UNDERSTANDING PAIN
A SCIENTIST'S PERSPECTIVE

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Introduction

At eight months, Ashlyn Blocker's parents brought her to an ophthalmologist for what they suspected was a case of pinkeye. What the doctor found was a severe corneal abrasion. He was startled, not by the injury, which wasn't uncommon, but by Ashlyn's behavior. An abrasion of this type would normally cause excruciating pain, but the child showed no signs of distress.

Ashlyn was diagnosed with a rare condition called *congenital insensitivity to pain* (CIP). This is a genetic disorder in which an individual is born without the ability to feel pain. Ashlyn's case is described at length in a 2012 article by Justin Heckert in the New York Times Magazine, *The Hazards of Growing Up Painlessly*[1]. In that article, Dr. Roland Staud, who worked with Ashlyn and her family, is quoted as saying, "Pain is a gift, and she doesn't have it."

I suspect that many of you reading this book may disagree with Dr. Staud. Sufferers are likely to see pain as more a curse than a gift. Of course, we know what Dr. Staud means here. The perception of pain informs us that something is wrong with the body. It allows us to take appropriate action.

Although unpleasant, the experience of pain offers an evolutionary advantage. The Neanderthal who sprained his ankle was forced by the pain to stop hunting for a while. This prevented further damage to the joint and allowed the injury time to heal. Had the pain not caused the man to rest, he might have continued to hunt until the foot became nonfunctional. The man's experience of pain allowed him to survive and continue to produce offspring.

Today, many causes of pain can be treated. That's the 'gift' part of pain. The body signals that we have pain, and we treat the underlying problem. Unfortunately, some conditions are chronic. The pain continues long after we've gotten the message that

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1 https://www.nytimes.com/2012/11/18/magazine/ashlyn-blocker-feels-no-pain.html

something is wrong. If you have back pain caused by tumors along the spine that have metastasized, experiencing that pain likely serves little purpose. You have an incurable condition.

Further, the nervous system itself can malfunction, causing it to generate false notifications of injury. We see this in amputees who experience phantom limb pain. A woman who loses an arm may continue to feel pain in that arm because a neuroma, a collection of disorganized nerve fibers, forms at the point where the nerve was severed. The neuroma sends signals that the brain falsely interprets as an injury to a non-existent limb.

Whether pain is associated with a problem that can't be fixed or is the result of bogus signals generated by the nervous system, the 'gift' becomes counterproductive. We'd like to have some way to turn off the pain.

One option is opiates. This may be the *only* option for some chronic pain sufferers. Unfortunately, the effect of opiates is systemic, so a person may lose the ability to think clearly. Still, for the chronic pain sufferer, this may be a reasonable solution. In some cases, pain is so extreme that opiates are ineffective. The pain of some terminal cancer patients is relieved by cutting the spinal cord, resulting in a significant loss of function.

It's fair to say the the holy grail for the treatment of pain would be an intervention that allows pain to be selectively switched off when the underlying cause is known and the experience of pain is no longer useful. We aren't there yet, but the material in this book may allow you to visualize how this might be accomplished in the future.

As often happens, effective treatments lag the results of basic research. There is reason to believe, however, that in the future, our understanding of the mechanisms of pain will lead to far more specific and effective methods of pain control than are currently available.

Fair warning, some of the material presented in this book may be challenging. The mechanisms associated with pain signaling and interpretation can be complex. I've tried to simplify the explanations as much as possible without losing important information. I hope I've found the right balance. Still, there may be places where your brain might burn a bit. I urge you to stick with it. If you're already suffering from chronic pain, you can probably endure just a bit more, particularly if it helps you understand the nature of pain.

This is *not* a book about pain management. Thousands of books have been published on that subject and there is no reason to add another. This is a book about how pain works. It is intended to be read by the lay person who wants to understand the fundamental mechanisms of pain.

Why do you need this knowledge?

If you're suffering from chronic pain, you will do just about anything to make that pain stop. You've probably been to pain management specialists and, chances are, you haven't been particularly satisfied with the results. You've scoured the Internet for ideas, but maybe tai chi and medicinal mushrooms didn't help either.

The search for a fix to pain can be frustrating. Having knowledge about pain can allow you to better communicate with your doctors. It can help you think more critically about ideas you encounter on the Internet or to make more informed decisions about taking medications or undergoing surgery. This knowledge may not fix your pain, but it may relieve the frustration of not understanding your pain.

What are my qualifications to write a book about pain?

I'm not a doctor. In fact, I'm a patient. I was motivated to study pain because I suffer from chronic pain. In order to effectively participate in my own treatment, I found that I needed to understand the scientific basis of pain. I hope to communicate to you what I learned, from a medical layman's point of view.

I have always enjoyed understanding how things work, whether it's an automobile engine, an old typewriter, or the grammatical rules of a language. I hope that you find pleasure in learning about pain, but, above all, I hope this knowledge helps in some way to alleviate your pain.

Chapter 1

Wiring of the Nervous System

Recall the last time you stubbed your toe. The pain pattern that you experienced is very specific, and maybe a bit surprising. Perhaps you've never thought about it.

As soon as your toe encounters the offending object, maybe a chair leg, you feel an immediate sharp pain localized to the site of the impact. An expletive escapes your lips. This initial pain subsides, but you prepare yourself because you know from experience that a second wave of pain is on the way. That second wave inevitably arrives a second or two later. This is a dull, aching, burning pain, less localized than the first. Your foot throbs. You emit a groan of annoyance. How could you have been so stupid? The chair leg was right there in plain sight.

There is an explanation for the two distinct waves of pain, but it requires some understanding of how pain is signaled within our bodies.

Please note that the .pdf appendix to this audiobook contains a number of figures that will aid the reader in understanding the path of pain signaling. The reader is urged to refer to these figures.

The human body is usually described as being organized into organ systems — groups of organs that work together to perform major functions; for example, the circulatory system, the respiratory system, and the digestive system. Fortunately, *all*[2] activities associated with our experience of pain occur within a single system, the *nervous system*. The human nervous system, like that of all mammals, is divided into two parts, the central nervous system

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[2] Some biochemical processes involved in the detection of pain may happen just outside the boundary of the peripheral nervous system. This is a somewhat theoretical argument. For all practical purposes, pain happens *within* the nervous system.

(CNS) and the peripheral nervous system (PNS). The central nervous system consists of the brain and the spinal cord while the peripheral nervous system includes nerves, nerve fibers, and sensory receptors distributed throughout the body(, illustrated by blue lines in the figure[3] at the left).

At the highest level, we can think of the peripheral nervous system as a collection of 'wires' that carry signals from sensory receptors located throughout the body to the central nervous system for processing. Signals sent in this direction are called *afferent* signals.

In the other direction, the central nervous system sends signals carried via the peripheral nervous system for distribution to muscles, glands, and organs. Signals sent in this direction are called *efferent* signals. For purposes of discussing pain, we can ignore these efferent signals. Signals related to pain travel *only* in the direction from pain receptors to the brain. This further simplifies our task of learning about pain.

Pain receptors are embedded in our skin, joints, muscle, and organs. They are present anywhere that a stimulus can cause us to feel pain, except where pain is caused by a fault in the nervous system itself.

A pain receptor converts a harmful, or potentially harmful, stimulus into one or more pain signals sent along a nerve fiber towards the brain. Pain signals may be processed to some degree in transit to the brain, but all activities associated with our *perception* of pain take place within the brain. So, for our purposes, pain signals travel from pain receptors to the brain.

A pain signal travels via a sequence of exactly three nerve fibers. These are called the primary, secondary, and tertiary nerve fibers.

The primary nerve fiber carries signals from a pain receptor to a structure inside the spinal cord called the *dorsal horn*. The dorsal

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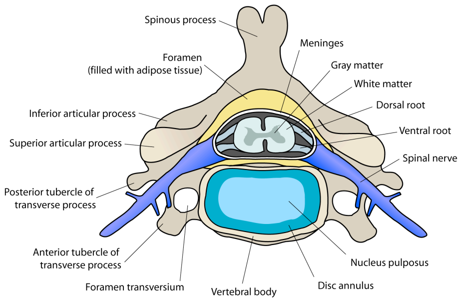
3 https://commons.wikimedia.org/wiki/File:Nervous_system_diagram.png
Figure placed in the public domain by the artist Persian Poet Gal.



horn is a column of material within the spinal cord composed of *gray matter*. Think of gray matter as 'intelligent' material.

The figure at the left[4] shows a cross-section of the spine. The dorsal horn lies within the 'butterfly shaped' feature labeled 'gray matter'.

In the magnified view at the right, the dorsal horn can be identified as the cross-hatched area of the gray matter. Since we are looking down along the spine in this cross-section, the dorsal horn is located towards the back of the spinal cord.

The dorsal horn collects signals received on multiple primary nerve fibers and sends new signals 'summarizing' the received information on a secondary fiber. This is why it's often difficult for us to pinpoint the exact location of pain. Some information from individual receptors is lost. This summarization reduces the number of signals that must be received and processed by the brain. This activity requires 'intelligence' and that is the role of the gray matter.

Some of you reading this book will be familiar with the structure of the spine because you have experienced pain resulting from disc degeneration or other structural problems associated with the spine. The spine is composed of bones called vertebrae separated by rubbery cushions called discs. The discs provide both stability and flexibility to the spine. The individual vertebrae are identified by letter and number combinations as shown in the figure at the

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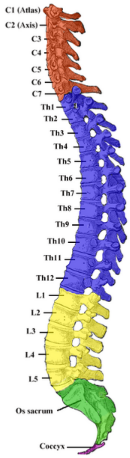
[4]https://www.wikidoc.org/index.php?title=File:Cervical_vertebra_english.png Author: Alexandra Almonacid E.

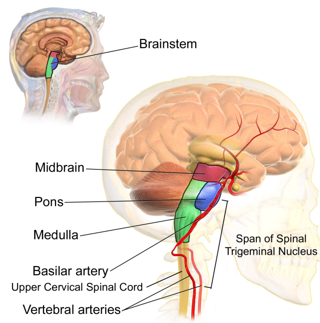
left[5].



The spinal cord is located inside the spine. It extends from C1, at the top of the figure to L1 or L2, lower in the figure, depending on individual anatomy. Thus, the primary nerve fiber can enter the dorsal horn at any of roughly 20 or 21 different vertebrae along the length of the spine.

The secondary nerve fiber crosses to the opposite side of the spinal cord before traveling up the cord towards the brain. As a result, pain stimuli occurring on the right side of the body are processed by the left side of the brain.

Not all primary nerve fibers carry signals to the dorsal horn. Primary nerve fibers originating from pain receptors in the head do not terminate in the dorsal horn, but in a structure called the *spinal trigeminal nucleus* which is located in the brain stem. This structure is another column of gray matter that functions in a manner similar to the dorsal horn. As shown in the figure on the left[6], the spinal trigeminal nucleus extends from the mid-pons, through the medulla, and as far down as C2 or C3 in the cervical spinal cord. The spinal trigeminal nucleus



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[5] https://en.wikipedia.org/wiki/Spinal_column#/media/File:Gray_111_-_Vertebral_column-coloured.png From Henry Gray 1858 Public Domain Note that thoracic vertebrae are labeled Th1 - Th13. Today these are more often labeled T1 - T13.

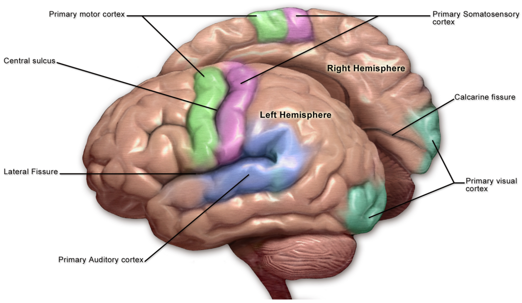
[6] By BruceBlaus. Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. - Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=28086431 Labels were added to identify the spinal trigeminal nucleus and the upper spinal cord.

receives, summarizes, and relays pain signals in the same manner as the dorsal horn.

For purposes of understanding pain signaling, the reader can view that the dorsal horn and the spinal trigeminal nucleus form one continuous sensory processing system aligned with the spine and brain stem. From the viewpoint of anatomists and clinicians these two structures are distinct, but for learning purposes, it is reasonable to view the two as forming a single continuous structure. As a convenience, let's call it the *spinal processing system*, although it continues upward into the brain stem.

Without regard to their origin, *all* secondary nerve fibers terminate at a structure deep in the brain called the thalamus, as indicated by the arrow in the figure at the right[7].

Like the dorsal horn and the spinal trigeminal nucleus, the thalamus is composed primarily of gray matter, and it performs the functions of receiving, summarizing, and sending signals from secondary to tertiary nerve fibers.



Tertiary nerve fibers carry signals the relatively short distance from the thalamus to the cerebral cortex, shown in the figure at the left. While the cortex appears quite large in the figure, it is only 2-4 mm thick. It can be visualized as a thin covering for structures that lie deeper in the brain. The surface of the cortex is

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[7] https://commons.wikimedia.org/wiki/File:Brain_chrischan_thalamus.jpg#Licensing Author: Axel Boldt

heavily folded. If unfolded, the surface area would be about 2000 cm^2 or about 4 sheets of newspaper.

The brain is divided into the *hemispheres*. A structure in each hemisphere called the *primary somatosensory cortex* is the main site of pain signal processing in the brain.

To review, primary nerve fibers carry signals from pain receptors to what we are calling the spinal processing system where signals are summarized and sent on secondary nerve fibers. Secondary nerve fibers carry signals to the thalamus where they are summarized and sent on tertiary nerve fibers. Tertiary nerve fibers terminate in the cortex pain processing occurs.

We need only add one more detail. There are two types of primary nerve fibers, slow and fast.

Aδ (A-delta) fibers carry signals relatively quickly, at a rate of about 5–40 meters/second. These signals convey a perception of pain that is sharp and localized. C fibers carry signals more slowly, at a rate of about 0.5–2 meters/second. These signals convey a perception of pain that is dull, aching, or burning.

Pain signals generated at the toe enter the dorsal horn at the S1 level of the spine. The length of primary nerve fiber from toe to S1 is roughly 1 meter in an adult human. Thus, a signal traveling on an Aδ fiber can take anywhere from 0.025 - 0.2 seconds to reach the dorsal horn. A signal traveling on a C fiber requires 0.5 - 2.0 seconds.

This is the explanation for the two waves of pain experienced when you stub your toe. Pain signals are transmitted on both Aδ and C primary fibers. Signals associated with the Aδ fiber arrive more quickly at the brain than those associated with C fibers. So, we first experience the sharp and localized pain associated with the Aδ fiber followed by the dull, aching, or burning pain associated with the C fiber.

If you suffer from chronic pain, it may be helpful to understand the path taken by signals traveling from receptors to brain. At the crudest level, pain can be blocked by cutting nerve fibers in order to disrupt the path of pain signals.

Some people suffer from a painful foot condition called a Morton’s neuroma. A neuroma is a tangle of nerve fibers that sends ‘false’ pain signals to the brain. When conservative treatments fail, the nerve fibers can be cut by a surgeon, preventing pain signals from reaching the brain. Unfortunately, it isn’t possible to *selectively* cut only the fibers carrying pain signals. As a result, the patient undergoing this treatment will lose sensation in a small portion of the foot. Sufferers are generally happy to trade some numbness for relief from the severe pain of a neuroma.

But, cutting nerve fibers is an extreme and often permanent measure. It would be better have a method of disrupting pain signals without cutting the fiber. This is exactly what happens when local anesthetics like lidocaine or novocaine are administered.

Of course, local anesthetics are not generally a good solution for chronic pain as their effect is temporary, and, like cutting the nerve, *all* signals are disrupted, so pain relief is accompanied by a loss of sensation and motor function.

Ideally, we would like to have a method of preventing pain signals from reaching to the brain without disrupting other types of signals. Further, we want this treatment to be effective until the cause of the pain has been eliminated and to be reversible so that normal function of the nerve fibers can be restored.

To understand how local anesthetics work and how more selective methods of pain control might be implemented in the future, it is necessary to drill deeper into what nerve fibers are and how exactly they carry pain signals.