

# How Pain Nerve Cells Act When *They* Are In Pain

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Pain is an experience common to everyone. And because everyone has experienced physical pain on some level, most people think they have a reasonable understanding of what pain is like for everyone else. However, when we're dealing with pain caused by nerve injury, such as central pain or peripheral neuropathy, the normal concept of pain is thrown out the window.

The sensations experienced in nerve pain are unlike anything else, ranging from the odd, "buzzing" sensation doctors call *paresthesia* that you might feel from a minor case of peripheral nerve damage, to the devastating complex, bizarre burning called *dysesthesia* that results from more severe nerve injury. Other types of pain that a patient with Central Pain or other nerve damage may feel are detailed at length in the Mnemonic of Central Pain section of this website. One thing common to all neuropathic pain is that there are no words sufficient to describe it, because the sensations are so different from anything experienced by a person without nerve damage.

The goal of this article is to describe what happens in the nervous system when severe pain occurs. When a nerve is damaged the nervous system can go haywire, using its chemicals and fibers in a way that causes pain to overwhelm every other aspect of a person's existence. According to one theory, when nerve damage occurs in a way that causes a person to lose *normal* sensation to part of the body, the nervous system might try to compensate. Using any resources it has available to learn what's going on in that area, it might even resort to depending on damaged pain nerves for tactile feedback. Whether or not that theory is accurate, the resulting pain can be raw agony.

In order to understand the processes involved in pain we need to discuss nerve fibers and

how they behave during pain. A nerve is a collection of many nerve cells, which are also called neurons. These nerve cells can be fibers up to a yard long, or they can be very short, such as some of the modifying neurons (interneurons) in the cord. Sometimes the vocabulary used in medical literature can be a little vague and "nerve" can mean either one nerve cell or many.

## Chemical Batteries in the Nervous System

The molecules that carry pain signals do not function unless they have a power source available. For the sake of simplicity we'll refer to that power as a battery. That battery comes in the form as a high-energy phosphate bond, which carries a negative charge. These batteries activate various chemicals in the body. As soon as molecules acquire a positive end and a negative high-energy phosphate bond end, there is a tendency for electrons to want to flow, which causes current, which is why we call them batteries.

A battery is really nothing more than a chemical container with negative and positive ends. When electrons flow from where there is an excess to where there is a deficit, that flow of electrons gives power. Sometimes the flow is of particles much bigger than electrons, but the principle still holds. If an atom is in a resting state and an electron is removed, that atom becomes positive, lacking one electron. An atom may also gain an electron, causing it to have a negative charge. The state of charge is called valence and an atom with a charge is called an ion. Atoms that move through the membrane of the neuron to propagate a nerve signal are ions. Their movement can generate voltage, or charge differences, and this difference is the basis of nerve signals, including pain signals.

Molecules in the body are usually inert (nonreactive) unless something, usually a kinase, phosphorylates them (attaches a high-

energy phosphate bond). The negative high-energy phosphate bond is taken from its supply carrier adenosine (a kind of delivery boy), and placed on the molecule that needs to be energized. The catalysts that accomplish this battery attachment are called kinases. Research by Ru-Rong Ji and Clifford Woolf indicates that mitogen-activated protein kinase is the master switch in Central Pain. MAPK initiates a process that begins to place high-energy phosphate bonds, or batteries, on all kinds of pain neurotransmitters, making pain nerves fire out of control. Such activity could explain why pain perceptions lose their normal characteristics and fire out of control together to create the unusual pain sensations in Central Pain.

This action is taking place in the spinal cord, where first order neurons from the body are relaying signal to the second order neurons within the cord, which then travel to the thalamus (or perhaps the submedial, if they serve emotional messaging). This process of overblown excitation is probably recreated in the thalamus in its turn, but little is known about it. Pain signals that occur in Central Pain can be measured in the thalamus. It was first measured in the cord by Ron Tasker and then found in the thalamus by Frederick Lenz. Little is known about the specific neurotransmitters that relay thalamic signals up to the conscious mind, or cortex, but they often go under the name, *thalamo-cortical relays*. That term, however, includes also fibers going back down to the thalamus. In this article, “upstream” means closer to the brain, and “upregulate” means excite or make more excitable. Pain neurons leading from the skin-level are called first order neurons. Neurons are referred to by higher numbers as they get closer to the brain. For example, marginal cells in the spine are one type of second order neuron.

Our focus here is what’s going on in the cord, between first order neurons and second order neurons, influenced by other neurons which occupy the cord, called interneurons, which excite or inhibit the frequency of firing, going from first order to second order neurons. It is more difficult to study neurons in the brain

than elsewhere in the body, so science has been more successful in discovering treatments for injury to peripheral nerves. Opioids, like morphine, act to quiet the pain signal in the cord, but Central Pain originates upstream of the opioid point of action in the cord, so it doesn’t stop Central Pain. Most people feel opioids act by sedating the patient, but do not actually stop the pain. Sometimes anticonvulsants are used as an alternative way to quiet the central nervous system and make Central Pain a little easier to bear, but there is no current treatment that is truly satisfactory.

Central Pain is driven by the thalamus and its connected structures, so don’t assume everything you read in this page may actually be part of Central Pain—it may apply only to peripheral nerve injury. The components of Central Pain and peripheral neuropathy can be difficult to distinguish and assign their specific role. Also, some believe that in at least some instances the effects and actions of Central Pain and peripheral neuropathy are inescapably intertwined.

To summarize, at the nerve endings in the skin, the chronic pain process is ignited by persistent production of excess inflammatory chemicals, like prostaglandins, which cause an acid pH. The irritated first order neuron sends its signal toward the cord along a long extension, called the axon, which goes clear to the dorsal region (back) of the cord. It enters the cord just beyond where the neuron cell body is located. The pain signal crosses to the other side of the cord, while being influenced by connections with nearby neurons, and then connects via a synapse (or gap which is bridged by chemicals) to a second order neuron. Signals in the second order neuron rise to the thalamus behind the eyes. The thalamus then forwards the pain signal through fibers that reach to the cortex, which results in conscious pain.

There are not only batteries (electrical voltage differences) in the synapses between nerves; there are also tiny “batteries” which carry the signal along the axon. The axon battery is created by an excess of sodium and chloride

(a chloride ion has borrowed an electron from sodium, so it is negative while the sodium makes fluid outside the cell positive), and an excess of potassium and large negative molecules inside the cell, making it negative. If electrically charged particles flow they can cause a current, which is exactly what happens when channels open in the cell membrane. The large organic molecules inside the cell have borrowed an electron from potassium making them negative. There are about seven positive ions just outside the cell membrane and about five negative ions. Inside the cell, there are about seven negative organic ions and about five positive ions—all ions are in motion and if the pores of the cell open the electrically charged ions will flow, generating a current and influencing the upstream pathway to perpetuate the signal. The inside of the cell is 60-90 millivolts more negative than the outside, measured at one point only, but there are so many points included in one square millimeter that the charge amounts to 12,000 volts per millimeter. That is a lot of power to be generated by mere chemicals. Since the membrane is only the thickness of 25 molecules of water, there is little distance across which the force of attraction must operate, but the cell membrane is a good insulator, so it is really the ion movement that performs the transmission. Most of the energy is expended by the ion pumps moving positively charged particles to the outside of the membrane although a lot of passive movement occurs because of the attraction between negative outside and positive inside. The inside is only slightly more acid than outside, but this small difference is extremely important, because the behavior of organic molecules is very dependent on the pH (outside/inside difference in hydrogen ions, which is about 9 millimoles of hydrogen atoms per cubic centimeter).

So you now know that the end of the first order axon, a long arm of the cell, reaches just below right the skin surface. If you were to travel along this axon to the cord, you would meet the cell body just outside the cord. On the other side of the cell body would be a

little more axon. Inside the cord, the message connects to other cells. At the near end of each axon from the skin is a small gap between it and the second order neuron, which is upstream (closer to the brain). The signal does not go across the gap directly, but by chemicals that are released into the gap, which then recreate a signal on the other side of the gap.

Making things more complicated, the cell body has the option of either forwarding the axon's signal into the cord or ignoring the signal. This decision by the cell body is determined by little fibers connecting to other cell bodies. The average cell body has thousands of these connections, about half are excitatory and about half are inhibitory of signal. So whether or not the near axon (end which enters the cord) actually carries pain signal is influenced by the connections that have already hit the cell body, which then decides the frequency of firing it will send to the near axon. Little globs or *vesicles* of excitatory chemicals are released from the near axon into the synaptic junction. The action of the kinases you hear so much about, such as the ones that turn on NMDA (a big bad chemical of pain) occurs on the other side of the gap beyond the first order axon. The genes in the second order neuron are influenced by the firing that reaches them to write (called *transcription*) for more pain causing proteins from these genes, or in other words to make more messenger RNA, which results in the manufacture (called *translation*) of pain causing proteins.

When the kinases attach batteries to the pain causing proteins, they are no longer silent. Very potent chemicals like NMDA initiate a powerful pain signal. The amino acid glutamate that enters the gap causes quick, short pain as it acts on short acting AMPA and kainite receptors in the second order neuron, while Substance P released from a vesicle acts on NK1 receptors in the second order neuron to cause persistent pain. Substance P can cause release of activated phospho-NMDA, the boogeyman of the pain system. As stated above, the attachment by kinases of high-energy phosphate bonds, or

batteries, to otherwise inert neurotransmitters is called “phosphorylation”. Even the boogeyman can’t get you unless its battery is installed, so the kinase pathway is an attractive target for those attempting to stop Central Pain. Because kinases also do lots of good things in the brain, such as permitting the recording of memories, current thinking is that safer treatments will be addressed at the ion channels in the cell membrane which allow action potentials (transmission of signal) to move along in the nerve cell. That is why everyone is watching Clifford Woolf, who discovered the first sodium channel found *only* in pain neurons. Hitting things confined to pain neurons is unlikely to interfere with brain function elsewhere. More of this research will follow, so be patient.

You remember that we said there are interneurons (in the zone crossing the cord) that act on the connection between first and second order neurons. These interneurons are mainly control devices coming down from the brain. Signals that come down from the brain are called *efferent*, while the signals carrying information to the brain are called *afferent*. We like efferent signals because they inhibit, but we don’t like afferent signals, because they excite our pain.

For general summary of what’s going on, you first have influence on the afferent signal by inflammatory chemicals bathing the nerve ending in the skin, modulation by connections between cell bodies in the swelling which contains them (dorsal root ganglion) just outside the cord, interneurons influencing the crossover by the near axon, and chemicals released from near axons, which may affect genetic expression in the second order neuron on the other side of the synaptic junction. Increase in genetic expression of chemicals produced in the second order neuron can create a tremendous upregulation of excitation in the pain process. This summarizes what is going on in regard to peripheral nerves and their signal. We do not know the set of chemicals or gene changes that take this pain process another step further, up through the thalamus into the cortex (conscious brain). Tarek Samad has

discovered interleukin-1-B (results in prostaglandins) in the thalamus with pain, so it would appear that these acid causing chemicals operate at every step to and including the thalamus.

It is worth mentioning that the axons of first order A-beta fibers are thick, insulated and rapidly tell about a very small area of skin, while C-fibers are thin, slow, have no insulation and tell about a much larger area of skin. If C-fibers get seriously and chronically irritated they can influence A-beta fibers entering the cord to send out signals to the normally quiet A-beta neighbors, so the whole neighborhood of A-betas is “buzzing” with pain. This is called “windup.”

A pain signal travels up an axon, kicked into action by what is called a *receptor potential* (generator) at the nerve ending at the skin. We call the current rushing up the axon an *action potential*. Potential means a difference in voltage. Doctors were using the word “potential” but battery makers preferred the word “voltage”. If the doctors had won, you would go to the store and ask for a 1.5 potential battery for your flashlight.

The action potential is accomplished by allowing positive sodium and other atoms to rush into the neuron, which makes electrical current flow and more or less upsets the next charged area up the line, like dominoes kicking each other over. Just as quick as the action potential passes, the cell pumps sodium out and potassium in, so there is a renewed voltage difference, and the potential to fire again is rapidly reestablished. It is amazing chemicals can act so swiftly. The little in the cell membrane that allow charged particles to move through the cell wall are called *ion channels*.

As stated earlier, Clifford Woolf has discovered an ion channel for sodium that is only present in pain nerves. It looks like a zig-zag path across the cell membrane. Obviously, it would be interesting to see the effect on pain if that ion channel could be blocked, since it might affect only pain and nothing else. It is called the SNS2 channel

and you will almost certainly be hearing more about it in the future.

There are voltage sensitive dyes that change color with charge, and in some animals, the nerves can be visualized and signal passing can be observed by changes in the dye color. Remember, a flashlight battery is 1.5 volts. A neuron action potential is only 0.1 volts, but remember there are many of these little tiny batteries adding up to BIG power. The combination of “little” discharges in an small electric eel can kill a horse or alligator, so don’t underestimate what abnormal pain signal from large areas of the body surface can do to the brain pain centers. People with Central Pain have said they are in torture. They weren’t exaggerating. Now you have some inkling why.

A capacitor is a device to store electrical charge and the cell membrane is a capacitor. It can store about one microfarad per square centimeter. This ability to store the electrical charge slows down conductance considerably in small nerve fibers.

Our pain system is configured to connect to our muscles to make them move away from pain. However, we don’t want to go around twitching with every insignificant bump, so a place was provided where integration of sensory inputs could occur. That place is called a synapse. It is a physical break, which is crossed by chemicals, which are themselves under control from higher brain centers. The chemical message across the synaptic junction travels at a mere 2mm per minute. Fortunately the gap is only about one-millionth of an inch, so even at slow speed the signal requires only about 0.6 milliseconds to cross. This delay of the synapse allows interneurons time to excite or inhibit the system and upregulate or downregulate the reactivity in sensory and muscle fibers. If there were no input at the synapse, every signal might cause a muscle twitch.

What is the function of the brain in all of this? It’s mainly to inhibit, or slow things down. We know the brain is primarily inhibitory, because if you remove the brain from a lab

animal you still get nerve transmission from the cord and nerves, and it is faster without the brain. The time for signal to pass from toe to the cord is about 8 milliseconds, and the time added to allow for all the all the synaptic junctions is about 9 milliseconds, depending on size and insulation of the nerve fiber. Two thirds of the axons in the body are unconscious nerves that regulate things like gland secretion and digestion. They are as small as about 0.0003 mm thick and they have no insulation.

The speedy pain fibers, the A-betas, are covered with myelin, and are as big as 0.022 mm. People with multiple sclerosis have lost some of this myelin, which can cause pain signals to occur in nearby neurons. Normally only the nerve ending can generate an action potential, but in axons with damaged myelin, uninjured neighbor neurons can begin to fire automatically. This is called “crossed afterdischarge” by its discoverer, Marshall Devor. It provides clues to how a damaged axon might set off a huge pain process, building up an amplifying circuit of nerve fibers reacting to excitatory chemicals that are released into an area through injury. If nerve injury is permanent, might it cause unending upregulation of genes that produce excitatory chemicals in pain nerves? We have something that on paper at least, and it looks like the possible mechanism behind Central Pain.

“Adaptation” means that responses can reach saturation. For example, if you turn the hot water up a bit on a cold day and step into a hot bath, it might feel too hot at first but in a short time, it feels okay. This means the receptor signal is falling back. You have reached saturation and the nerve doesn’t want to fire much anymore. If overproduced exciter chemicals drive the nerve ending receptor to fire at continuing high frequency, adaptation might never occur. Some touch receptors are never completely quiet, so adaptation would be permanent, but if something removed the chemical means of adaptation, the nerves would refuse to be quiet. It’s not hard to imagine how Central Pain patients might feel burning from touch, pressure, cramps, and tightness, if adaptation were abolished.

It is said that temperature receptors in the skin require a relatively large overall receptor potential. However, measurements indicate that once 10 millivolts has been reached, it is the *change* in receptor potential that matters, so a pain signal in injured nerves could come from a very small voltage change indeed. Thermoreceptors (specialized nerve endings for temperature), must develop 10 millivolts to generate any action potentials, but only generates 10.2 millivolts when a hot surface is touched. In other words, the generator potential only rises to around 10.2 millivolts. It is this tiny 0.2 millivolt difference that starts the action potential firing rapidly to generate a significant burning sensation.

The brain hears a lot of noise from sensory fibers all the time. It's astounding it can "hear" these very small voltage differences and know that it is a real signal and not just the "noise" of neurons just below the significant firing threshold. The state of readiness in sensory nerves, which drift over the firing threshold periodically, add up to a tremendous amount of noise that the brain must inhibit or ignore. Remember, in sensation most of the work of the brain is to inhibit or suppress signals. That is so you can think about only one thing at a time. The brain integrates all the many signals reaching the thalamus. Only when characteristics of a pain signal show a clear deviation from normal (one theory is that the brain has a template or pattern of normality against which to compare all sensory messages coming in) will the brain consciously generate a pain perception.

Pattern matching, or template comparison would be a highly sophisticated operation and susceptible to dysfunction. The chemical brew that churns up in synaptic junctions after nerve injury might be too much for the brain to inhibit; thus causing Central Pain. It is a paradox that incompletely injured nerves in sensory systems increase their signal powerfully, while injured nerves going to muscles carry less current. Still, this makes sense when looking at the alerting function of pain systems.

In a normal pain system "noise" is ignored by the brain, but how well the brain ignores "noise" in nerve injury is unknown. It is also unknown why adaptation fails to stop the burning pain of nerve injury. Perhaps adaptation does diminish it, but what is left is still so powerful that the burning continues. Somehow the brain is able to make very small increases into major signals. Theoretically, anything causing a change of 0.2 millivolts in a temperature receptor could result in a perception of burning in normal individuals, and if the system were sensitized through injury, a small change in voltage might well create an even greater perception of being burned.

Fluid associated with nerve injury includes acid materials (like arachidonic acid), and could theoretically act on C-fibers to create a generalized sense of burning. However, the finely placed, location specific A-betas are thought to be chemically insensitive, so the burning would come through the sparse C-fibers in nerve injury, and would not be well localized. Again, this is theoretical and unproven, but it could suggest why burning that is poorly localized could occur in Central Pain. The A-betas are probably damaged as well, since touch sensation is diminished, but A-beta fibers apparently don't respond to the chemical soup of nerve injury near the skin.

A highly potent generation of pain signals could, over time, burn out the control (dampening) signal in the dorsal cord and in the thalamus, so that relatively light signals could make a major impact. This would be like pouring salt into a wound, or in this case, like pouring excitatory proteins into a system which has already been made vulnerable to them by injury. The end point of that injury may simply be to reset the regulatory genes in pain neurons so that they produce too much kinase, which attaches batteries to every excitatory protein, without waiting properly for the control signal from the brain, to do so. The control center may have been burned out, and like pointing a camera element directly at the sun can burn a hole in the shutter, the "bursting" pain signals pour straight through.

Functional MRI shows metabolism (function) going on in the brain. Images of pain centers in the brain when nerve injury has occurred are inconsistent, even in the same individual. These imaging studies show anything from excessive metabolism, to normal metabolism, to shutdown in those areas of the brain. Perhaps the brain is damaged and is failing to regulate in its normal sense, giving in to adaptation, and then periodically tries unsuccessfully to bring things under control. Of course, “normal” brain metabolism in a system designed to actively inhibit, is highly abnormal if the brain ought to be powered up and doing its job of inhibiting pain signals. In Central Pain, pain centers appear confused, overwhelmed, and haphazard. Surgical removal of these centers does stop the central pain for about six months. However, then the nerves upstream regain function, but it is abnormal function since the Central pain returns, recreating the pain state. So, surgery is not felt to be an answer at this time.

A few brain surgeons feel differently and have very specialized approaches, but the pain world, which has been “burned” before, skeptically awaits positive confirmation that newer approaches actually work.

Most surgeons prefer to place electrodes in the malfunctioning brain areas and send a “buzz,” or blocking paresthesia signal, into the nerve in the hopes that it will override the pain signal coming through. This is said to benefit about 50% of patients who have it; the difficulty and number of necessary electrodes depending on the location and the size of the area of skin involved.

Only the cerebellum (the motor area of the brain) seems to send out a consistent fMRI image of “alertness to escape from pain” in Central Pain, and the studies done are few in number and performed only on lab animals with Central Pain. It is not clear that “alertness” alone is responsible for the bright signal in the cerebellum, but since the cerebellum controls muscle tone, that is the tentative conclusion. It is not known whether the reports of loss of muscle memory in Central Pain are due to blanking out of

muscle memory by an excess of signal in the cerebellum, by the underlying injury that caused the Central Pain, or some other factor.

One of the questions from Central Pain patients is why they feel the pain so intensely. Often, patients will describe a type of nerve proximity feature to their pain, such as the direct feeling one gets when a dentist touches a filling with a metal instrument. It is a complex sensation that some describe this feeling as metallic, others as cold, but it is a common feature of Central Pain. Perhaps a comparison could be made to heat. A person may tolerate 42 degrees Centigrade but at 45 degrees Centigrade there is pain. However, if a piece of wood is heated to 50 degrees, you can tolerate contact with it because wood is a poor conductor. The metallic/cold component of Central Pain suggests the brain is picking up on some very good conduction in the pain pathway. Regardless, this “nerve proximity” feature is sometimes called a “paradoxical component of cold” in the dysesthetic burning. In spite of that dysesthesia is typically described as a burning sensation, one person said they used the term “cold” because the sensation feels so well conducted, like touching a cold pipe in wintertime. Another said it was like “tin foil under her skin”. You can read more about this under the page on dysesthesia. We mention it here only to point out that conduction and stimulus are two different things.

Normal stimulation of pain nerves results in a rise in output of signal, but it may not run directly with the increase in stimulation. In fact, there are three ways the action potential may respond. These three are step, ramp, and oscillatory.

**Step:** In a pure step arrangement, if the stimulus goes up a certain amount, the response goes up a certain amount, only to fade over time from saturation due to adaptation.

**Ramp:** The ramp response is more linear with continual increases, rather than jumps in the nerve output.

**Oscillatory:** Oscillatory output in sensory nerves would occur when walking, as weight shifts back and forth from one dysesthetic foot to the other. If this system failed completely, you wouldn't be able to walk because you couldn't sense when your foot hit bottom.

The brain has a drive for survival. Your brain has an interest in sensation continuing, even if it is painful, because there are functions that require some sensation. The brain does not like to be shut out entirely from its environment, so it apparently recruits pain for information if it has to. It may even be withholding inhibition of which it is capable in order to maintain contact with the outside world.

Unfortunately, most pain fibers can't be tested for their output characteristics because the output occurs so close to the cell body that the results are unreliable, especially with thermal receptors. In Central Pain, nerves continue the sensation of burning after touch stimulus stops. In fact, the continual or spontaneous burning never stops, but evoked or elicited burning does. This suggests there may be outputs operating at two different levels, each with its own characteristics.

### **How the Action Potential is Generated**

The axon isn't a very good conductor because the signal generated fades out in less than a millimeter. However, the progressive re-creation of action potentials as described above maintains a current that can travel along the nerve. The frequency with which action potential spikes generate corresponds roughly with the degree of change in the current that is generating the volleys of action potentials in the first place. In small fibers, the action potential travels at about the speed of walking, 1.2 meters per second, or a little more than 2 miles per hour. Thick insulated fibers are about a hundred times faster. Because they have nodes, or gaps in the insulation, these nerves look like a string of sausages about 1 mm in length. In these, the voltage spikes "jump" from one node to the next.

Of course, the action potentials can follow closely on the heels of one another, up to about 50 per second potentially able to reach the near end of the small fibers with maximum stimulation. A-betas are faster. Imagine the result if a horse or giraffe stepped on a rock. Seconds would lapse before the animal could respond if only C-fibers were involved. Because the brain reads the *frequency* of action potentials, we have frequency modulation. You have heard of fm radio—well, this is much the same thing. Consequently in Central Pain, we will be concerned with things that can increase the frequency of firing. Although it oversimplifies, we can think of an action potential as sodium rushing in and potassium rushing out of the cell. Some of the rushing occurs because energy is expended by chemical pumps and the remainder of the rushing occurs because of the electrical voltage pull due to different potential inside and outside the cell.

You may have heard that people only use 95% of their nerve and brain cells. This is untrue because signal is always present in nerves, even those "at rest". Most of you know that atoms and molecules do not remain still so long as there is any heat at all in the environment. This is called the kinetic theory of heat. The ions responsible for action potentials move around a lot because of the kinetic energy of heat. This makes for a large amount of noise in the pain system. The normal brain sorts out the noise by performing its inhibition functions. We do not know if the brain could become so poor at inhibition (GABAergic system) or so exquisitely sensitive (glutamergic system) that even a level of noise would be read as pain. It is not impossible.

An unmyelinated axon causes the voltage to drop to 37% of its original strength in only 0.15 mm, where the voltage is unusable. This is called the *length constant*. The length constant varies by the square root of the axon diameter, so that the largest myelinated axon has a length constant of 0.33 mm, or twice as long as the small unmyelinated fibers. The material in the middle of the axon (called

axoplasm) is *very* important to the rate of transmission. Cellular fluid is not a good conductor, but if something altered its chemistry, conductance would change also. If the axoplasm were copper, the length constant would be nine feet. In natural systems, the action potential either fires or it doesn't and the intensity of pain is in the frequency, not the strength of the action potential.

As a theoretical picture, suppose the receptor in a nerve initiates a generator potential whenever the stimulus causes an output of 10 millivolts. When any section of the axonal membrane senses 8mv, then it generates an action potential spike (electrical current from ions rushing across the cell membrane) of 100 millivolts. The intensity would not be in the strength of the action potential, but in how many times per minute the action potential fires. This again, is frequency modulation. Suppose that the nerve fires ten times per minute if the generator potential is 10 millivolts, but at 30 millivolts, let's say it fires fifty times per minute. A tripling of the generator current has quintupled the firing frequency. This means if a stimulus is doubled, the response in the pain nerve would likely more than double. If something changed the chemical content inside the receptor ending of the nerve, it might be more or less prone to more rapid firing. This, unfortunately, has not been studied in nerve injury pain, but the work should be forthcoming.

Much work has been done on chemicals that irritate nerve endings and sensitize them in the external environment, but we don't know much yet about those big organic molecules that reside in the nerve or what they really do to conductance. Some receptors are much more noisy than others. If there is so much noise, how come more accidental firings don't occur? The answer is that there are millions of action potentials firing in a second and errors mostly balance each other out. The higher the requirement for voltage a receptor has to set off a generator signal, the less noise there is. A highly irritable, low voltage receptor would be most likely to start introducing accidents into the pain system

because of the large amounts of noise. Again, we do not know what the consequence of nerve injury is on generator voltages.

### **The Significance of Sodium**

The opening and closing of channels is affected by the jostling of atoms due to kinetic heat and it may be that the acidity inside the cell plays a role as well. Kinases may activate channel proteins. Sodium usually enters the cell passively without expenditure of energy but it requires an active pump to be moved back out into the fluid outside the cell. Channels are involved in these actions, so they are important in understanding pain generation. Action potential spikes don't usually occur at the same interval because of noise canceling some out and adding to others. The interval might be five times longer than the last action potential, but the brain averages them all out over a second's time. Again, anything increasing the necessary voltage for a given receptor will decrease noise and make firing more regular. We do not know how the brain reacts to highly irregular spacing of action potentials when the generator potential drops. Perhaps there is an increase in sensitizing chemicals that attempts to make firing more regular, creating a paradox of a damaged nerve stimulating release of excitatory chemicals.

Why should we care about Clifford Woolf's work on sodium channels? We have already discussed how sodium is drawn into cells passively by negatively charged organic ions inside the cell, but then pumped out by the sodium pump. If the small diameter or unmyelinated fibers are considered, the number of Na ions flowing in with an action potential is about a 16% change in the number of sodium ions inside the cell. This means that with the sodium pump going full force, a new action potential will require an interval so that small fibers cannot fire faster than 50 action potentials per second. In large myelinated fibers, with their much greater reservoir, the percentage change in sodium ions is not very significant, and frequency of firing could be much, much faster. This would suggest that the rapid bursting firing in

Central Pain has its origin in larger diameter fibers. However, those larger fibers are sensitized by small C-fibers so sodium channels are still important. Yet, for the really wicked evoked pain, the big A-betas probably play a role, since the pain can be massive. The link between C-fiber output and A-beta output, or their equivalents, may be subject to more thoroughgoing regulation in the higher brain centers, since evoked pain from peripheral nerve injury is instantaneous, but time is required for temporal summation before evocation of pain from central origin occurs. In this respect temporal summation is a merciful event, since severe Central Pain is so agonizing, but it provides some time for a person to move away from a stimulus before evocation occurs.

Myelinated axons have nodes at intervals where the action potential is regenerated. These nodes have no myelin, so the flow of ions can regenerate a spike in voltage to travel to the next node, at which point a new ion flow generates a new voltage spike. This process continues all along the axon. The time to jump from node to node is about 17 microseconds, regardless of the diameter of the fiber. Once the new node is reached, the action potential is regenerated and propagated at full strength without loss of amplitude.

One of the ways to measure the diameter of an axon is to measure its resistance in Ohms. A known resistance formula gives the value for the diameter of the fiber. The thicker fiber has less resistance. If an action potential hits a defective portion in an axon, it may still be able to generate another 100 millivolt action potential a little further down the axon so long as the millivoltage does not drop to a level too weak (perhaps less than 8mv) to generate a new 100 millivolt spike, but the speed of transmission past the injury may be reduced by a factor of ten or more. In general, small fibers cannot bridge a damaged area longer than 0.3mm, and larger fibers cannot bridge more than 0.6 mm. In myelinated (insulated) fibers the signal can bridge a gap of 0.9 mm. Flow of an action potential toward the brain in pain cells is called *orthodromic*, but the same axon can conduct equally

rapidly away from the brain, which is called *antidromic*. The same terms are used for movement of chemicals from the cell body either up or down the axon, but this is not the same thing as conduction of an action potential generated by ion flow. Dr. Garcia-Anaveros has discovered specific pain-stimulated chemicals that move down the axon but not up.

The action potential in myelinated fibers doesn't look so much like a series of spikes, but more like a zig-zag line jerking up and down across the tracing, but remaining more or less at the same average level. This is because by the time the action potential starts to fall, it has jumped to the next node, raising the voltage again. (This has been compared to a watching a point at the tip of a bird's wing as it rises up and down, but moves forward). Thus, really major injury stops all conduction and lesser injuries merely slow it. This raises the interesting question in nerve injury of whether the delay required for evocation of burning pain (termed *temporal summation*) might represent a signal which is being slowed by sites of injury and therefore taking more time to elicit heightened pain.

### Summary

Now is a good time to review what happens in Central Pain.

- At the skin there is *irritation*
- In the cord there is *amplification*
- In the brain there is *feature extraction and interpretation* (integration)

Unfortunately, doctors can confuse these three steps. That is why pain clinics may grow frustrated when something shown to work for peripheral nerve injury does nothing to help a Central Pain patient. The clinician may be giving a drug that avoids irritation, or even amplification, but it may have no effect on the integration of signals in the thalamus, which causes the brain to mistake the signal's character and generate a pain message. If we assume that lateral inhibition occurs at each of the three stages; irritation, amplification, and integration, then we see how the brain

derives so much information so quickly. But, if lateral inhibition failed in an injured neuron, this signal would also be less clear and perhaps the sensation would also be harder to recognize.

Well, as if your condition weren't bad enough, you now have to be bothered by trying to understand it. The purpose of trying to understand is to suggest to you that research money is needed and that scientists already know what needs to be evaluated, or at least enough to get a good start. If we make our condition clear to physicians, they will be more curious about stage three, the integration by the thalamus and cortex, which is all important in Central Pain.

Although much of this article will be beyond the reach of the layperson, it gives you something to read on a quiet evening and mainly, it lets you know that if you get Congress to appropriate more money for the NIH to study basic pain mechanisms, we *will* find medications to bring the pain message under control and defeat Central Pain.