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Pain is a complex experience that affects millions globally, impacting quality of life and daily functioning. Understanding its mechanisms can lead to effective treatments. Recent research has illuminated the intricate processes involved in pain perception, highlighting key molecular players and pathways.These discoveries underscore the importance of examining both the peripheral and central components of the nervous system to understand how pain signals are generated, transmitted, and perceived by the brain. Classification Of PainPain is categorized based on its origin and underlying mechanisms, aiding in tailoring treatment strategies. The primary types include nociceptive, neuropathic, and visceral pain, each with distinct characteristics and implications for therapy.NociceptiveNociceptive pain arises from tissue damage or inflammation, activating specialized sensory neurons called nociceptors. These respond to mechanical, thermal, or chemical stimuli, transmitting signals to the central nervous system. A classic example is the acute pain from a cut or burn. Nociceptive pain is often protective, alerting individuals to potential harm and promoting healing. Management typically involves NSAIDs or opioids, targeting inflammatory processes or sensory pathways. Understanding these pathways is crucial for developing interventions that alleviate pain without significant side effects.NeuropathicNeuropathic pain results from damage or dysfunction within the nervous system. Unlike nociceptive pain, it tends to be chronic and can persist long after the initial injury. Conditions like diabetic neuropathy, postherpetic neuralgia, and phantom limb pain are examples. Aberrant neural activity and maladaptive plasticity play roles in its development. Treatments may include anticonvulsants and antidepressants, which modulate neuronal excitability and neurotransmitter levels. The complexity of neuropathic pain necessitates a multifaceted approach, combining pharmacological treatments with physical therapy and psychological support.VisceralVisceral pain originates from internal organs and is often associated with conditions like irritable bowel syndrome or kidney stones. It is typically diffuse and poorly localized, complicating diagnosis and management. Unlike somatic pain, visceral pain can be referred to other areas of the body. Research suggests that visceral pain involves unique pathways, with sensory neurons responding to mechanical stretching and inflammation of organ walls. Treatment often involves addressing the underlying condition and may include antispasmodics or lithotripsy. A holistic approach, including medical and behavioral interventions, is essential for improving patient outcomes. Peripheral NociceptionPeripheral nociception is the initial step in pain perception, where nociceptors detect harmful stimuli. These nerve endings, located throughout the body, convert noxious stimuli into electrical signals. Receptors like TRP channels detect temperature changes and noxious chemicals, illustrating the molecular mechanisms at play. Once activated, nociceptors transmit impulses through peripheral nerves to the spinal cord. This involves neurotransmitters and ion channels, including sodium and calcium channels, facilitating action potential propagation. Modulation of these channels can influence pain perception, offering therapeutic targets. Peripheral sensitization occurs when nociceptors become hyper-responsive following tissue injury or inflammation, often mediated by inflammatory mediators like prostaglandins and cytokines. This highlights the importance of targeting inflammatory pathways to improve pain outcomes. Neurotransmission In The Spinal CordThe spinal cord serves as a relay center for pain signals from peripheral nociceptors to the brain. When impulses reach the dorsal horn, they trigger neurochemical events that facilitate their journey upwards. Neurotransmitters such as glutamate and substance P are released, binding to receptors like NMDA and AMPA, triggering depolarization and pain signal propagation. This synaptic transmission is modulated by excitatory and inhibitory influences, which fine-tune pain signals. Inhibitory neurotransmitters like GABA and glycine dampen excitatory inputs, acting as a brake on the flow of painful stimuli. Dysregulation in this balance can lead to heightened pain sensitivity. Interneurons in the spinal cord add complexity to pain modulation, influencing how pain is perceived. Neuromodulators such as serotonin and norepinephrine, released from descending pathways, further modulate this process. Central SensitizationCentral sensitization represents a shift in how the nervous system processes pain, leading to an amplified response to stimuli. This occurs when repeated or intense nociceptive inputs result in hyperexcitability of neurons in the dorsal horn and beyond. As neurons become more responsive, even non-noxious stimuli can trigger pain, a hallmark of conditions like fibromyalgia. The processes underlying central sensitization involve long-lasting synaptic changes, similar to those in learning and memory, where increased receptor activity and signaling pathways result in sustained neuronal activation. Molecular underpinnings include the upregulation of NMDA receptors and involvement of intracellular messengers like calcium ions and protein kinases. Key Molecular MediatorsPain transmission and perception involve molecular mediators that orchestrate complex signaling pathways. Neuropeptides and cytokines modulate pain sensitivity and inflammatory responses. Neuropeptides like substance P and CGRP amplify pain signals. Cytokines like TNF-alpha and IL-1 promote inflammatory states, sensitizing nociceptors and contributing to chronic pain. Ion channels, specifically voltage-gated sodium and TRP channels, regulate nociceptive neuron excitability, influencing action potential propagation. Targeting these channels has shown promise in reducing pain sensitivity, highlighting their therapeutic potential. Glial Cell InvolvementGlial cells, once seen as mere support cells, are now recognized as active participants in pain modulation. Microglia and astrocytes respond to neuronal activity and injury by releasing signaling molecules that influence pain pathways. Microglia, the resident immune cells of the central nervous system, release pro-inflammatory cytokines and chemokines, contributing to neuropathic pain. Inhibiting microglial activation can alleviate pain symptoms. Astrocytes regulate the extracellular environment, modulate neurotransmitter uptake, and release gliotransmitters affecting synaptic transmission. In chronic pain, astrocytes undergo reactive changes that exacerbate central sensitization. Targeting glial activity could provide novel therapeutic avenues for pain relief.Somatosensory Processing In The BrainOnce pain signals reach the brain, somatosensory processing integrates sensory information to form the perception of pain. The thalamus acts as a relay station, directing signals to cortical areas involved in localization and intensity assessment of pain. These regions distinguish between stimuli, contributing to the conscious experience of pain. Studies have shown altered activation patterns in these areas in chronic pain individuals. Beyond the sensory cortices, regions like the anterior cingulate cortex and insula are involved in the emotional components of pain, highlighting its multidimensional nature. The descending pain modulatory system, involving neurotransmitters like serotonin and norepinephrine, influences pain processing by exerting control over spinal cord neurons. Understanding how the brain processes and modulates pain is fundamental to developing therapies that address both the sensory and emotional dimensions of pain. Pain is a universal human experience, one that is protective at its core: Acute pain warns us of harm and prevents us from damaging our bodies, or limits that damage. We experience pain as unpleasant, and it generally signals us to move away from a dangerous situation or stimuli. Acute pain often disappears fairly quickly once were safe.But acute pain doesnt always resolve as expected, especially if its part of a disease process or begins with an injury that isnt treated appropriately and swiftly. An estimated 21% of the U.S. population51 million peoplesuffered from chronic pain in 2021, according to the Centers for Disease Control and Prevention (CDC). And, that number may have increased during the pandemic.Chronic pain is one of the most common reasons U.S. adults seek medical treatment. The lack of adequate medical treatment for chronic pain is also a catalyst that fuels the ongoing opioid epidemic, a massive increase in addiction to prescription or illegal opioids and the cause of more than 100,000 overdose deaths in 2021, according to the CDC.Researchers are working hard to understand the complex mechanisms that underlie our experience of pain. According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. There are three types of pain classified by cause.The pain you feel when you stub your toe or put your hand on a hot pan is called nociceptive pain. A sensory neuronor nociceptortransmits an electrical impulse to the spinal cord and then to the brain, where it is experienced as pain.Inflammatory pain results from infection or tissue injury, leading to activation of the immune system. The body produces proinflammatory mediator molecules that include cytokines, chemokines, nerve growth factors and more. Both of these types of pain are protective.The third type, pathological pain, is not protective and often results from peripheral nerve damage. In some cases of neuropathy, nerves begin to fire spontaneously, leading to pain sensation in the absence of a stimulus. In other forms of dysfunctional pain after nerve injury, the central nervous system relays pain messages to the brain, regardless of input from peripheral nerves, says Bradley Taylor, PhD, professor of anesthesiology at the University of Pittsburgh.One thing that would help would be to find a biomarker for chronic pain. If you want to treat, you need an endpoint that you can target.Allan Basbaum, PhDOur experience of pain is often described as made up of two components, Taylor says. One is a sensory component where the noxious stimulusanything from a bee sting to hitting your elbow on a doorjambactivates nociceptors in the skin. Or, if the stimulus comes from inside the body, receptors within the organ or area of injury are activated, leading to electrical impulses that travel first to the spinal cord and then up to the brain.The spinal cord isnt a mere relay station for the electrical input. Really, theres a lot going on in the spinal cord before it sends the brain signals that are rich in information, Taylor explains.The second component of pain is affective and cognitive in nature, where the brain experiences the sensation of pain as something unpleasant, a form of suffering. While this experience is generated in the brain, its influenced by the specific nature of the message it receives from the spinal cord, according to Steve Prescott, MD, PhD, professor at the Hospital for Sick Children and University of Toronto in Canada. Pain is a really multidimensional experience, and while your experience of the emotional component of it is dependent on cortical processing, its typically triggered by sensory input from the periphery, he says.Chronic pain: a central nervous system gone awryAccording to the World Health Organizations International Classification of Diseases, chronic pain is pain that lasts more than three months. Our pain systems become sensitized for days to weeks as we heal from an injury. Theres inflammation around the tissues and they experience pain from even light touch or movement, Taylor says.Sometimes those sensitization processes dont go away and the person is in a state of chronic pain hypersensitivity. Some chronic pain sufferers experience pain even in the absence of touch or movement, Taylor adds. The induction of pain by a normally innocuous stimulus is the major problem that people who have chronic pain experience.When pain persists after an injury or infection has healed, changes in the central nervous system may have occurred. Its somewhat controversial, but Im a firm believer that chronic pain can exist completely in the central nervous system, Taylor says. In these cases, pain is no longer driven by nerves at the site of the initial injury, but instead by pathological changes in the brain or spinal cord.I believe that the pain experience is governed in a very homeostatic fashion, Taylor says. There are excitatory systems that drive the initial response to pain and pain sensitivity, and there are very powerful endogenous inhibitory systems within the body that inhibit the pain experience. These work together as a rheostat. If inhibitory systems function properly, then pain should resolve. In my laboratory, our overarching concept is that chronic pain pathology involves not only a foot stuck on the accelerator, but also a dysfunction with the brakethe inhibitory system.Allan Basbaum, PhD, professor and chair of anatomy at the University of California, San Francisco, agrees. He compares chronic painat least that produced after nerve injuryto epilepsy, a disease process that involves a loss of inhibition in the cortex, which manifests as seizures. In neuropathic pain, comparable changes occur, he says. Theres loss of inhibition at different levels, particularly in the spinal cord. Theres hyperexcitability. Theres new connections being made, new genes being inducedall these constitute features of the disease.In my laboratory, our overarching concept is that chronic pain pathology involves not only a foot stuck on the accelerator, but also a dysfunction with the brakethe inhibitory system.Bradley Taylor, PhDSome cases of neuropathic pain occur after damage in the central nervous system (such as after spinal cord injury, post-stroke and in patients with multiple sclerosis). Here, the disease of pain is independent of inputs. In the case of neuropathic pain that is peripherally induced, such as in diabetic neuropathy where there is nerve damage, there is still a peripherally located driver of the pain, but its now engaging an altered central nervous system, Basbaum says.Ru-Rong Ji, PhD, professor of anesthesiology at Duke University School of Medicine in Durham, North Carolina, believes that chronic pain may be caused by dysregulation of glial cells, the supportive nervous system cells that provide nutrition, immune support, insulation and protection to neurons. Glial cells include microglia and astrocytes, which are found throughout the spinal cord and brain and help maintain the homeostasis of the nervous system.Ji and other researchers have found that during the transition stage from acute to chronic pain, there is activation of certain signal transduction pathways that involve glial cells. This activation switches them from their anti-inflammatory, supportive role to a pro-inflammatory one. The glial cells then produce inflammatory mediators, cytokines and chemokines that increase the intensity and amplitude of pain and enhance its duration, Ji says.It is a major shift in thinking that glia may be a driver of chronic pain, he says. Glia in the central nervous system may underlie a specific type of central nervous system inflammation called neuroinflammation.Those same glial cells seem also to contain the potential to resolve chronic pain. Resolvins are a specific family of mediator molecules that are part of the brake or inhibitory system. Enzymatically generated in glia from the polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in fish oil, they are thought to be involved in the active phase of resolution of inflammation. Resolvins are very exciting potential mediators, Ji says. They produce a very potent analgesic effect at much lower doses than morphine and without any side effects.New approaches to treating chronic painChronic pain is not just an extension of acute pain. The mechanisms underlying it are different. Thus, treating it merits a different approach: Instead of treating pain as a symptom by blocking the pain transmission pathway from periphery to brain, researchers hope to address the underlying disease process that is keeping the pain sensation alive. We know that some treatments like non-steroidal anti-inflammatory drugs and opioids that are effective for acute pain only give transient mild relief for chronic pain, if at all, and may even make it worse in some cases, Ji says. Steroids can reduce inflammation-induced pain temporarily, but they have potent side effects and cant be used safely long-term. Steroids have also been shown to delay the resolution of inflammation.The longer the chronic pain process continues, the more difficult it is to resolve. We have started to ask: How can we promote resolution of recovery? Ji says. Neuromodulation and spinal cord stimulation have been used for years, but usually as a last resort. But neuromodulation can be extended to different regionsnot just the spinal cord, but the dorsal root ganglia and peripheral nerves. Vagus nerve stimulation can help control inflammation system-wide, and exercise can help modulate sympathetic tone.Ji believes that fish oil, which contains the precursors to resolvins, in concert with neuromodulation or exercise, can help the body produce resolvins and move toward a state of resolution of chronic pain. Treatments such as acupuncture have long worked to help resolve chronic pain, but now, Ji says, we have a better understanding why: They may reduce inflammation in the body.Basbaum agrees that neuromodulation has potential to treat chronic pain at its root, even though researchers dont yet fully understand the mechanisms by which it works. Its hard to have a placebo-controlled trial because patients often can tell when theyre being stimulated. But some of these approaches, in particular dorsal root ganglion stimulation, have been remarkable for some patients, he says. Transcranial magnetic stimulation of the motor cortex also works in many cases. Why would you stimulate the motor cortex to relieve pain? Stimulating the somatosensory cortex doesnt work, but the motor cortex does. How does it work? We dont really know, he says.These approaches have the potential not just to relieve ongoing pain, but also to reverse dysregulation and promote pain resolution.The glial cells then produce inflammatory mediators, cytokines and chemokines that increase the intensity and amplitude of pain and enhance its duration.Ru-Rong Ji, PhDTaylors lab studies how interconnections between interneurons in the dorsal horn of the spinal cord can change after injury. The changes in circuitry may explain the transition from acute pain to chronic pain, he says. The lab has focused on a neuropeptide receptor system that they think may be a potential target for chronic pain. Its called neuropeptide Y (NPY). Weve been finding for 25 years now that application of NPY to the spinal cord can inhibit pain transmission in rodents, he says. And along the way, we started to realize that what we were doing was to mimic a natural, endogenous pain inhibitory system.To better understand the mechanisms of action of NPY, Taylors lab is using chemogenetics and optogenetics to manipulate the activity of the neurons that express specific types of NPY receptors found in the dorsal horn of the spinal cord, most notably the Y1R type. When they selectively ablated Y1R interneurons in rodents, the intensity of pain-like behaviors after peripheral nerve injury were reduced. They concluded that spinal Y1R interneurons can contribute to pathological painand present a potential target for treatment of chronic neuropathic pain.After an injury, connections between spinal neurons change in such a way that touch information becomes cross-wired and enters into the pain pathways, so that even a light touch activates Y1R-expressing neurons, producing pain, Taylor says. There are some challenges with turning NPY into a therapeutic for humans, as it can have off-target effects on hunger and blood pressure, but his lab is searching for a solution. Were now conducting studies to understand how endogenous opioid and NPY receptor mechanisms might interact to prevent chronic pain.The Taylor lab is also interested in repurposing existing drugs to see if they work for chronic pain. They are studying a specific class of drug that targets peroxisome proliferator-activated receptors (PPARs), currently used to treat diabetes, which shows promise as an analgesic for chronic pain. The thiazolidinedione class of drugs approved by the U.S. Food and Drug Administration include rosiglitazone and pioglitazone and target a specific isoform of PPAR called PPAR. The lab discovered that PPAR mRNA and protein are expressed in the dorsal horn of the spinal cord and that PPAR agonists reduce inflammatory and neuropathic painlikely through actions at the spinal glia. Were hoping to move those studies to clinical trials, Taylor says.While the search continues for potential therapeutic treatments, one thing that would help, Basbaum says, would be to find a biomarker for chronic pain. If you want to treat, you need an endpoint that you can target, he says. Ideally, this biomarker would arise from a more complete understanding of the mechanisms that cause chronic pain in the bodyan understanding that researchers are getting closer to day by day.This article was originally published in the March 2022 issue of The Physiologist Magazine. Send questions or comments to tphysmag@physiology.org. Pain has been described as a unpleasant sensory and emotional experience. It is influenced by biological, psychological and social factors that together form our perception of pain and its intensity. Therefore, pain is not simply inferred or described as nociception the detection of noxious chemical, thermal or mechanical stimuli. Rather, the perception of pain is founded on the complex integration of physiologic signaling at three major levels: Transduction, Transmission and the Perception of Pain. In its most fundamental form, the peripheral nervous system has evolved to detect noxious stimuli that signals actual or impending tissue damage. This is accomplished by the specialization of sensory neurons as primary afferent nociceptors capable of detecting noxious stimuli from somatic and visceral tissues. Nociceptors innervate nearly all tissues in the body less the nervous system itself and are activated through specialized channels and receptor-proteins such as the capsaicin receptor - TRPV1 (1). Signaling the central nervous system of actual or impending tissue injury requires linking peripheral nociceptive terminals, through dorsal root or trigeminal ganglion to spinal dorsal horn and cranial nerve entry points. This step requires axonal nerve conduction propagated by voltage gated sodium channels. Interruption of transmission by local anesthetic sodium channel blockade can be utilized for anesthesia and analgesia. Subsequently, nociceptive signaling to higher centers allows for multiple sites of modulation throughout the spinal cord and midbrain. Where does the sensation and emotional experience of pain reside? Utilizing wide-ranging neural networks, our conscious awareness of pain, usually associated with cortical function is dependent and influenced by multiple brain regions. For example, distraction reduces pain through the somatosensory cortex, insula and thalamus, whereas states of hypervigilance seen with anxiety disorders and catastrophizing can produce exaggerated and/or persistent perceptions of pain. Cognitive and behavior therapies can access these pathways and help reduce and sometimes resolve disabling chronic painful perceptions (2). Just as the perception of pain may be amplified peripherally through the production and release of inflammatory mediators arising from tissue injury, subsequent transmission and perception of pain can be positively (or negatively) modulated based on the physiologic state of the central nervous system (3). Activation of the endogenous opioid-peptide system is one example of how the nervous system functions to negatively modulate or dampen pain signaling. The central action of selective norepinephrine and serotonin reuptake inhibitors are another way to blunt or reverse painful conditions that are dependent on endogenous pain modulatory pathways. References:Schumacher, M. A. (2010) Transient Receptor Potential Channels in Pain and Inflammation: Therapeutic Opportunities. Pain PractTracey, I., and Mantyh, P. W. (2007) The cerebral signature for pain perception and its modulation. Neuron 55, 377-391Woolf, C. J. (2011) Central sensitization: implications for the diagnosis and treatment of pain. Pain 152, S2-15Interdisciplinary approach for easing painThis article is about pain management across medicine. For cancer-related pain management specifically, see Cancer pain. For the album by Bubba Sparxxx, see Pain Management (album).Pain Medicine PhysicianOccupationNamesPhysicianOccupation typeSpecialtyActivity sectorsMedicineDescriptionEducation requiredDoctor of Medicine (M.D.)Doctor of Osteopathic medicine (D.O.)Bachelor of Medicine, Bachelor of Surgery (M.B.B.S.)Bachelor of Medicine, Bachelor of Surgery (MBChB)Fields ofemploymentHospitals, clinicsActive and inactive -opioid receptors[1]Image of visual painPain management is an aspect of medicine and health care involving relief of pain (pain relief, analgesia, pain control) in various dimensions, from acute and simple to chronic and challenging. Most physicians and other health professionals provide some pain control in the normal course of their practice, and for the more complex instances of pain, they also call on additional help from a specific medical specialty devoted to pain, which is called pain medicine.Pain management often uses a multidisciplinary approach for easing the suffering and improving the quality of life of anyone experiencing pain,[2] whether acute pain or chronic pain. Relieving pain (analgesia) is typically an acute process, while managing chronic pain involves additional complexities and ideally a multidisciplinary approach.A typical multidisciplinary pain management team may include: medical practitioners, pharmacists, clinical psychologists, physiotherapists, occupational therapists, recreational therapists, physician assistants, nurses, and dentists.[3] The team may also include other mental health specialists and massage therapists. Pain sometimes resolves quickly once the underlying trauma or pathology has healed, and is treated by one practitioner, with drugs such as pain relievers (analgesics) and occasionally also anxiolytics.Effective management of chronic (long-term) pain, however, frequently requires the coordinated efforts of the pain management team.[4] Effective pain management does not always mean total eradication of all pain. Rather, it often means achieving adequate quality of life in the presence of pain, through any combination of lessening the pain and/or better understanding it and being able to live happily despite it. Medicine treats injuries and diseases to support and speed healing. It treats distressing symptoms such as pain and discomfort to reduce any suffering during treatment, healing, and dying.The task of medicine is to relieve suffering under three circumstances. The first is when a painful injury or pathology is resistant to treatment and persists. The second is when pain persists after the injury or pathology has healed. Finally, the third circumstance is when medical science cannot identify the cause of pain. Treatment approaches to chronic pain include pharmacological measures, such as analgesics (pain killer drugs), antidepressants, and anticonvulsants; interventional procedures, physical therapy, physical exercise, application of ice or heat; and psychological measures, such as biofeedback and cognitive behavioral therapy. [citation needed]See also: Threshold of pain and Pain toleranceIn the nursing profession, one common definition of pain is any problem that is "whatever the experiencing person says it is, existing whenever the experiencing person says it does".[5]Pain management includes patient and communication about the pain problem.[6] To define the pain problem, a health care provider will likely ask questions such as:[6]How intense is the pain?How does the pain feel?Where is the pain?What, if anything, makes the pain lessen?What, if anything, makes the pain increase?When did the pain start?After asking such questions, the health care provider will have a description of the pain.[6] Pain is often rated on a scale from 1 to 10, known as the Numeric Rating Scale (NRS);[7] RatingPain Level0No Pain1 3Mild Pain (nagging, annoying, interfering little with ADLs)4 6Moderate Pain (interferes significantly with ADLs)7 10Severe Pain (disabling; unable to perform ADLs)This pain scale is based on a person reporting their pain intensity, with 0 representing no pain experienced and 10 indicating the worst possible pain.[8] The NRS is a common tool used by clinicians and in research to understand personal pain levels and monitor changes over time.[8] In the clinical context, pain management will then be used to address that pain.[6]There are many types of pain management. Each have their own benefits, drawbacks, and limits.[6]A common challenge in pain management is communication between the health care provider and the person experiencing pain.[6] People experiencing pain may have difficulty recognizing or describing what they feel and how intense it is.[6] Health care providers and patients may have difficulty communicating with each other about how pain responds to treatments.[6] There is a risk in many types of pain management for the patient to take treatment that is less effective than needed or which causes other difficulties and side effects.[6] Some treatments for pain can be harmful if overused.[6] A goal of pain management for the patient and their health care provider is to identify the amount of treatment needed to address the pain without going beyond that limit.[6]Another problem with pain management is that pain is the body's natural way of communicating a problem.[6] Pain is supposed to resolve as the body heals itself with time and pain management.[6] Sometimes pain management covers a problem, and the patient might be less aware that they need treatment for a deeper problem.[6]Physical medicine and rehabilitation (PM&R), a medical specialty, uses a range of physical techniques, such as heat and electrotherapy, as well as therapeutic exercises and behavioral therapy in the management of pain.[citation needed] PM&R techniques are usually part of an interdisciplinary or multidisciplinary program that might also include pharmaceuticals.[9] Spa therapy has shown positive effects in reducing pain among patients with chronic low back pain, but its evidence base is limited.[10] Studies have shown that kinesiotape can be used to reduce chronic low back pain.[11] The US Centers for Disease Control recommended that physical therapy and exercise be prescribed as first-line treatments (rather than opioids) for multiple causes of chronic pain in 2016 guidelines.[12] Applicable disorders include chronic low back pain, osteoarthritis of the hip and knee, and fibromyalgia.[12] Exercise alone or with other rehabilitation disciplines (including psychotherapeutic approaches) can have a positive effects on pain.[12] Besides improving the experience of pain itself, exercise can also improve individuals' well-being and general health.[12]Manipulative and mobilization therapies are considered safe interventions for low back pain, with manipulation potentially offering a larger therapeutic effect.[13]Specifically in chronic low back pain, education about the way the brain processes pain in conjunction with routine physiotherapy interventions may provide short-term relief of disability and pain.[14]Aerobic exercise can help when it comes to pain managementPhysical activity interventions, such as tai chi, yoga, and Pilates, promote harmony of the mind and body through total body awareness. These practices incorporate breathing techniques, meditation, and a wide variety of movements while training the body to perform functionally by increasing strength, flexibility, and range of motion.[15] Physical activity can also benefit chronic sufferers by reducing inflammation and sensitivity and boosting overall energy.[16] Physical activity and exercise may improve chronic pain (pain lasting more than 12 weeks),[17] and overall quality of life, while minimizing the need for pain medications.[15] More specifically, walking has been effective in improving pain management in chronic low back pain.[18]Main article: Transcutaneous electrical nerve stimulationTranscutaneous electrical nerve stimulation (TENS) is a self-operated portable device intended to help regulate and control chronic pain via electrical impulses.[19] Limited research has explored the effectiveness of TENS in relation to pain management of multiple sclerosis (MS). MS is a chronic autoimmune neurological disorder, which consists of the demyelination of the nerve axons and the disruption of nerve conduction velocity and efficiency.[19] In one study, electrodes were placed over the lumbar spine, and participants received treatment twice a day and at any time when they experienced a painful episode.[19] This study found that TENS would benefit MS patients with localized or limited symptoms in one limb.[19] The research is mixed with whether or not TENS helps manage pain in MS patients.[citation needed]Transcutaneous electrical nerve stimulation is ineffective for lower back pain. However, it might help with diabetic neuropathy[20] as well as other illnesses. [citation needed]Main article: Transcranial direct-current stimulationTranscranial direct current stimulation (tDCS) is a non-invasive technique of brain stimulation that can modulate activity in specific brain cortex regions, and it involves the application of low-intensity (up to 2mA) constant direct current to the scalp through electrodes in order to modulate the excitability of large cortical areas.[21] tDCS may have a role in pain assessment by contributing to efforts in distinguishing between somatic and affective aspects of pain experience.[21] Zaghi and colleagues (2011) found that the motor cortex, when stimulated with tDCS, increases the threshold for both the perception of non-painful and painful stimuli.[21] Although there is a greater need for research examining the mechanism of electrical stimulation in pain treatment, one theory suggests that the changes in thalamic activity may be due to the influence of motor cortex stimulation on the decrease in pain sensations.[21]Concerning MS, a study found that daily tDCS sessions resulted in an individual's subjective report of pain decreased when compared to a sham condition.[19] In addition, the study found a similar improvement at 1 to 3 days before and after each tDCS session.[19]Fibromyalgia is a disorder in which an individual experiences dysfunctional brain activity, musculoskeletal pain, fatigue, and tenderness in localized areas.[22] Research examining tDCS for pain treatment in fibromyalgia has found initial evidence for pain decreases.[22] Specifically, the stimulation of the primary motor cortex resulted in significantly greater pain improvement in comparison to the control group (e.g., sham stimulation, stimulation of the DLPFC).[22] However, this effect decreased after treatment ended, but remained significant for three weeks following the extinction of treatment.[22]Main article: AcupunctureAcupuncture can sometimes help to relieve painAcupuncture involves the insertion and manipulation of needles into specific points on the body to relieve pain or for therapeutic purposes. An analysis of the 13 highest quality studies of pain treatment with acupuncture, published in January 2009 in the British Medical Journal, was unable to quantify the difference in the effect on pain of real, sham and no acupuncture.[23] A systematic review in 2019 reported that acupuncture injection therapy was an effective treatment for patients with nonspecific chronic low back pain, and is widely used in Southeast Asian countries.[24]Research has found evidence that light therapy such as low level laser therapy is an effective therapy for relieving low back pain.[25][26] Instead of thermal therapy, where reactant energy is originated through heat, Low-Level Light Therapy (LLLT) utilizes photochemical reactions requiring light to function.[citation needed] Photochemical reactions need light in order to function. Photons, the energy created from light, from these photochemical reactions provide the reactants with energy to embed in muscles, thus managing pain.[27] One study conducted by Stausholm et al. showed that at certain wavelengths, LLLT reduced pain in participants with knee osteoarthritis.[28] LLLT stimulates a variety of cell types, which in turn can help treat tendonitis, arthritis, and pain relating to muscles.[citation needed]Main articles: Audioanalgesia and Music therapyAudioanalgesia and music therapy are both examples of using auditory stimuli to manage pain or other distress. They are generally viewed as insufficient when used alone but also as helpful adjuncts to other forms of therapy.[citation needed]Main article: Interventional pain managementInterventional radiology procedures for pain control, typically used for chronic back pain, include epidural steroid injections, facet joint injections, neurolytic blocks, spinal cord stimulators and intrathecal drug delivery system implants.Pulsed radiofrequency, neuromodulation, direct introduction of medication and nerve ablation may be used to target either the tissue structures and organ/systems responsible for persistent nociception or the nociceptors from the structures implicated as the source of chronic pain.[29][30][31][32][33] Radiofrequency treatment has been seen to improve pain in patients with facet joint low back pain. However, continuous radiofrequency is more effective in managing pain than pulsed radiofrequency.[34]An intrathecal pump is sometimes used to deliver very small quantities of medications directly to the spinal fluid. This is similar to epidural infusions used in labour and postoperatively. The major differences are that it is much more common for the drug to be delivered into the spinal fluid (intrathecal) rather than epidurally, and the pump can be fully implanted under the skin. [medical citation needed]A spinal cord stimulator is an implantable medical device that creates electric impulses and applies them near the dorsal surface of the spinal cord, providing a paresthesia ("tingling") sensation that alters the perception of pain by the patient.[medical citation needed]Intra-articular ozone therapy has been seen to alleviate chronic pain in patients with knee osteoarthritis efficiently.[35]Main article: Acceptance and commitment therapyAcceptance and Commitment Therapy (ACT) is a form of cognitive behavioral therapy that focuses on behavior change rather than symptom change, includes methods designed to alter the context around psychological experiences rather than to alter the makeup of the experiences, and emphasizes the use of experiential behavior change methods.[36] The central process in ACT revolves around psychological flexibility, which in turn includes processes of acceptance, awareness, a present-oriented quality in interacting with experiences, an ability to persist or change behavior, and an ability to be guided by one's values.[36] ACT has an increased evidence base for range of health and behavior problems, including chronic pain.[36] ACT influences patients to adopt a tandem process to acceptance and change, which allows for a greater flexibility in the focus of treatment.[36]Recent research has applied ACT successfully to chronic pain in older adults due to in part of its direction from individual values and being highly customizable to any stage of life.[36] In line with the therapeutic model of ACT, significant increases in process variables, pain acceptance, and mindfulness were also observed in a study applying ACT to chronic pain in older adults.[36] In addition, these primary results suggested that an ACT based treatment may significantly improve levels of physical disability, psychosocial disability, and depression post-treatment and at a three-month follow-up for older adults with chronic pain.[36]Main article: Cognitive behavioral therapyCognitive behavioral therapy (CBT) helps patients with pain to understand the relationship between their pain, thoughts, emotions, and behaviors. A main goal in treatment is cognitive (thinking, reasoning or remembering) restructuring to encourage helpful thought patterns.[37] This will target healthy activities such as regular exercise and pacing. Lifestyle changes are also trained to improve sleep patterns and to develop better coping skills for pain and other stressors using various techniques (e.g., relaxation, diaphragmatic breathing, and even biofeedback).[citation needed]Studies have demonstrated the usefulness of cognitive behavioral therapy in the management of chronic low back pain, producing significant decreases in physical and psychosocial disability.[38] CBT is significantly more effective than standard care in treatment of people with body-wide pain, like fibromyalgia. Evidence for the usefulness of CBT in the management of adult chronic pain is generally poorly understood, due partly to the proliferation of techniques of doubtful quality, and the poor quality of reporting in clinical trials.[citation needed] The crucial content of individual interventions has not been isolated and the important contextual elements, such as therapist training and development of treatment manuals, have not been determined. The widely varying nature of the resulting data makes useful systematic review and meta-analysis within the field very difficult.[39]In 2020, a systematic review of randomized controlled trials (RCTs) evaluated the clinical effectiveness of psychological therapies for the management of adult chronic pain (excluding headaches). There is no evidence that behaviour therapy (BT) is effective for reducing this type of pain, however BT may be useful for improving a person's mood immediately after treatment. This improvement appears to be small, and is short term in duration.[40] CBT may have a small positive short-term effect on pain immediately following treatment. CBT may also have a small effect on reducing disability and potential catastrophizing that may be associated with adult chronic pain. These benefits do not appear to last very long following the therapy.[40] CBT may contribute towards improving the mood of an adult who experiences chronic pain, which could possibility be maintained for longer periods of time.[40]For children and adolescents, a review of RCTs evaluating the effectiveness of psychological therapy for the management of chronic and recurrent pain found that psychological treatments are effective in reducing pain when people under 18 years old have headaches.[41] This beneficial effect may be maintained for at least three months following the therapy.[42] Psychological treatments may also improve pain control for children or adolescents who experience pain not related to headaches. It is not known if psychological therapy improves a child or adolescents mood and the potential for disability related to their chronic pain.[42]A 2007 review of 13 studies found evidence for the efficacy of hypnosis in the reduction of pain in some conditions. However the studies had some limitations like small study sizes, bringing up issues of power to detect group differences, and lacking credible controls for placebo or expectation. The authors concluded that "although the findings provide support for the general applicability of hypnosis in the treatment of chronic pain, considerably more research will be needed to fully determine the effects of hypnosis for different chronic-pain conditions."[43]:283Hypnosis has reduced the pain of some harmful medical procedures in children and adolescents.[44] In clinical trials addressing other patient groups, it has significantly reduced pain compared to no treatment or some other non-hypnotic interventions.[45] The effects of self hypnosis on chronic pain are roughly comparable to those of progressive muscle relaxation.[46]A 2019 systematic review of 85 studies showed it to be significantly effective at reducing pain for people with high and medium levels of suggestibility, but of minimal effectiveness for people with low suggestibility. However, high quality clinical data is needed to generalize to the whole chronic pain population.[47]A 2013 meta-analysis of studies that used techniques centered around the concept of mindfulness, concluded, "that MBIs [mindfulness-based interventions] decrease the intensity of pain for chronic pain patients."[48] A 2019 review of studies of brief mindfulness-based interventions (BMBI) concluded that BMBI are not recommended as a first-line treatment and could not confirm their efficacy in managing chronic or acute pain.[49]Mindfulness-based pain management (MBPM) is a mindfulness-based intervention (MBI) providing specific applications for people living with chronic pain and illness.[50][51] Adapting the core concepts and practices of mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT), MBPM includes a distinctive emphasis on the practice of 'loving-kindness', and has been seen as sensitive to concerns about removing mindfulness teaching from its original ethical framework within Buddhism.[50][52] It was developed by Vidyamala Burch and is delivered through the programs of Breathworks.[50][51]The World Health Organization (WHO) recommends a pain ladder for managing pain relief with pharmaceutical medicine. It was first described for use in cancer pain. However it can be used by medical professionals as a general principle when managing any type of pain.[53][54] In the treatment of chronic pain, the three-step WHO Analgesic Ladder provides guidelines for selecting the appropriate medicine. The exact medications recommended will vary by country and the individual treatment center, but the following gives an example of the WHO approach to treating chronic pain with medications. If, at any point, treatment fails to provide adequate pain relief, then the doctor and patient move onto the next step.[citation needed]Common types of pain and typical drug managementPain typetypical initial drug treatmentcommentsheadacheparacetamol/acetaminophen, NSAIDs[55]doctor consultation is appropriate if headaches are severe, persistent, accompanied by fever, vomiting, or speech or balance problems;[55] self-medication should be limited to two weeks[55]migraineparacetamol, NSAIDs[55]triptans are used when the others do not work, or when migraines are frequent or severe[55]menstrual crampsNSAIDs[55]some NSAIDs are marketed for cramps, but any NSAID would work[55]minor trauma, such as a bruise, abrasions, sprainparacetamol, NSAIDs[55]opioids not recommended[55]severe trauma, such as a wound, burn, bone fracture, or severe sprainopioids[55]more than two weeks of pain requiring opioid treatment is unusual[55]strain or pulled muscleNSAIDs, muscle relaxants[55]if inflammation is involved, NSAIDs may work better; short-term use only[55]minor pain after surgeryparacetamol, NSAIDs[55]opioids rarely needed[55]severe pain after surgeryopioids[55]combinations of opioids may be prescribed if pain is severe[55]muscle acheparacetamol, NSAIDs[55]if inflammation involved, NSAIDs may work better.[55]toothache or pain from dental proceduresparacetamol, NSAIDs[55]this should be short term use; opioids may be necessary for severe pain[55]kidney stone painparacetamol, NSAIDs, opioids[55]opioids usually needed if pain is severe.[55]pain due to heartburn or gastroesophageal reflux diseaseantacid, H2 antagonist, proton-pump inhibitor[55]heartburn lasting more than a week requires medical attention; aspirin and NSAIDs should be avoided[55]chronic back painparacetamol, NSAIDs[55]opioids may be necessary if other drugs do not control pain and pain is persistent[55]osteoarthritis painparacetamol, NSAIDs[55]medical attention is recommended if pain persists.[55]fibromyalgiaantidepressant, anticonvulsant[55]evidence suggests that opioids are not effective in treating fibromyalgia[55]Paracetamol (acetaminophen), or a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen will relieve mild pain.[56]Paracetamol, an NSAID or paracetamol in a combination product with a weak opioid such as tramadol, may provide greater relief than their separate use. A combination of opioid with acetaminophen can be frequently used such as Percocet, Vicodin, or Norco. [citation needed]When treating moderate to severe pain, the type of the pain, acute or chronic, needs to be considered. The type of pain can result in different medications being prescribed. Certain medications may work better for acute pain, others for chronic pain, and some may work equally well on both. Acute pain medication is for rapid onset of pain such as from an inflicted trauma or to treat post-operative pain. Chronic pain medication is for alleviating long-lasting, ongoing pain.[citation needed]Morphine is the gold standard to which all narcotics are compared. Semi-synthetic derivatives of morphine such as hydromorphone (Dilaudid), oxymorphone (Numorphan, Opana), nicomorphine (Vilan), hydromorphinol and others vary in such ways as duration of action, side effect profile and milligramme potency. Fentanyl has the benefit of less histamine release and thus fewer side effects. It can also be administered via transdermal patch which is convenient for chronic pain management. In addition to the transdermal patch and injectable fentanyl formulations, the FDA (Food and Drug Administration) has approved various immediate release fentanyl products for breakthrough cancer pain (Actiq/OTFC/Fentora/Onsolis/Subsys/Lazanda/Abstral). Oxycodone is used across the Americas and Europe for relief of serious chronic pain. Its main slow-release formula is known as OxyContin. Short-acting tablets, capsules, syrups and ampules which contain oxycodone are available making it suitable for acute intractable pain or breakthrough pain. Diamorphine, and methadone are used less frequently.[citation needed] Clinical studies have shown that transdermal buprenorphine is effective at reducing chronic pain.[57] Pethidine, known in North America as meperidine, is not recommended [by whom?] for pain management due to its low potency, short duration of action, and toxicity associated with repeated use.[citation needed] Pentazocine, dextromoramide and dipipanone are also not recommended in new patients except for acute pain where other analgesics are not tolerated or are inappropriate, for pharmacological and misuse-related reasons. In some countries potent synthetics such as piritramide and ketobemidone are used for severe pain. Tapentadol is a newer agent introduced in the last decade.[citation needed]For moderate pain, tramadol, codeine, dihydrocodeine, and hydrocodone are used, with nicocodeine, ethylmorphine and propoxyphene or dextropropoxyphene (less commonly).Drugs of other types can be used to help opioids combat certain types of pain. Amitriptyline is prescribed for chronic muscular pain in the arms, legs, neck and lower back with an opiate, or sometimes without it or with an NSAID.While opiates are often used in the management of chronic pain, high doses are associated with an increased risk of opioid overdose.[58]In the U.S., the illegal use of opioids has led to an increasingly high threshold of prescribing analgesics to patients, and as a result minor pain killers were prescribed. Some medical analysts have criticized that development as it might cause premature deaths among cancer patients.[59]In 2009, the Food and Drug Administration stated: "According to the National Institutes of Health, studies have shown that properly managed medical use of opioid analgesic compounds (taken exactly as prescribed) is safe, can manage pain effectively, and rarely causes addiction."[60] In 2013, the FDA stated that "abuse and misuse of these products have created a serious and growing public health problem".[61]Opioid medications can provide short, intermediate or long acting analgesia depending upon the specific properties of the medication and whether it is formulated as an extended release drug. Opioid medications may be administered orally, by injection, via nasal mucosa or oral mucosa, rectally, transdermally, intravenously, epidurally and intrathecally. In chronic pain conditions that are opioid responsive, a combination of a long-acting (OxyContin, MS Contin, Opana ER, Exalgo and Methadone) or extended release medication is often prescribed along with a shorter-acting medication (oxycodone, morphine or hydromorphone) for breakthrough pain, or exacerbations.Most opioid treatment used by patients outside of healthcare settings is oral (tablet, capsule or liquid), but suppositories and skin patches can be prescribed. An opioid injection is rarely needed for patients with chronic pain.Although opioids are strong analgesics, they do not provide complete analgesia regardless of whether the pain is acute or chronic in origin. Opioids are effective analgesics in chronic malignant pain and modestly effective in nonmalignant pain management.[62] However, there are associated adverse effects, especially during the commencement or change in dose. When opioids are used for prolonged periods drug tolerance will occur. Other risks can include chemical dependency, diversion and addiction.[63][64]Clinical guidelines for prescribing opioids for chronic pain have been issued by the American Pain Society and the American Academy of Pain Medicine. Included in these guidelines is the importance of assessing the patient for the risk of substance abuse, misuse, or addiction. Factors correlated with an elevated risk of opioid misuse include a history of substance use disorder, younger age, major depression, and the use of psychotropic medications.[65] Physicians who prescribe opioids should integrate this treatment with any psychotherapeutic intervention the patient may be receiving. The guidelines also recommend monitoring not only the pain but also the level of functioning and the achievement of therapeutic goals. The prescribing physician should be suspicious of abuse when a patient reports a reduction in pain but has no accompanying improvement in function or progress in achieving identified goals.[66]The list below consists of commonly used opioid analgesics which have long-acting formulations. Common brand names for the extended release formulation are in parentheses.Oxycodone (OxyContin)Hydromorphone (Exalgo, Hydromorph Contin)Morphine (M-Eslon, MS Contin)Oxymorphone (Opana ER)Fentanyl, transdermal (Duragesic)Buprenorphine*, transdermal (Butrans)Tramadol (Ultram ER)Tapentadol (Nucynta ER)Methadone* (Metadol, Methadose)Hydrocodone bitartrate (Hysingla ER) and bicarbonate (Zohydro ER)*Methadone and buprenorphine are each used both for the treatment of opioid addiction and as analgesicsThe other major group of analgesics are nonsteroidal anti-inflammatory drugs (NSAID). They work by inhibiting the release of prostaglandins, which cause inflammatory pain. Acetaminophen/paracetamol is not always included in this class of medications. However, acetaminophen may be administered as a single medication or in combination with other analgesics (both NSAIDs and opioids). The alternatively prescribed NSAIDs such as ketoprofen and piroxicam have limited benefit in chronic pain disorders and with long-term use are associated with significant adverse effects. The use of selective NSAIDs designated as selective COX-2 inhibitors have significant cardiovascular and cerebrovascular risks which have limited their utilization.[67][68] Common NSAIDs include aspirin, ibuprofen, and naproxen. There are many NSAIDs such as parecoxib (selective COX-2 inhibitor) with proven effectiveness after different surgical procedures. Wide use of non-opioid analgesics can reduce opioid-induced side-effects.[69]Some antidepressant and antiepileptic drugs are used in chronic pain management and act primarily within the pain pathways of the central nervous system, though peripheral mechanisms have been attributed as well. They are generally used to treat nerve brain that results from injury to the nervous system. Neuropathy can be due to chronic high blood sugar levels (diabetic neuropathy). These drugs also reduce pain from viruses such as shingles, phantom limb pain and post-stroke pain.[citation needed] These mechanisms vary and in general are more effective in neuropathic pain disorders as well as complex regional pain syndrome.[70] A common anti-epileptic drug is gabapentin, and an example of an antidepressant would be amitriptyline.[citation needed]The evidence for using cannabis for pain control varies in quality, but overall there is no good evidence cannabis is effective for any type of pain management, or that it is viable as a means of reducing opioid use.[71]Low-dose ketamine is sometimes used as an alternative to opioids for the treatment of acute pain in hospital emergency departments.[72][73] Ketamine probably? reduces pain more than opioids and with less nausea and vomiting.[74]Other drugs which can potentiate conventional analgesics or have analgesic properties in certain circumstances are called analgesic adjuvant medications.[75] Gabapentin, an anticonvulsant, can reduce neuropathic pain itself and can also potentiate opiates.[76] Drugs with anticholinergic activity, such as orphenadrine and cyclobenzaprine, are given in conjunction with opioids for neuropathic pain. Orphenadrine and cyclobenzaprine are also muscle relaxants, and are useful in painful musculoskeletal conditions. Clonidine, an alpha-2 receptor agonist, is another drug that has found use as an analgesic adjuvant.[75] In 2021, researchers described a novel type of pain therapy a CRISPR-dCas9 epigenome editing method for repressing Nav1.7 gene expression which showed therapeutic potential in three mouse models of chronic pain.[77][78]Nefopam may be used when common alternatives are contraindicated or ineffective, or as an add-on therapy. However it is associated with adverse drug reactions and is toxic in overdose.[79]As of 2024, the patient is encouraged to play a major role in the management of their pain.[80]Self-management of chronic pain has been described as the individual's ability to manage various aspects of their chronic pain.[81] Self-management can include building self-efficacy, monitoring one's own symptoms, goal setting and action planning. It also includes patient-physician shared decision-making, among others.[81] The benefits of self-management vary depending on self-management techniques used. They only have marginal benefits in management of chronic musculoskeletal pain.[82] Some research has shown that self-management of pain can use different approaches. Those approaches can range from different therapies such as yoga, acupuncture, exercise and other relaxation techniques. Patients could also take a more natural approach by taking different minerals, vitamins or herbs. However, research has shown there is a difference between rural patients and non-rural patients having more access to different self-management approaches. Physicians in these areas may be readily prescribing more pain medication in these rural cities due to being less experienced with pain management. Simply put, it is sometimes easier for rural patients to get a prescription that insurance pays for instead of natural approaches that cost more money than they can afford to spend on their pain management. Self-management may be a more expensive alternative.[83]A 2023 review said that future chronic pain diagnosis and treatment would be more personalized and precision based.[84]The medical treatment of pain as practiced in Greece and Turkey is called algology (from the Greek , algos, "pain"). The Hellenic Society of Algology and the Turkish Algology-Pain Society are the relevant local bodies affiliated to the International Association for the Study of Pain (IASP).[85]Main article: Undertreatment of painUndertreatment of pain is the absence of pain management therapy for a person in pain when treatment is indicated.Consensus in evidence-based medicine and the recommendations of medical specialty organizations establish guidelines to determine the treatment for pain which health care providers ought to offer.[86] For various social reasons, persons in pain may not seek or may not be able to access treatment for their pain.[86] Health care providers may not provide the treatment which authorities recommend.[86] Some studies about gender biases have concluded that female pain recipients are often overlooked when it comes to the perception of their pain. Whether they appeared to be in high levels of pain didn't make a difference for their observers. The women participants in the studies were still perceived to be in less pain than they actually were. Men participants on the other hand were offered pain relief while their self reporting indicated that their pain levels didn't necessarily warrant treatment. Biases exist when it comes to gender. Prescribers have been seen over and under prescribing treatment to individuals based on them being male or female [87].There are other prevalent reasons that undertreatment of pain occurs. Gender is a factor as well as race. When it comes to prescribers treating patients racial disparities has become a real factor. Research has shown that non-white individuals pain perception has affected their pain treatment. The African-American community has been shown to suffer significantly when it comes to trusting the medical community to treat them. Oftentimes medication although available to be prescribed is dispensed in less quantities due to their pain being perceived on a smaller scale. The black community could be undermined by physicians thinking they are not in as much pain as they are reporting. Another occurrence may be physicians simply making the choice not to treat the patient accordingly in spite of the self-reported pain level. Racial disparity is definitely a real issue in the world of pain management.[88]Main article: Pain management in childrenAcute pain is common in children and adolescents as a result of injury, illness, or necessary medical procedures.[89] Chronic pain is present in approximately 1525% of children and adolescents. It may be caused by an underlying disease, such as sickle cell anemia, cystic fibrosis, rheumatoid arthritis. Cancer or functional disorders such as migraines, fibromyalgia, and complex regional pain could also cause chronic pain in children.[90]Young children can indicate

their level of pain by pointing to the appropriate face on a children's pain scale.Pain assessment in children is often challenging due to limitations in developmental level, cognitive ability, or their previous pain experiences. Clinicians must observe physiological and behavioral cues exhibited by the child to make an assessment. Self-report, if possible, is the most accurate measure of pain. Self-report pain scales involve younger kids matching their pain intensity to photographs of other children's faces, such as the Oucher Scale, pointing to schematics of faces showing different pain levels, or pointing out the location of pain on a body outline.[91] Questionnaires for older children and adolescents include the Varni-Thompson Pediatric Pain Questionnaire (PPQ) and the Children's Comprehensive Pain Questionnaire. They are often utilized for individuals with chronic or persistent pain.[91]Acetaminophen, nonsteroidal anti-inflammatory agents, and opioid analgesics are commonly used to treat acute or chronic pain symptoms in children and adolescents. However a pediatrician should be consulted before administering any medication.[91]Caregivers may provide nonpharmacological treatment for children and adolescents because it carries minimal risk and is cost effective compared to pharmacological treatment. Nonpharmacologic interventions vary by age and developmental factors. Physical interventions to ease pain in infants include swaddling, rocking, or sucrose via a pacifier. For children and adolescents physical interventions include hot or cold application, massage, or acupuncture.[92] Cognitive behavioral therapy (CBT) aims to reduce the emotional distress and improve the daily functioning of school-aged children and adolescents with pain by changing the relationship between their thoughts and emotions. In addition this therapy teaches them adaptive coping strategies. Integrated interventions in CBT include relaxation technique, mindfulness, biofeedback, and acceptance (in the case of chronic pain).[93] Many therapists will hold sessions for caregivers to provide them with effective management strategies.[90]In red-haired individualsIn recent studies, it has been noted that people who have red-hair through the MC1R receptor gene may react to opioids and perceive pain differently than the rest of the population.[94] The studies on this developing topic have only become notable in the past few years with researchers looking into how red-haired individuals may experience a different threshold in pain and react to pain management differently than others. Most studies find that redheads with this gene have a higher pain tolerance and can also react more sensitively to opiates but require more anesthesia.[95]Pain management practitioners come from all fields of medicine. In addition to medical practitioners, a pain management team may often benefit from the input of pharmacists, physiotherapists, clinical psychologists and occupational therapists, among others. Together the multidisciplinary team can help create a package of care suitable to the patient.Pain physicians are often fellowship-trained board-certified anesthesiologists, neurologists, physiatrists, emergency physicians, or psychiatrists. Palliative care doctors are also specialists in pain management. The American Society of Interventional Pain Physicians, the American Board of Anesthesiology, the American Osteopathic Board of Anesthesiology (recognized by the AOABOS), the American Board of Physical Medicine and Rehabilitation, the American Board of Emergency Medicine and the American Board of Psychiatry and Neurology[96] each provide certification for a subspecialty in pain management following fellowship training. The fellowship training is recognized by the American Board of Medical Specialties (ABMS) or the American Osteopathic Association Bureau of Osteopathic Specialists (AOABOS). As the field of pain medicine has grown rapidly, many practitioners have entered the field, some non-ACGME board-certified.[97]EquianalgesicList of investigational analgesicsOpioid comparison, an example of an equianalgesic chartPain Catastrophizing ScalePain ladderPain management during childbirthPain psychology

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Innovation in pain management: the transcript of a witness seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 12 December 2002. Wellcome Trust Centre for the History of Medicine at UCL. ISBN978-0-85484-097-7.Wailoo, Keith (2014). Pain: A Political History. JHU Press. ISBN978-1-4214-1365-5. ProjectMUSEbook30085.Wikimedia Commons has media related to Pain management.World Health Organization (WHO) Treatment Guidelines on PainRetrieved from " plays an important in the survival of all animals. It acts as a signal, alerting us to potential tissue damage, and leads to a wide range of actions to prevent or limit further damage.Physiologically, pain occurs when sensory nerve endings called nociceptors (also referred to as pain receptors) come into contact with a painful or noxious stimulus. The resulting nerve impulse travels from the sensory nerve ending to the spinal cord, where the impulse is rapidly shunted to the brain via nerve tracts in the spinal cord and brainstem. The brain processes the pain sensation and quickly responds with a motor response in an attempt to cease the action causing the pain.Nociceptive PathwaysThe classic nociceptive pathway involves three types of neurons:Primary sensory neurons in the peripheral nervous system, which conduct painful sensations from the periphery to the dorsal root of the spinal cordSecondary sensory neurons in the spinal cord or brainstem, which transmit the painful sensation to the thalamusTertiary sensory neurons, which transmit the painful sensation from the thalamus to the somatosensory areas of the cerebral cortex.Sensory Nerves Entering the Spinal CordA section of a lumbar vertebra showing the sensory nerves (in yellow, with bulge) entering the dorsal part of the spinal cord. Illustration provided by 3DScience.com. Used by permission.There are two major classes of nerve fibers associated with the transmission of pain:Unmyelinated C fibersMyelinated A-delta fibersDestinations of the Spinothalamic and Spinoreticular Tracts in the BrainThe thalamus is the destination of spinothalamic tractthe sensory pathway responsible for processing pain, temperature, and crude touch. The brainstem reticular formation, which forms a diffuse, central core within the brainstem is the destination of the spinoreticular tract. Source: 3DScience.com. Used by permission.The C fibers are small and conduct impulses slowly. They respond to thermal, mechanical, and chemical stimuli and produce the sensation of dull, diffuse, aching, burning, and delayed pain. A-delta fibers, which are myelinated and thus conduct impulses rapidly, respond to mechanical (pressure) stimulus and produce the sensation of sharp, localized, fast pain.One of the most important central pain pathways is the spinothalamic tract, which originates in the spinal cord and extends to the thalamus. This spinal tract transmits sensory information related to pain, temperature, and crude touch.Another prominent pathway is the spinoreticular tract, which is involved in nociceptive processing. The spinoreticular tract is similar to the spinothalamic tract in that it is excited by similar sensory fibers. Rather than ascending to the thalamus however, spinoreticular neurons terminate within the brainstem.Mechanisms of PainPain can be caused by a mechanical, chemical or inflammatory, or thermal mechanism. Pain of mechanical origin can be caused by acute trauma, injury, or overuse. It may be constant, variable, or intermittent in nature and is affected by movement and position.Pain of chemical or inflammatory origin is associated with arthritis and other inflammatory disorders. It is often constant but responds to positioning, therapy, rest, and gentle movement. Medications are usually a part of the management regimen for chemical or inflammatory pain.Pain of thermal origin is the result of excessive heat or cold.If an acute pain sensation is intense enough, it can cause system-wide responses: increased alertness; focused attention; the suppression of feeding, sleep, and reproduction; and increased vascular tone, respiration, and blood sugar levels. If pain persists or becomes chronic it can even change the circuitry in the central nervous system.Using Neuroimaging to Understand PainOur understanding of how the brain changes in response to chronic pain or to pharmacologic or other therapeutic interventions has been significantly improved as a result of neuroimaging techniques. Until the advent of these techniques, the living brain was largely invisible to clinicians and researchers. The development of computed tomography (CT) and, soon thereafter, magnetic resonance imaging (MRI), allowed researchers to look into the living brain and gain some understanding of the parts of the brain affected by certain types of pain. The development of positron emission tomography (PET) has allowed researchers, for the first time, to investigate neuronal activity throughout the entire brain (Casey, 2015).Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), and scalp electroencephalography (EEG) have been used to study the neural bases of pain. Other magnetic resonance-based measures such as diffusion tensor imaging, spectroscopy, and volumetric imaging are being used to assess pain-related changes in the brains wiring, chemistry, and structure; this will help gain further insights into the neurobiology of pain, particularly chronic pain (Lee & Tracey, 2013).As a result, we now know that pain sensation is more complex than previously thought and involves diverse regions of the brain. Imaging techniques have allowed us to understand that pain results from activation of a number of brain regions such as the amygdala, insula, or the anterior cingulate cortex. We are learning that pain is a result of complex interactions between the immune, nervous (both CNS and autonomic nervous system), and endocrine systems (Zouikr et al., 2016).In a study of patients with chronic low back pain, neuroimaging showed significant differences in brain function. Compared to healthy controls, chronic low back pain patients showed activation in pain-related brain regions during administration of experimental pain, differences in activation during emotional decision-making tasks, and changes in specific brain regions during a simple visual attention task (Kong et al., 2013).Other imaging studies have reported structural changes in the brains of patients with chronic low back pain. One study found that these patients showed 5% to 11% less neocortical gray matter volume than control subjects and that the decreased volume was related to pain duration. These studies indicate that chronic low back pain is also associated with structural pathologic changes in the brain (Kong et al., 2013).Neuroimaging studies are also being used to predict which patients might transition from acute to chronic pain. Using MRI scans in people with acute low back pain, researchers at Northwestern University Feinberg School of Medicine found abnormalities in the white matter in areas of the brain associated with the processing of pain and emotion. After one year, study participants were scanned again, and those with persistent pain showed the same abnormalities identified at the onset of the injury. In patients with ongoing low back pain, these abnormalities may be an indication of which patients will go on to develop chronic low back pain (Paul, 2013).In patients with chronic pain, a number of research groups have reported significant changes in pain processing at a functional level including allodynia* (a stimulus not normally painful is perceived as painful), functional plasticity, and alterations in basic processes in the brain and brainstem. Alterations in neurotransmitters have also been reported in chronic pain patients using magnetic resonance spectroscopy. Such approaches have been applied to migraine, back pain, and spinal cord injury. The approach can be used to define neuronal and axonal markers, including specific metabolites such as glutamate, aspartate, glycine, and GABA (Borsook et al., 2007).At a macroscopic level, a number of studies have shown changes in volume in brain regions in patients with chronic neuropathic pain, complex regional pain syndrome, and fibromyalgia. This insight has been seminal in transforming our approach and thinking on chronic pain, since these changes indicate the potential of chronic pain being a neurodegenerative disease. At a microscopic level, changes in dendritic spine density or alterations in neuronal count have been observed in pain and stress. Such changes also have implications for the development of co-morbid disease such as depression (Borsook et al., 2007).SensitizationWe can become sensitized to pain. Sensitization is a neurophysiologic term that describes the increased responsiveness of nociceptive neurons (the pain pathways become more sensitive). This can include a drop in the threshold for activating nociceptors and an increase in the frequency of firing for all stimuli (IASP, 2012). Hyperalgesia (exaggerated responses to stimuli) and allodynia (see above) are clinical markers used to detect the presence of sensitization (Zouikr et al., 2016).In sensitization, stimuli that would not normally cause pain, such as the light touch of a sheet on the skin, can cause intense pain. Sensitization can also cause tenderness and soreness, particularly when deep tissue such as joints and hollow viscera are affected.There are two types of sensitization: peripheral and central. Peripheral sensitization occurs in response to the release of inflammatory molecules such as histamine, prostaglandins, and pro-inflammatory cytokines. These substances sensitize (increase the excitability of) nociceptors by creating an inflammatory soup environment that enhances pain sensitivity by reducing the threshold of nociceptors activation (Zouikr et al., 2016). Under normal circumstances, peripheral hypersensitivity returns to normal when inflammation subsides or the source of the injury is removed (Kyranou & Puntillo, 2012).In central sensitization, nociceptive-specific neurons may progressively increase their response to repeated non-painful stimuli, develop spontaneous activity, and increase the area of the body that is involved with the pain. The hyperalgesia of central sensitization usually develops as part of ongoing pathology (ie, damage to peripheral or central nerve fibers, cancer, rheumatoid arthritis) and is considered maladaptive (Kyranou & Puntillo, 2012).Physiologic Effects of Unrelieved PainUnrelieved pain is a stressor that can lead to physiologic changes and negative effects on the endocrine, cardiovascular, gastrointestinal, and immune systems. The endocrine system reacts to unrelieved pain by releasing an excessive amount of hormones, ultimately resulting in carbohydrate, protein, and fat catabolism, poor glucose utilization, and other harmful effects. This reaction combined with inflammatory processes can produce weight loss, tachycardia, increased respiratory rate, fever, shock, and death.The cardiovascular system responds to the stress of unrelieved pain by activating the sympathetic nervous system. Following a surgical procedure, for example, this can include hypercoagulation and increased heart rate, blood pressure, cardiac workload, and oxygen demand. Since the stress response causes an increase in sympathetic nervous system activity, intestinal secretions and smooth muscle sphincter tone increase, and gastric emptying and intestinal motility decrease. This response can cause temporary impairment of gastrointestinal function and increase the risk of ileus (intestinal obstruction). Aggressive pain control may be needed to reduce these effects and prevent thromboembolic complications.Unrelieved pain may be especially harmful for patients with metastatic cancers. Stress and pain can suppress immune function, including the natural killer cells that play a role in preventing tumor growth and controlling metastasis. A comprehensive guide to the anatomy and physiology of pain managementMany nurses have a poor understanding of pain and its management, which can result in failure to treat pain effectively. An insight into the anatomy and physiology of pain is essential to increase nurses understanding of what it is and how interventions can help to manage it. This section outlines the basic anatomy and physiology of pain.Acute painAcute pain is a physiological response that warns us of danger. The process of nociception describes the normal processing of pain and the responses to noxious stimuli that are damaging or potentially damaging to normal tissue. There are four basic processes involved in nociception (McCaffery and Pasero, 1999). These are;transduction;transmission;perception;modulation.Transduction of painTransduction begins when the free nerve endings (nociceptors) of C fibres and A-delta fibres of primary afferent neurones respond to noxious stimuli. Nociceptors are exposed to noxious stimuli when tissue damage and inflammation occurs as a result of, for example, trauma, surgery, inflammation, infection, and ischemia.The nociceptors are distributed in the;somatic structures (skin, muscles, connective tissue, bones, joints);visceral structures (visceral organs such as liver, gastro-intestinal tract).The C fibre and A-delta fibres are associated with different qualities of pain. These are listed in table 1.Table 1. Characteristics and functions of C fibre and A-delta fibresC fibresA-delta fibresPrimary afferent fibresSmall diameterUnmyelinatedSlow conductingPolymodal respond to more than one type of noxious stimuli:MechanicalThermalChemicalDiffuseDullBurningAchingReferred to as slow or second painPrimary afferent fibresLarge diameterMyelinatedFast conductingHigh-threshold mechanoreceptors respond mechanical stimuli over a certain intensity.Well-localisedSharpStingingPrickingReferred to as fast or first painNoxious stimuli and responsesThere are three categories of noxious stimuli: mechanical (pressure, swelling, abscess, incision, tumour growth);thermal (burn, scald);chemical (excitatory neurotransmitter, toxic substance, ischaemia, infection).The cause of stimulation may be internal, such as pressure exerted by a tumour or external, for example, a burn. This noxious stimulation causes a release of chemical mediators from the damaged cells including:prostaglandin;bradykinin;serotonin;substance P;potassium;histamine.These chemical mediators activate and/or sensitise the nociceptors to the noxious stimuli. In order for a pain impulse to be generated, an exchange of sodium and potassium ions (de-polarisation and re-polarisation) occurs at the cell membranes. This results in an action potential and generation of a pain impulse.Transmission of painThe transmission process occurs in three stages. The pain impulse is transmitted:from the site of transduction along the nociceptor fibres to the dorsal horn in the spinal cord;from the spinal cord to the brain stem;through connections between the thalamus, cortex and higher levels of the brain.The C fibre and A-delta fibres terminate in the dorsal horn of the spinal cord. There is a synaptic cleft between the terminal ends of the C fibre and A-delta fibres and the nociceptive dorsal horn neurones (NDHN). In order for the pain impulses to be transmitted across the synaptic cleft to the NDHN, excitatory neurotransmitters are released, which bind to specific receptors in the NDHN. These neurotransmitters are:adenosine triphosphate;glutamate;calcitonin gene-related peptide;bradykinin;nitric oxide;substance P.The pain impulse is then transmitted from the spinal cord to the brain stem and thalamus via two main nociceptive ascending pathways. These are the spinothalamic pathway and the spinoparabrachial pathway.The brain does not have a discrete pain centre, so when impulses arrive in the thalamus they are directed to multiple areas in the brain where they are processed.Perception of painPerception of pain is the end result of the neuronal activity of pain transmission and where pain becomes a conscious multidimensional experience. The multidimensional experience of pain has affective-motivational, sensory-discriminative, emotional and behavioural components.When the painful stimuli are transmitted to the brain stem and thalamus, multiple cortical areas are activated and responses are elicited.These areas are:The reticular system: This is responsible for the autonomic and motor response to pain and for warning the individual to do something, for example, automatically removing a hand when it touches a hot saucepan. It also has a role in the affective-motivational response to pain such as looking at and assessing the injury to the hand once it has been removed form the hot saucepan.Somatosensory cortex: This is involved with the perception and interpretation of sensations. It identifies the intensity, type and location of the pain sensation and relates the sensation to past experiences, memory and cognitive activities. It identifies the nature of the stimulus before it triggers a response, for example, where the pain is, how strong it is and what it feels like.Limbic system: This is responsible for the emotional and behavioural responses to pain for example, attention, mood, and motivation, and also with processing pain and past experiences of pain.Modulation of painThe modulation of pain involves changing or inhibiting transmission of pain impulses in the spinal cord. The multiple, complex pathways involved in the modulation of pain are referred to as the descending modulatory pain pathways (DMPP) and these can lead to either an increase in the transmission of pain impulses (excitatory) or a decrease in transmission (inhibition).Descending inhibition involves the release of inhibitory neurotransmitters that block or partially block the transmission of pain impulses, and therefore produce analgesia. Inhibitory neurotransmitters involved with the modulation of pain include:endogenous opioids (enkephalins and endorphins);serotonin (5-HT);norepinephrine (noradrenalin);gamma-aminobutyric acid (GABA);neurotensin;acetylcholine;oxytocin.Endogenous pain modulation helps to explain the wide variations in the perception of pain in different people as individuals produce different amounts of inhibitory neurotransmitters. Endogenous opioids are found throughout the central nervous system (CNS) and prevent the release of some excitatory neurotransmitters, for example, substance P, therefore, inhibiting the transmission of pain impulses.Chronic painChronic pain can be a major problem for some people and affect their quality of life. It can be caused by alterations in nociception, injury or disease and may result from current or past damage to the peripheral nervous system (PNS), CNS, or may have no organic cause (Calvino and Grilo, 2006).Pathophysiology of chronic painThe exact mechanisms involved in the pathophysiology of chronic pain are complex and remain unclear. It is believed that following injury, rapid and long-term changes occur in parts of the CNS that are involved in the transmission and modulation of pain (nociceptive information) (Ko and Zhuo, 2004).A central mechanism in the spinal cord, called wind-up, also referred to as hypersensitivity or hyperexcitability, may occur. Wind-up occurs when repeated, prolonged, noxious stimulation causes the dorsal horn neurones to transmit progressively increasing numbers of pain impulses.The patient can feel intense pain in response to a stimulus that is not usually associated with pain, for example, touch. This is called allodynia.This abnormal processing of pain within the PNS and CNS may become independent of the original painful event. In some cases, for example, amputation, the original injury may have occurred in the peripheral nerves, but the mechanisms that underlie the phantom pain are generated in both the PNS and the CNS.Neuropathic painNeuropathic pain can be defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system resulting from;trauma, for example, complex regional pain syndrome, chronic post-surgical pain;infection, for example, post-herpetic neuralgia;ischaemia, for example, diabetic neuropathy;cancer;chemically induced, for example, as a result of chemotherapy (Farquhar-Smith, 2007).Some types of neuropathic pain may develop when the PNS has become damaged, causing the pain fibres to transmit pain impulses repetitively and become increasingly sensitive to stimuli. Neuroplasticity may also develop and is characterised by abnormal neuronal sprouting in the PNS and within the dorsal horn of the spinal cord. This sprouting may result in additional generation of and increased transmission of pain impulses.Characteristics of neuropathic painNeuropathic pain is distinctly different from nociceptive pain and is described as:burning;dull;aching;tingling;like an electric shock;shooting.The types of neuropathic pain are divided into categories and these are listed in Fig 1.ConclusionThis anatomy and physiology section has briefly illustrated the processes that are involved in generating the sensation of pain. This provided the basis for the assessment of pain and the selection of appropriate interventions for managing this pain effectively. McCaffery, M., Pasero, C. (1999) Pain: A Clinical Manual. St Louis, MO: Mosby.Calvino, B., Grilo, R.M. (2006) Central pain control. Joint Bone Spine; 73: 1, 10-16.Farquhar-Smith, P. (2007) Anatomy, physiology and pharmacology of pain. Anaesthesia and Intensive CareMedicine; 9: 1, 3-7.Ko, S.M., Zhou, M. (2004) Central plasticity and persistent pain; Drug Discovery Today: Disease Models; Painand Anaesthesia; 1: 2, 101-106 Pain is a subjective experience with two complementary aspects: one is a localized sensation in a particular body part; the other is an unpleasant quality of varying severity commonly associated with behaviors directed at relieving or terminating the experience.Pain has much in common with other sensory modalities (National Academy of Sciences, 1985). First, there are specific pain receptors. These are nerve endings, present in most body tissues, that only respond to damaging or potentially damaging stimuli. Second, the messages initiated by these noxious stimuli are transmitted by specific, identified nerves to the spinal cord. The sensitive nerve ending in the tissue and the nerve attached to it together form a unit called the primary afferent nociceptor. The primary afferent nociceptor contacts second-order pain-transmission neurons in the spinal cord. The second-order cells relay the message through well-defined pathways to higher centers, including the brain stem reticular formation, thalamus, somatosensory cortex, and limbic system. It is thought that the processes underlying pain perception involve primarily the thalamus and cortex.In this chapter we review the anatomy and physiology of pain pathways. We also discuss some of the physiological processes that modify the pain experience and that may contribute to the development of chronicity. For obvious reasons, most of this information comes from animal experiments. However, in recent years, experimental studies of human subjects using physiological, pharmacological, and psychophysical methods indicate that much of what has been learned in animals is applicable to humans (National Academy of Sciences, 1985). Research into basic mechanisms underlying pain is an increasingly exciting and promising area. However, most of what is known about the anatomy and physiology of pain is from studies of experimentally induced cutaneous (skin) pain, while most clinical pain arises from deep tissues. Thus, while experimental studies provide fairly good models for acute pain, they are poor models for clinical syndromes of chronic pain. Not only do they provide little information about the muscles, joints, and tendons that are most often affected by chronically painful conditions, but they do not address the vast array of psychosocial factors that influence the pain experience profoundly. To improve our understanding and treatment of pain we will need better animal models of human pain and better tools for studying clinical pain.Figure 7-1 illustrates the major components of the brain systems involved in processing pain-related information. There are four major processes: transduction, transmission, modulation, and perception. Transduction refers to the processes by which tissue-damaging stimuli activate nerve endings. Transmission refers to the relay functions by which the message is carried from the site of tissue injury to the brain regions underlying perception. Modulation is a recently discovered neural process that acts specifically to reduce activity in the transmission system. Perception is the subjective awareness produced by sensory signals; it involves the integration of many sensory messages into a coherent and meaningful whole. Perception is a complex function of several processes, including attention, expectation, and interpretation.Transduction, transmission, and modulation are neural processes that can be studied objectively using methods that involve direct observation. In contrast, although there is unquestionably a neural basis for it, the awareness of pain is a perception and, therefore, subjective, so it cannot be directly and objectively measured. Even if we could measure the activity of pain-transmission neurons in another person, concluding that that person feels pain would require an inference based on indirect evidence.Three types of stimuli can activate pain receptors in peripheral tissues: mechanical (pressure, pinch), heat, and chemical. Mechanical and heat stimuli are usually brief, whereas chemical stimuli are usually long lasting. Nothing is known about how these stimuli activate nociceptors. The nociceptive nerve endings are so small and scattered that they are difficult to find, let alone study. Nonetheless, there have been some studies of the effects of chemicals on the firing frequency of identified primary afferent nociceptors.A variety of pain-producing chemicals activate or sensitize primary afferent nociceptors (Bisgaard and Kristensen, 1985; Juan and Lembeck, 1974; Keele, 1966). Some of them, such as potassium, histamine, and serotonin, may be released by damaged tissue cells or by the circulating blood cells that migrate out of blood vessels into the area of tissue damage. Other chemicals, such as bradykinin, prostaglandins, and leukotrienes, are synthesized by enzymes activated by tissue damage (Armstrong, 1970; Ferreira, 1972; Moncada et al., 1985; Vane, 1971). All of these pain-producing chemicals are found in increased concentrations in regions of inflammation as well as pain. Obviously, the process of transduction involves a host of chemical processes that probably act together to activate the primary afferent nociceptor. In theory, any of these substances could be measured to give an estimate of the peripheral stimulus for pain. In practice, such assays are not available to clinicians.It should be pointed out that most of our knowledge of primary afferent nociceptors is derived from studies of cutaneous nerves. Although this work is of general importance, the bulk of clinically significant pain is generated by processes in deep musculoskeletal or visceral tissues. Scientists are beginning to study the stimuli that activate nociceptors in these deep tissues (Cervero, 1982, 1985; Coggeshall et al., 1983; National Academy of Sciences, 1985). In muscle, there are primary afferent nociceptors that respond to pressure, muscle contraction, and irritating chemicals (Kumazawa and Mizumura, 1977; Mense and Meyer, 1985; Mense and Stahnke, 1983). Muscle contraction under conditions of ischemia is an especially potent stimulus for some of these nociceptors.Despite progress in our understanding of the physiology of musculoskeletal nociceptors, we still know very little about the mechanisms underlying common clinical problems such as low back pain. Even when there is degeneration of the spine and compression of a nerve roota condition generally acknowledged to be extremely painfulwe do not know which nociceptors are activated or how they are activated. Neither do we know what it is about the process that leads to pain.The nociceptive message is transmitted from the periphery to the central nervous system by the axon of the primary afferent nociceptor. This neuron has its cell body in the dorsal root ganglion and a long process, the axon, that divides and sends one branch out to the periphery and one into the spinal cord (Figure 7-2). The axons of primary afferent nociceptors are relatively thin and conduct impulses slowly.It is possible to place an electrode into a human peripheral nerve and record the activity of primary afferent nociceptors (Fitzgerald and Lynn, 1977; Torebjork and Hallin, 1973). The nociceptor is characterized by its response to noxious heat, pressure, or chemical stimuli. The ''pain'' message is coded in the pattern and frequency of impulses in the axons of the primary afferent nociceptors. There is a direct relation between the intensity of the stimulus and the frequency of nociceptor discharge (Figure 7-3). Furthermore, combined neurophysiological and psychophysical studies in humans have shown a direct relation between discharge frequency in a primary afferent nociceptor and the reported intensity of pain (Fitzgerald and Lynn, 1977; LaMotte et al., 1983). Blocking transmission in the small-diameter axons of the nociceptors blocks pain, whereas blocking activity of the larger-diameter axons in a peripheral nerve does not. These identified primary afferent nociceptors are thus necessary for detecting noxious stimuli.Monitoring activity in identified primary afferent nociceptors is a potential tool for the evaluation of certain types of clinical pain. In fact, this method has been used clinically to demonstrate pain-producing neural activity arising from a damaged nerve (Nystrom and Hagbarth, 1981). At present, this method should be considered just a research tool; however, it is technically feasible and is of great potential value for evaluating pain patients. It raises the possibility of actually demonstrating nociceptor activity coming from a painful area. This method could be an advance over other correlative techniques for assessing pain because it measures the presumed noxious input, that is, the neural activity that ordinarily causes pain. Most of the other measures assess responses that could be, but are not necessarily, caused by noxious stimuli.It is important to point out that (1) there can be pain without activity in primary afferent nociceptors, and (2) there can be activity in primary afferent nociceptors without pain. These phenomena occur when there has been damage to the central or peripheral nervous systems. In addition, the modulating system can suppress central transmission of activity elicited by nociceptor input. Thus, there is a variable relation between nociceptor input and perceived pain intensity. For this reason the method of recording primary afferent nociceptors could be used to confirm the presence of an input, but it could not be used to prove that pain was not present.Besides these theoretical limitations of trying to assess subjective pain intensity by recording primary afferent nociceptors, there are important practical problems in measuring either pain-producing substances or primary afferent nociceptor activity. One is that the largest group of patients disabled by pain localize it to musculoskeletal structures in the lower back. Because the nerves innervating these structures are not near the skin, they are difficult to find. Another problem is that pain arising from deep structures is often felt at sites distant from where the tissue damage occurs. In contrast to the pain produced by skin damage, which is sharp or burning and well localized to the site of injury, the pain that arises from deep tissue injury is generally aching, dull, and poorly localized (Lewis, 1942). When the damage to deep tissues is severe or long lasting, the sensation it produces may be misperceived as arising from a site that is distant from the actual site of damage (Head, 1893; Kellgren, 1938; Lewis, 1942; Sinclair et al., 1948). This phenomenon, known as referred pain, helps to explain the frequent discrepancy between physical findings and patient complaints. The mechanism of referred pain is unknown for any particular case.Referred pain can be a major source of confusion in the examination of patients complaining primarily of pain. The fact that pain is referred from visceral internal organs to somatic body structures is well known and commonly used by physicians. For example, the pain of a heart attack is not always localized to the heart but commonly is felt diffusely in the chest, the left arm, and sometimes in the upper abdomen. Less widely recognized is the fact that irritable spots, such as myofascial trigger points, in skeletal muscles also cause feelings of pain in locations distant from the irritable spot. This was demonstrated experimentally in muscle and fascia by Kellgren in the late 1930s (Kellgren, 1938). Specific patterns of pain referred from particular muscles have been described clinically (Travell and Rinzler, 1952; Travell and Simons, 1983). (See Chapter 10 and Appendix.)At least four physiological mechanisms have been proposed to explain referred pain: (1) activity in sympathetic nerves, (2) peripheral branching of primary afferent nociceptors, (3) convergence projection, and (4) convergence facilitation. The latter two involve primarily central nervous system mechanisms.1.Sympathetic nerves may cause referred pain by releasing substances that sensitize primary afferent nerve endings in the region of referred pain (Procacci and Zoppi, 1981), or possibly by restricting the flow of blood in the vessels that nourish the sensory nerve fiber itself.2.Peripheral branching of a nerve to separate parts of the body causes the brain to misinterpret messages originating from nerve endings in one part of the body as coming from the nerve branch supplying the other part of the body.3.According to the convergence-projection hypothesis, a single nerve cell in the spinal cord receives nociceptive input both from the internal organs and from nociceptors coming from the skin and muscles. The brain has no way of distinguishing whether the excitation arose from the somatic structures or from the visceral organs. It is proposed that the brain interprets any such messages as coming from skin and muscle nerves rather than from an internal organ. The convergence of visceral and somatic sensory inputs onto pain projection neurons in the spinal cord has been demonstrated (Milne et al., 1981; Foreman et al., 1979).4.According to the convergence-facilitation hypothesis, the background (resting) activity of pain projection neurons in the spinal cord that receive input from one somatic region is amplified (facilitated) in the spinal cord by activity arising in nociceptors originating in another region of the body. In this model, nociceptors producing the background activity originate in the region of perceived pain and tenderness; the nerve activity producing the facilitation originates elsewhere, for example, at a myofascial trigger point. This convergence-facilitation mechanism is of clinical interest because one would expect that blocking sensory input in the reference zone with cold or a local anesthetic should provide temporary pain relief. One would not expect such relief according to the convergence-projection theory. Clinical experiments have demonstrated both kinds of responses.This phenomenon of referred pain can present a serious problem to both patients and physicians when it goes unrecognized. Because the source of the pain lies overlooked at a distant location, the lack of any demonstrable lesion at the site of pain and tenderness often leads to the suspicion that the pain has a strong psychological component. When health professionals insist that there is no reason for the pain, patients sometimes begin to wonder whether the pain is "all in their head." As is discussed in later chapters, this can exacerbate anxiety and other psychological reactions to the pain, is likely to frustrate both the doctor and the patient, and may lead to "doctor shopping" and inappropriate treatment.Primary afferent nociceptors transmit impulses into the spinal cord (or if they arise from the head, into the medulla oblongata of the brain stem). In the spinal cord, the primary afferent nociceptors terminate near second-order nerve cells in the dorsal horn of the gray matter (Willis, 1985). The primary afferent nociceptors release chemical transmitter substances from their spinal terminals. These transmitters activate the second-order pain-transmission cells. The identity of these transmitters has not been established, but candidates include small polypeptides such as substance P and somatostatin, as well as amino acids such as glutamic or aspartic acid.The axons of some of these second-order cells cross over to the opposite side of the spinal cord and project for long distances to the brain stem and thalamus. The pathway for pain transmission lies in the anterolateral quadrant of the spinal cord. Most of our information about the anatomy and physiology of pain-transmission pathways in the central nervous system is derived from animal studies. However, it is known that in humans, lesions of this anterolateral pathway permanently impairs pain sensation and that electrical stimulation of it produces pain (Cassinari and Pagni, 1969; White et al., 1950; Willis, 1985).There are two major targets for ascending nociceptive axons in the anterolateral quadrant of the spinal cord: the thalamus and the medial reticular formation of the brain stem. Our knowledge is most extensive for the spinal cells whose axons project directly to the thalamus, that is, the spinothalamic tract cells. The spinothalamic pathway is implicated in human pain perception because lesions of it, at any level, produce lasting impairments of pain sensation.Studies of the properties of spinothalamic tract cells have been carried out in several species. In all these species, a major proportion of spinothalamic neurons respond maximally to noxious stimulation. Furthermore, there is a direct relationship in spinothalamic tract cells of firing frequency to stimulus intensities in the noxious range for human subjects (Kenshalo et al., 1980; Willis, 1985). These observations, coupled with decades of careful clinical studies, strongly implicate the spinothalamic tract as a major pathway for pain in humans.The other major ascending nociceptive pathway in the anterolateral quadrant is the spinoreticular tract. The medullary reticular formation receives a major direct projection from the spinal cord as well as from branches of some of the spinal neurons that project to the thalamus (Kevetter and Willis, 1984; Mehler, 1962).At the thalamic level, pain pathways have two major sites of termination: ventrocaudal and medial. The ventrocaudal thalamus receives nociceptive input directly from projecting spinal neurons. Neurons in the ventrocaudal thalamus project directly to the somatosensory cortex (Willis, 1985). The medial thalamus receives some indirect input from the spinal cord, but in addition, it receives a major input from the region of the brain stem reticular formation to which the nociceptive spinoreticular neurons project. The medial thalamus projects to widespread areas of the forebrain, including the somatosensory cortex (Jones and Leavitt, 1974). Thus there are two major ascending pathways for pain: a direct lateral spinothalamic pathway and an indirect medial spinoreticulothalamic pathway. It is thought that the lateral pathway from the spinal cord to the ventrocaudal thalamus and to the cortex is responsible primarily for sharp, well-localized pains that arise near the body surface. In contrast, the medial spinoreticulothalamic pathway responds more to stimuli of deep somatic and visceral structures.There is some evidence for further functional differences between medial and lateral thalamic pathways. Lesions of the ventrocaudal thalamus and somatosensory cortex produce long-lasting deficits in the sensory aspects of pain that are very similar to those produced by lesions of the anterolateral spinal cord pathway. Lesions of the medial thalamus have very little effect on pain sensation per se; pain threshold is unaffected, as are the other sensory aspects of the pain experience. In contrast, the emotional or reactive aspects may be totally abolished (Barber, 1959).The processes set in motion by noxious stimuli can be divided into two broad categories. On one hand, there are the sensory processes that lead to the detection and identification of the stimulus. On the other hand, presumably because of the tissue-damaging potential of the noxious stimulus, aversive behavioral sequelae such as withdrawal and escape can terminate the stimulus and protect the organism. Correlated with these two categories of response are two subjective aspects of pain: sensory and affective.The sensory aspects concern detecting, localizing, assessing the intensity of, and identifying the stimulus. Focusing on the sensory aspects, a person might describe his or her pain as a mild burning pain located on the back of the hand. In contrast, the affective or unpleasantness aspect of pain correlates with the aversive drive to terminate the noxious stimulus and is described by terms that are not specifically tied to a sensory experience, for example, nagging, uncomfortable, or excruciating. The affective aspects would also be accompanied by mood changes such as anxiety and depression, which are usually considered psychological rather than sensory.The difference between the sensory and affective aspects of pain can be illustrated further by distinguishing between pain threshold and pain tolerance. For example, if one delivers calibrated thermal stimuli to the skin, most people will report that the sensation becomes painful over a narrow range of skin temperatures (43-46C) (LaMotte et al., 1983; Willis, 1985). The temperature that is called painful 50 percent of the time would be the pain detection or sensory threshold.In contrast to this relatively reproducible pain-detection threshold, tolerance for pain differs widely among individuals. For example, subjects immersing their hands in ice water fall into distinct groups those who keep their hands in for over 5 minutes and those who pull them out after less than 90 seconds (Turk and Kerns, 1983-1984). The tolerance for pain is a complex function that may be modified by personality traits, attitudes, previous experience, economic factors, gender, and the particular circumstance under which the pain is experienced. Tolerance may be thought of as a response threshold. Pain of a certain intensity and duration may be ignored, whereas a somewhat more intense pain might induce some people to take painkillers, stay home from work, or consult a physician. The particular behavior elicited by pain of a given intensity is highly individual and greatly influenced by what the patient believes will be helpful and how serious he or she thinks the situation is. For example, most people with headaches do not seek medical attention because headaches are not considered indicative of serious disease (and usually are not). In contrast, a person whose father died recently from a brain tumor might be very frightened by even a mild headache and seek medical attention (see Chapter 8).Tolerance is also tied to the cognitive and affective aspects of pain. For patients with cancer, pain may be a sign that the tumor has recurred or spread and that death is near. For such patients, the suffering is due not only to the pain's intensity but also to its meaning. Anguish, suffering, and anxiety commonly accompany pain.In the 1950s many patients with severe pain due to malignancy were given frontal lobotomies (Barber, 1959). These operations disrupt the projections to the frontal lobe from the medial spinoreticulothalamic pathway. In such patients, pain intensity and threshold were unaffected, but the emotional aspects (suffering and anguish) were abolished. Unfortunately, the severe personality changes that accompanied the elimination of suffering made this an unacceptable approach to the treatment of pain. However, these clinical observations show that the affective component of pain has a separate anatomical substrate from the sensory component.The abovementioned processes were discussed in terms of a highly reliable pain-transmission system, the assumption being that pain intensity is a direct function of nociceptor activity. In fact, the excellent correlation among stimulus intensity, impulses in primary afferent nociceptors, and reported pain intensity demonstrated in human subjects under experimental conditions often does not apply to the clinical situation. The most remarkable observations are those in which patients subjected to injuries that ought to be very painful report no significant pain (Beecher, 1959).An hypothesis for spontaneous analgesia emerged when it was discovered that electrical stimulation of certain brain regions blocks responses to noxious stimulation in laboratory animals (Basbaum and Fields, 1978). This

phenomenon, stimulation-produced analgesia (SPA), became more than a laboratory curiosity when it was shown that stimulating homologous brain regions provided relief for patients suffering from chronic pain (Hosobuchi et al., 1977; Richardson and Akil, 1977). SPA has been demonstrated in a variety of animal species and in hundreds of patients.SPA can be elicited from well-defined brain stem sites. A body of evidence now indicates that SPA is mediated by a discrete neuronal network running from the midbrain to the medulla and then to the spinal cord (Figure 7-1) (Basbaum and Fields, 1978, 1984). This descending, pain-modulating pathway projects to regions of the spinal cord that contain pain-transmission neurons. Stimulation at brain stem sites that produce behavioral analgesia also selectively inhibits identified nociceptive spinothalamic tract neurons. This inhibition may underly the behavioral and clinical analgesia produced by brain stem stimulation.In addition to electrical stimulation, the analgesia network can be activated by morphine and other opiate analgesic drugs (Yaksh, 1978). The brain stem sites for SPA and the spinal cord are both sensitive to directly applied opiates. The weight of evidence indicates that opiates produce analgesia in part by activating these pain-modulating networks.One of the most important discoveries in pain research was that the brain contains substances that have the same pharmacological properties as plant-derived opiates and synthetic opioid drugs. These substances, called endogenous opioid peptides, axe present within nerve cells of the peripheral and central nervous systems (Palkovits, 1984). Of particular importance for our discussion is the presence in high concentrations of these peptides in those brain stem sites implicated in pain suppression (Basbaum and Fields, 1984). As discussed in Chapter 9, these findings have led to some promising new psychopharmacological applications.Studies of this endorphin-mediated analgesia system in laboratory animals have shown that it can be activated by a variety of stressful manipulations, including painful stimuli (Basbaum and Fields, 1984). Clinical studies indicate that it is activated after surgery and can have a significant analgesic effect (Fields and Levine, 1984; Levine et al., 1979). The important point is that there is a well-defined network for controlling pain transmission. Current evidence indicates that this network accounts for some of the striking variability of reported pain intensity in different patients who have had apparently similar noxious stimuli.It has been suggested that failure of the pain-suppression system accounts for certain types of chronic pain states (Sicuteri et al., 1984; Terenius, 1985), but most pain experts consider this conclusion premature. Much more work is needed to determine the extent to which this pain-modulating network operates on chronic pain.One of the most troublesome issues for patients, clinicians, and disability examiners is how to account for pain experiences that seem disproportionate to physical findings or objectively verifiable disease or injury. Although it is well known and well accepted that various psychosocial factors may enhance pain, the role of several physiological processes in amplifying and maintaining pain is perhaps not adequately taken into account when assessing patients' complaints.Tissue damage initiates a variety of processes that sustain and amplify pain. With repeated stimuli, the thresholds of primary afferent nociceptors progressively decrease, so that normally innocuous stimuli become painful (Campbell et al., 1979; Gybels et al., 1979; LaMotte et al., 1983). For some primary afferent nociceptors, repeated noxious stimuli may induce continuous activity lasting for hours (National Academy of Sciences, 1985). The most familiar example of this is sunburn, in which the skin becomes a source of pain; hot water applied to the skin is perceived as unbearably painful and a friendly slap on the back is excruciating. Other examples are the tenderness of a sprained ankle or an arthritic joint. In these situations it is painful to bear weight or even move the affected joint. Sensitization is a major feature of many and perhaps most clinically significant pains, but its cellular mechanism is unknown.Patients with relatively minor injuries occasionally develop pain disproportionate to their injuries. Such pain often becomes progressively worse rather than following the usual course of lessening with time. It is important to stress that the pain persists well beyond the time when the original tissue-damaging process has ended. Furthermore, the location of the pain may be quite different from the site of the precipitating pathology.In some of these patients hyperactivity of the sympathetic nervous system clearly plays a major role in sustaining the pain because selective blockade of the sympathetic outflow produces immediate and dramatic relief. The pain is usually accompanied by signs of sympathetic hyperactivity, such as a cold (vasoconstricted), sweaty limb. In addition, the skin may be hypersensitive to touch, as if the nociceptors were sensitized. With time, osteoporosis, arthritis, and muscle atrophy may set in and a permanent impairment of function may ensue. This condition, called reflex sympathetic dystrophy, usually responds to sympathetic blocks and physical therapy (De Takats, 1937; Livingston, 1943; Procacci et al., 1975). Physiological studies in animals indicate that the sympathetic outflow can induce discharge of primary afferent nociceptors. This is most prominent in damaged and regenerating afferents (Devor, 1984) but also occurs in undamaged, sensitized afferents (Roberts, 1986) (Figure 7-4).The reflex sympathetic dystrophy syndrome is relatively uncommon in its full-blown form, but sympathetic activity could be a common factor in sustaining or amplifying pain that would ordinarily fade as the injured tissues heal. If this were the ease, local signs of increased sympathetic activity could help provide objective evidence that a pain-producing pathological process is present.Nociceptor activity results in sustained contraction in muscles. In limbs, this muscle contraction produces flexion, a form of primitive withdrawal that is presumably a protective movement. Disease in the abdominal viscera (e.g., gut, liver) produces tension in the muscles of the abdominal wall. Pain arising from musculoskeletal structures also produces contraction and tenderness in other muscles innervated by the same spinal segment (Head, 1893; Kellgren, 1938).There is some evidence that this spreading muscle contraction plays an important role in clinically significant pains. In patients with persistent pain it is common to find small areas in muscles that are quite tender. Pressure over these myofascial trigger points can reproduce the patient's pain, and locally anesthetizing the points (or other manipulations of them) can give relief lasting days to months (Simons and Travell, 1983). The physiological basis of these trigger points is unknown, but the clinical evidence suggests that they are often involved in sustaining pain in the absence of ongoing tissue damage.From the material just discussed, clinical observations clearly indicate that several processes are set in motion by tissue-damaging stimuli that activate nociceptors. In the peripheral tissues, pain-producing substances are released that sensitize the nociceptors so that normally innocuous stimuli can activate them. In addition, nociceptors themselves release factors such as substance P that in turn cause vasodilation, edema, and the release of sensitizing substances from nonneural cells (Lembeck, 1983). Presumably, these processes play a role in the activation of host defenses against infection or toxins. However, they do prolong and amplify pain.For example, a noxious stimulus to the skin would activate nociceptors. These nociceptors then activate spinal reflexes that produce sustained muscle contraction with consequent activation of muscle nociceptors (Figure 7-4). In this case, the production of a second site of noxious input in muscle is due to a spinal reflex. In some cases (e.g., reflex sympathetic dystrophy), the nociceptive input also activates the sympathetic nervous system, which can feed back to the periphery to sensitize or even activate nociceptive primary afferents. Livingston (1943) was the first to emphasize the clinical importance of these positive feedback loops; that is, the pain produces muscle contraction and sympathetic outflow that in turn activate nociceptors, which produce more sympathetic outflow and muscle contraction, and so on (Figure 7-4). The point is that painful injuries set in motion secondary processes, not associated with tissue damage, that cause a prolongation and spread of nociceptive input and may contribute to chronicity. These secondary processes set up foci of nociceptive input that are independent of the original site of injury. The pain acquires, so to speak, a life of its own.Although there is no question that these factors contribute to the pain in some cases, it is not clear what proportion of patients with chronic pain have it because of these factors. This would obviously be an important area for future research on chronic pain.Damage to the peripheral or central nervous systems can produce chronic pain. For example, in some diseases that affect peripheral nerves, such as diabetes mellitus or alcohol toxicity, pain is very common. Traumatic injury to a peripheral nerve is rarely painful, but when it is, it may be dramatically so. Causalgia (heat pain) is an example of pain induced by traumatic injury to a peripheral nerve. Causalgia is a syndrome characterized by severe burning pain and signs of sympathetic nervous system hyperactivity (Mitchell, 1965; Roberts, 1986). Similarly, lesions of the central nervous system are rarely painful, but when they are, the pain is severe and resistant to treatment (Cassinari and Pagni, 1969; Riddoch, 1938).There are certain characteristics of neuropathic pain. It frequently begins several days to weeks after the injury that produces it and tends to worsen before stabilizing. It is usually accompanied by sensory abnormalities, including, paradoxically, deficits in pain sensation and painful hyperreactivity to ordinarily innocuous stimuli (Noordenbos, 1959; Ochoa, 1982).The mechanisms of neuropathic pain are not completely understood, but there are several factors that could contribute to them (Ochoa, 1982). Damaged primary afferents, presumably including nociceptors, acquire certain properties when they begin to regenerate. These include spontaneous activity, mechanical sensitivity, and sensitivity to sympathetic nervous system activity (Ochoa, 1982; Scadding, 1981).Note that under these circumstances there can be pain either without any stimulus or with a very gentle, non-tissue-damaging stimulus.In addition to the peripheral sources of pain, damage to primary afferents produces changes in the pain-transmission neurons to which they project in the central nervous system. These cells become spontaneously active and could be a source of pain, again in the absence of any noxious stimuli (Lombard and Larabi, 1983; Roberts, 1986).Trigeminal neuralgia and post-herpetic neuralgia are among the most common types of neuropathic pains. These conditions tend to strike older individuals, many of whom are retired. This may be why patients with pains that are obviously neuropathic account for only a small proportion of those who seek disability benefits. On the other hand, some patients with low back pain might have an element of nerve damage that adds to the painfulness of their problem as well as to its chronicity and resistance to conventional treatment. Further research on this issue is clearly needed, as are better methods for detecting injuries to nerves that innervate deep structures.Is there any physiological basis for differentiating between acute and chronic pain? Little is known about the effects of prolonged pain on the central nervous system. There is some evidence that the transition from acute pain to chronic pain alters patients' neurophysiology in a way that makes them somewhat different from people with acute pain. In arthritic rats, for example, there are changes in the peripheral nerves that alter their range of response to applied stimuli, and there may be changes in the central pathways for pain transmission as well (Guilbaud et al., 1985; Kayser and Guilbaud, 1984). Experiments with rats in which nerves have been injured and observed over time have shown changes in the central nervous system, but it is not known how these changes relate to pain (Markus et al., 1984).People with recurrent headaches, arthritis, low back pain, angina, or low-grade malignancies may have had pain for years. The complaints, treatment, and patients' reactions may be different for each of these conditions. In some cases, psychological factors loom large. These factors are particularly prominent in patients with low back pain, facial pain, and headaches and seem to be more prominent the longer the pain persists.Psychological and somatic factors are not completely separate in maintaining pain. For example, stress and anxiety increase both muscle contraction and sympathetic outflow and would be expected to exacerbate any ongoing pain problem to which they contribute. Conversely, any treatment that induces relaxation will reduce these factors and lessen pain. This may be one important connection between the psychosocial and the somatic factors that influence pain tolerance.In this chapter we have briefly surveyed the anatomy, physiology, and pharmacology of nociceptive transduction, transmission, and modulation. These are objective and potentially observable phenomena initiated by stimuli that damage or threaten tissue.As we learn more about the transduction process, it may be feasible to measure the concentration of substances in regions of ongoing tissue damage that activate or sensitize primary afferent nociceptors. This could give an estimate of the level of stimulation of chemically sensitive nociceptors. The most promising technique at present is direct recording of the electrical activity in primary afferents. This is technically feasible and has been used in research, but it is not presently available for general clinical use.The monitoring of central pain transmission pathways is not practical with the technology available. Although it is theoretically possible, recording single units within the human nervous system requires a potentially dangerous surgical procedure. Multiunit, or evoked-potential, studies do not have the required specificity or spatial resolution to permit collecting meaningful data about clinical pain. It is technically possible to measure the chemicals released at spinal synapses by primary afferent nociceptors. If the concentration of such chemicals in the cerebrospinal fluid could be shown to correlate with either the activity of the primary afferent nociceptors or with the severity of clinical pain, this could provide evidence similar to that derived from recording the activity of the primary afferents. However, at the present time, the transmitter or transmitters for the primary afferent nociceptors are unknown.Another approach is to use positron emission tomography (PET) to monitor metabolic activity in central nervous system pain pathways. PET is a noninvasive scanning technique that can provide evidence of focal brain activity and of the concentration of certain chemicals. This technique requires that enough neurons be active in a large enough region for a long enough period of time to be detected. Because of the topographical organization of the cortex, this technique might be used to monitor the somatosensory cortex. A precise map of the body surface spreads over many millimeters of the cortex. Representation of the face and hand on this map is very large, so it might be possible to detect ongoing activity produced by nociceptive input from these regions. At present, there is no evidence that such measurements show anything in patients with chronic pain.Indirect measures, such as those of sympathetic nervous system activity (skin temperature or skin resistance) or of muscle contraction in painful areas might be helpful in providing objective evidence of sustained nociceptive input. The measurement of skin temperature over extensive areas of the body surface, thermography, is being used clinically but is still not widely accepted as a reliable indicator of pain. Although they are simple, painless, and safe indicators of sympathetic function, indirect measures of painful input like thermography could be misleading. Sympathetic changes could be produced by nonspecific factors such as surprise or anxiety that do not involve pain. On the other hand, if the changes in sympathetic activity are highly localized, persistent, and consistent with the reported location of the patients' pain, routine evaluation of sympathetic function with techniques like thermography in patients with chronic pain might provide clues about the mechanisms sustaining the pain.Ultimately, the presence of pain in another individual is always inferred. Even if we could measure pain directly, such a measure would not be adequate to describe the experience of pain, and it is the experience that affects functioning, including the ability to work.ReferencesArmstrong, D.Bradykinin, Kallidin and Kallikrein. Vol. 25 of Handbook of Experimental Pharmacology (Erdos, E.G., editor. , ed.). Berlin: Springer-Verlag, 1970.Barber, T.X.Toward a theory of pain: relief of chronic pain by prefrontal leucotomy, opiates, placebos, and hypnosis. Psychological Bulletin 56:430-460, 1959. [PubMed: 13796585]Basbaum, A.I., and Fields, H.L.Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annual Review of Neuroscience 7:309-338, 1984. [PubMed: 6143527]Basbaum, A.I., and Fields, H.L.Endogenous pain control mechanisms: review and hypothesis. Annals of Neurology 4:451-462, 1978. [PubMed: 216303]Beechef, H.K.The Measurement of Subjective Responses. 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What are the 4 physiological processes of normal pain. Physiological pains. 4 processes of pain. 4 phases of pain process.