable [39].

And One Word of Advice . . . Plastics

C-fos oncogene protein may be a marker for the acquisition of hypersensitivity to pain signals by different areas of the spinal cord. This can explain how many patients who have persistent pain find that, after months and years of under-treatment, the pain begins to spread to other organs than the one originally involved. For example, patients with long-standing proctitis due to irritable bowel syndrome will often develop noncardiac chest pain if their chronic pain goes untreated. In the case of somatic pain, this hypersensitization can cause the pain to spread outside dermatomal boundaries. Unfortunately, when this happens, physicians who are not familiar with the concept of neural plasticity will think that the abnormal area affected by the pain is not “physiological,” and therefore come to the conclusion that the patient is either mentally ill or faking [40].

Nerves Will Remodel and So Must We All

Hypersecretion of NGF may be responsible for the maintenance of chronic pain states. Therapeutic trials of NGF in the treatment of diabetic neuropathy have resulted in persistent
The idea that chronic pain can result from injury to nerves is not really new, but it is still not yet widely accepted. In the 19th century, the idea of “pain without lesion,” the neuralgias, was first described by Francois Chaussier, a professor at the Ecole de Sante in Paris who is credited with coining the term “tic doloureux” and describing the characteristics of neuropathic pain. He associated this type of pain with damage to a nerve trunk or disruption of branches of nerves. He observed this type of pain in instances where tumors compressed nerves or in wounds severing nerves. He described a type of pain that persisted after healing was complete. He noted that a distinctive sign of neuralgia was that sectioning of the nerve stopped the pain temporarily and it was often much worse [43].

One would expect that nerve damage would result in lack of function. Certainly, if one cuts a motor nerve, it results in persistent paralysis. That used to be interpreted to mean that the motor nerve had died. For hundreds of years, physicians have been treating people in pain by cutting or damaging pain nerves, in the hope that they would reduce or eliminate the ability to feel the pain. Many surgeries and procedures that are done for pain—ranging from occipital neurectomies for chronic headaches to many of the back surgeries that used to be performed to hysterectomies for poorly defined pelvic pain—involve neurodestruction. Some of these procedures do give relief—but often, the relief is only temporary and is followed by a worsening of the previous pain. This is because injured nerves can heal, and when they do, they can get pretty angry.

If a nerve fiber is severed distal to the cell body, the cut surface can heal. If it is a healed motor fiber, it will not be able to reestablish its connection to its target. The nerve cell may heal and begin generating signals but these signals will not be meaningful. The limb affected will remain paralyzed. However, if that nerve is a nociceptor, then the healed end can start to generate electrical impulses spontaneously, which will reach the spinal cord and will be “misinterpreted” as peripheral pain [44]. This damaged nerve can now generate signals with an abnormal intensity without any input from the periphery. It also will not be subject to many of the mechanisms that put limits on the generation of normal pain, such as reduced sensitivity to bradykinin. This is apparently the mechanism of a lot of the pain related to advanced cancer, which is usually related to the disruption of nerve fibers by tumor [45].

Neural (Not Neurogenic) Inflammation

Just as injury to other tissues triggers an inflammatory reaction, neural injury can result in neural inflammation. Because of the structure of the nervous system, inflammation of nerve cells involves cellular components that differ from those in peripheral tissue. When peripheral nerves are injured, macrophages are recruited and glial cells are activated to create an environment that supports nerve regeneration. There are three major types of glial cells in the nervous system: 1) microglia; 2) astrocytes; and 3) oligodendrocytes.

Microglia are mediators of neural inflammation and a source of pro-inflammatory cytokines. Astrocytes surround synapses and can sense synaptic activity—they have glutamate receptors and regulate glucose utilization at the synapse. Oligodendrocytes are myelin-forming cells. Trauma within the nervous system triggers the proliferation of astrocytes and microglia. This reactive gliosis is stimulated by tumor necrosis factor and...
IL-1. Microglia themselves can secrete additional IL-1 and promote their own growth. Reactive gliosis is a prominent consequence of most neuro-pathological processes in the CNS and can be associated with accumulation of immunocompetent cells in an area of pathologically persistent hyperalgesia [46,47].

**Painful Scars?**

This neural inflammation—which is distinct from neurogenic inflammation—may be responsible for a lot of the pain that used to be (and still is) attributed to “scarred nerves.”

This was explored clinically over 60 years ago, when orthopedic surgeons attributed chronic back pain to nerve compression due to scarring. In studies where a Fogarty catheter was threaded up the dorsum of the spinal cord, it was found that inflation of the balloon against a normal dorsal nerve root did not cause pain—it caused hypohesthesia. When the balloon was inflated against an inflamed nerve, the subjects experienced radicular back pain. This experiment has been repeated in a variety of ways, with the results implicating neural inflammation as a driver of pain, hyperalgesia, and allodynia [48,49].

**Other Ways That Nerve Damage Can Cause Pain**

Damage to sensory nerves can cause neuropathic pain syndromes, which are relatively insensitive to suppression by the natural antinociceptive system. This is commonly seen in patients who have had a stroke or spinal cord injury, where the nerves that carry tactile signals may be destroyed. If enough pain-carrying fibers regenerate, tissues presumed to be anesthetic can generate considerable pain if reinjured or inflamed.

This “deafferentation pain” is most common among patients with spinal cord injuries. Although they may have no normal sensation below the waist, they are not anesthetic. For example, surgery on decubitus ulcers or even a simple bladder infection can be extremely painful. Without the interference of continuous tactile inputs, some patients with spinal cord injuries can discriminate among different types of pain to the point where they can even identify what type of bacteria is infecting their bladder by “the way it feels.” This type of pain is also seen in postoperative pain syndromes (e.g., postthoracotomy or postmastectomy pains) where a common finding is pain accompanied by an area of tactile hypohesthesia [50].

**Nerves in the Balance: The Ecology of Peripheral Nerve Bundles**

Peripheral sensory nerve fibers, both nociceptive and nonnociceptive, exist in a balance within their nerve bundles. Their population mix is regulated by various neurotrophins (NGFs) secreted by supporting cells. Disruption of this balance can lead to abnormal growth of one population. If one population of nerves is injured, another population may become activated. This is invoked as one of the many mechanisms of neuropathic pain. In an experimental model that reflects clinical experience, resection of the sciatic nerve causes the destruction of the C-fiber terminals where they synapse in the pain-sensing areas of the superficial dorsal horn of the spinal cord. The loss of these connections causes the endings of large myelinated A-fibers to sprout and form new connections with the spinal cord [51].

A-fibers are not nociceptors but rather nerves that carry the sensation of touch. The endings of these large fibers can now invade the superficial dorsal horn region. These large nerves, which are activated by touch, now carry a signal to an area of the spinal cord that interprets the incoming signal as pain. The person will now experience pain to the noninjurious stimulus of touch. This type of allodynia is commonly seen in patients with chronic back pain who have undergone surgery and may be part of the explanation of the “postlaminectomy syndrome.” It is easy to assess clinically but does not show up on CT scans, MRIs, electromyograms, or nerve conduction studies. Not only can these tactile cells mediate allodynia, but they are also relatively insensitive to the effects of endorphins or opioid medications because A-fibers do not produce opioid receptors. This may be an important part of the mechanism of the agonizing pain of “reflex sympathetic dystrophy” and explain its relative insensitivity to opioid medications [52].

**Neuropathy: When Nerves Function Too Poorly . . . or When They Function Too Well**

In persons with diabetes, loss of tactile A-fibers due to destruction by persistent hyperglycemia can result in a neuropathic syndrome characterized as mononeuropathy multiplex. In this syndrome, C-fibers remain intact. The oligodendrocytes that
form the myelin sheath around the dying A-fibers migrate and insulate the pain fibers, which can now transmit their signals with greater efficiency and deliver them to the spinal cord unopposed.

These patients will experience a loss of tactile function and experience a worsening sensation of “painful numbness.” Biopsies of the affected areas show drop-out of tactile fibers and abnormal myelination of C-fibers. In experimental models that bear close resemblance to what we see in the clinic, damage to motor or sensory nerves in one dermatome (mimicking damage caused by back surgery or rhizotomy), can lead to spontaneous activity among nociceptors in adjacent dermatomes. Schwann cells can then be stimulated to proliferate in peripheral nerve Remak bundles causing abnormal myelination (and hyperefficiency) of uninjured peripheral nociceptors [53].

**Afferent Becomes Efferent: The Pathophysiology of Dorsal Root Reflexes**

Medical school taught us that nerve cells transmit signals in only one direction, either toward (afferent) or away (efferent) from the brain. We now know that many neurons can carry signals in both directions. With the prolonged generation of pain signals, a pathological phenomenon called a dorsal root reflex can become established in which afferent cells in the dorsal horn of the spinal cord release mediators that stimulate nociceptors to fire action potentials antidromically (i.e., backward).

**The Dangerous Balance: Trauma Causing Pain and Pain Causing Trauma**

Antidromic stimulation of pain fibers cause release of packets of chemicals located at their peripheral terminals (Figure 2). These chemicals include nerve growth factor and substance P, which is not only a neurotransmitter but is also a potent inflammatory agent. Pain signals from peripheral nerves are thus heightened and the cycle of chronic pain continues. Calcitonin-gene-related peptide released in the periphery causes vasodilatation, extravasation of proteins, and release of bradykinin from vascular endothelial cells. It also triggers the degranulation of mast cells and release of histamines and serotonin, which cause a long-lasting lowering of nociceptive thresholds. Other peripheral mediators of this process of neurogenic inflammation probably include NO and vasoactive intestinal peptide (VIP). From [9].

In this way, pain-transmitting nerve cells, specifically nonmyelinated C-fibers and small-caliber myelinated A-delta fibers, appear to play a dual role. They translate trauma into pain and can also translate pain into more trauma. This efferent function for nociceptive nerves was first suggested...
over 70 years ago when it was ascertained that these peripheral fibers mediated the “flare reaction” surrounding acute cutaneous injuries [55]. This can be commonly seen in patients who develop rashes—e.g., redness of the skin on their necks—due to cognitive stress. This can be prevented by the use of medications that specifically block elements of neurogenic inflammation, such as inhibitors of mast cell degranulation.

Neurogenic Inflammation: How Chronic Pain Can Cause Organ Damage

Biopsy specimens from neurogenically inflammed tissues—e.g., the synovium in certain forms of chronic arthritis, the bladder in interstitial cystitis, or the colon in ulcerative colitis—typically show vasodilatation, plasma extravasation, abnormal sprouting of peripheral nerve terminals, and an accumulation of mast cells.

Dorsal root reflexes apparently occur only under circumstances in which there has been prolonged and unsuppressed nociception. This model of the CNS’s assumption of control over peripheral inflammation explains why many painful conditions do not respond to standard “end-organ-oriented” treatments. These conditions can include long-standing rheumatoid arthritis, reflex sympathetic dystrophy, certain cases of chronic headache, certain severe cases of irritable bowel syndrome, and noncardiac chest pain. Pathological findings linked to neurogenic inflammation are commonly seen in inflammatory diseases of gastrointestinal tract such as that in ulcerative colitis and Crohn’s disease, and in some nonpainful chronic inflammatory states such as psoriasis and certain cases of chronic asthma [56–60].

In some sense, many of these diseases could thus be regarded as pain disorders. This mechanism explains why we have to treat and suppress certain inflammatory conditions, such as rheumatoid arthritis, within a limited time frame. If we do not, the inflammatory process escapes control by the traditional anti-inflammatory medications. This is because these medications are active against immunogenic inflammation and not against neurogenic inflammation.

Neuromodulatory Strategies for Chronic Pain

By understanding the different pathophysologies underlying chronic pain, we can begin to understand the utility of various neuromodulatory approaches. What follows is a very brief description of several approaches to electronic analgesic neuromodulation, all of which are covered in greater detail in other articles in this issue.

Spinal Cord (Dorsal Column) Stimulation

Electrical stimulation of the dorsal horn of the spinal cord goes by the equivalent terms of spinal cord stimulation (SCS) or dorsal column stimulation. SCS involves transmitting an electrical signal through an implanted lead that is placed in the epidural space. This technique was inspired by the gate theory of pain control of Melzack and Wall [61] and first put into clinical use by Shealy and colleagues in 1967 [62]. At frequencies that are generally used, SCS probably does not block perception or transmission of acute pain.

SCS may work by activating supraspinal circuits that probably work by activating descending tracts to inhibit pain. For example, there is relief at low frequencies down to 5 Hz, which would not block conduction [63]. SCS may specifically inhibit the allodynic phase of chronic pain. In many neuropathic pain conditions, perception of paresthesias (e.g., a tingling or humming sensation) in the painful region is mandatory to obtain pain relief with SCS [64]. Because of this, it often will not help patients with pain associated with deafferentation, such as plexus avulsion or nerve resection, where it can be impossible to produce paresthesias with adequate distribution. In essence, if there is no “neural substrate” for the stimulation, then SCS treatment will be ineffective [65].

SCS may also work through the modulation of dorsal horn “wide dynamic range” interneurons in the substantia gelatinosa of the dorsal horn whose responsiveness has been distorted as a consequence of peripheral nerve injury. Studies show that successful SCS may work through activation of interneurons in dorsal horn laminae I-III and inhibition of cells in laminae IV-V [66]. The analgesic effects of SCS persist after the stimulation ceases. For example, 30 minutes of SCS may produce analgesic effects that can last for hours. Pain relief by SCS is not inhibited by naloxone [67] and SCS is often helpful in “opiate-resistant” pain syndromes. One the most important mechanisms of SCS may be triggering of the release of GABA and suppressing the release of glutamate and aspartate in the dorsal horn. The development of allodynia after peripheral nerve injury seems to be related to dysfunction of the spinal GABA systems, and SCS may act by restoring normal GABA levels in...
the dorsal horn, working mainly through GABA-B receptors [68].

SCS works for axial lumbar back and radicular leg pains due to failed back syndrome, spinal stenosis, and other neuropathies involving dorsal nerve roots. SCS has shown great success in the treatment of chronic regional pain syndromes (CRPS I and II, formerly known as reflex sympathetic dystrophy and causalgia, respectively). The success of SCS for CRPS has been so good that many experts have recommended that it be considered early on in the course of disease if medications and nerve blocks are not giving good relief [69]. SCS is also effective for the ischemic pain of peripheral vascular disease and conditions that involve peripheral vasospasm, such as Raynaud’s syndrome, Buerger’s disease (thromboangiitis obliterans), and scleroderma. In some studies, SCS has been shown to give up to 80% relief of intractable angina pectoris [70]. As well as being a pain reliever, there is mounting evidence that SCS may exert beneficial effects on the ischemic condition per se [71].

SCS has been so effective for intractable chronic pain syndromes that every pain center should be able to offer this therapy in its treatment program. Many prominent pain centers will consider SCS for every patient with nonmalignant chronic pain that has not come under control with more conservative treatments [72]. For most patients, temporary leads can be placed percutaneously for up to 10 days to provide a trial of the effects of stimulation on pain. Temporary leads can be quickly placed as an outpatient and are easily removed in the office.

Deep Brain Stimulation (DBS)
The thalamus is, in a sense, the doorway between the body and the brain. The pain-conducting neospinothalamic pathway terminates in the somatosensory parts of the thalamus. During sleep, the normal thalamus shuts down, blocking ascending inputs from the spinal cord. In certain cases, the thalamus can develop bypass tracts, neural “superhighways” that can carry pain to the brain that do not shut down. This explains the characteristics of certain types of central pain and may account for severe sleep disorders that afflict many of our patients with chronic pain that do not respond to the usual doses of sedative–hypnotic medications.

Another source of this type of central pain can be a lesion in the thalamus or brainstem, which can spontaneously and continuously generate continuous intense pain signals. DBS targets both thalamic areas and the periaqueductal gray area of the cortex that is responsible for endorphin release. Stimulation of these two areas probably confers pain relief through different mechanisms. Elevation of endogenous opioids such as beta-endorphin and met-enkephalin is found in patients after periaqueductal gray and periventricular gray matter stimulation but not after thalamic stimulation [73]. Stimulation of the thalamus can activate both neospinothalamic pathways and areas of the limbic cortex, including the cingulated gyrus and the hippocampus, which may store pain memories and mediate pain-related emotions.

DBS has had its best success in thalamic pain, deafferentation pain, facial pain, and other central pain syndromes. The fact that bodily pain has a central generator can often be diagnosed by performing a “differential” spinal block, where an anesthetic is injected into the intrathecal space at a spinal level above the pain. This can cause temporary paralysis, hypotension, and should cause anesthesia below the level of the block. If the pain persists in spite of paralysis, then the generator of the pain has spread to a higher spinal level or to the thalamus itself. Success has also been reported on the use of DBS for peripherally generated pain from “failed back syndrome,” providing relief of both the axial and radicular components of the pain [74].

DBS leads are implanted under general anesthesia through a burr hole using a bolted stereotactic frame. The anesthesia is lightened to conduct intraoperative testing. Stimulation of endorphin-releasing sites can cause a feeling of floating or dizziness. Stimulation of the thalamus can cause contralateral paresthesias. Misplacement of the leads can result in the stimulator evoking pain or causing gaze palsies. Permanent neurological damage occurs in about 2% of patients undergoing DBS and ranges from diplopia to cerebral hemorrhage [75].

Motor Cortex Stimulation (MCS)
Epidural MCS has been shown to confer good pain control in patients with severe neuropathic pain related to deafferentation. It was first proposed in 1991 for the treatment of poststroke pain, pain due to thalamic lesions, and trigeminal neuralgia [76]. The procedure requires craniotomy or a burr-hole procedure under general anesthesia, and electrophysiological testing is conducted intraoperatively. Implants done through a burr-hole carry
a higher risk of epidural or subdural hematoma. There are several proposed mechanisms for this type of stimulation.

Pain relief due to MCS is not associated with muscle contraction or any evoked sensation. Positron emission tomography imaging shows that successful MCS is related to stimulation of the anterior cingulated gyrus of the brain, the area connected to investing pain with its affective and emotional components [77]. The medial thalamus, anterior insula, and upper brain stem are also typically activated. Recent work suggests that MCS may restore the balance between nociceptive and nonnociceptive sensory processing. People who respond well to MCS either show normal thermal thresholds (to hot and cold stimuli) in the painful areas or abnormal thresholds that are corrected by MCS [78]. A noninvasive form of cortical stimulation, transcranial magnetic stimulation may replicate the analgesic effects of MCS in patients with chronic neuropathic pain [79].

Potential additional indications for MCS include deafferentation pain syndromes of the trunk and limbs, including brachial plexus injury and phantom limb pain. Some investigators feel that MCS may soon replace DBS [80].

**Peripheral Nerve Stimulation (PNS)**

In 1859, Althaus found that electrical stimulation of peripheral nerve trunks caused paresthesias that could develop into analgesia and anesthesia in the affected area [81]. The modern age of PNS began in 1967 with the work of Wall and Sweet [82]. Predictors of success with PNS include demonstrable abnormalities in the distribution of the nerve (e.g., evidence of remodeling) using electromyography or sensory evoked potentials, effectiveness of repeated nerve blocks, and >50% relief of pain with a trial of percutaneous electrical stimulation [83].

The most common targets for peripheral nerve stimulation are the upper and lower extremities in the distribution of the sciatic, medial, ulnar, or radial nerves. Newer applications of PNS include treatment of intractable migraine by stimulation of the occipital nerves, chronic pelvic pain (including interstitial cystitis and chronic prostatitis), and cranial neuropathies. The stimulating lead is implanted in an open surgical procedure, where a flap of fascial tissue is mobilized and interposed between the lead and the targeted nerve. A second stage of surgery involves implantation of the implantable pulse generator and the creation of a tunnel through which the stimulator cable can be drawn. The generators are usually implanted under the pectoralis fascia and below the clavicle for upper extremity pain (much like a cardiac pacemaker) and in the buttock for PNS of the lower extremities. Although controlled, randomized studies of PNS have yet to be done, early results showing reduction in narcotic use and improvement in function support the success of PNS [84].

**Transcutaneous Electrical Nerve Stimulation (TENS)**

TENS units have been effective for both acute and chronic pains. By using vibration and activation of A-beta fibers, TENS units may close the spinal cord “gate” for the transmission of pain signals through smaller A-delta and C-fibers. Although originally dependent on percutaneous needle electrodes, current TENS units use noninvasive skin-pad electrodes. The pads are placed proximal to the painful area and the stimulation is directed at the afferent nerve endings. For patients with longstanding chronic pain, relief with a TENS unit may require several weeks of continuous stimulation. In certain cases, such as postoperative orthopedic pain or incisional pain after abdominal surgery, and even labor pain, [85] analgesia may begin with as little as 20 minutes of stimulation.

TENS units have been used with success in the treatment of pain arising from angina pectoris, post-laminectomy syndrome, postherpetic neuralgia and diabetic neuropathy. Another indication for TENS units is intractable localized itching [83], which may be a manifestation of neurogenic inflammation.

Specific high-frequency TENS therapy may act through the dynorphin system and the kappa receptors, which are less effectively antagonized by naloxone. High-frequency TENS may also cause release of substance P at spinal sites where it has antinociceptive effects [86].

**And in the End . . . Back to the Smoke Alarms**

In closing, one last brief reference to smoke alarms. I asked people whose alarms went off how they felt about these unpleasant episodes. They all told me the same thing. They said they felt “grateful” that they had functioning smoke alarm systems. I think that that is the way our patients should feel about having a well-balanced and functioning pain system. When we safely restore the balance to people with chronic pain, the most important thing that
we restore is not comfort or function, it is the feeling of being grateful for being alive.

References
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