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Focus Article
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The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms

C. Richard Chapman* and Charles J. Vierck†

**Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah.*
†Department of Neuroscience and the McKnight Brain Institute, University of Florida College of Medicine, Gainesville, Florida.

Abstract: **The nature of the transition from acute to chronic pain still eludes explanation, but chronic pain resulting from surgery provides a natural experiment that invites clinical epidemiological investigation and basic scientific inquiry into the mechanisms of this transition. The primary purpose of this article is to review current knowledge and hypotheses on the transition from acute to persistent postsurgical pain, summarizing literature on clinical epidemiological studies of persistent postsurgical pain development, as well as basic neurophysiological studies targeting mechanisms in the periphery, spinal cord, and brain. The second purpose of this article is to integrate theory, information, and causal reasoning in these areas. Conceptual mapping reveals 5 classes of hypotheses pertaining to pain. These propose that chronic pain results from: 1) persistent noxious signaling in the periphery; 2) enduring maladaptive neuroplastic changes at the spinal dorsal horn and/or higher central nervous system structures reflecting a multiplicity of factors, including peripherally released neurotrophic factors and interactions between neurons and microglia; 3) compromised inhibitory modulation of noxious signaling in medullary-spinal pathways; 4) descending facilitatory modulation; and 5) maladaptive brain remodeling in function, structure, and connectivity. The third purpose of this article is to identify barriers to progress and review opportunities for advancing the field. This review reveals a need for a concerted, strategic effort toward integrating clinical epidemiology, basic science research, and current theory about pain mechanisms to hasten progress toward understanding, managing, and preventing persistent postsurgical pain.**

Perspective: ***The development of chronic pain after surgery is a major clinical problem that provides an opportunity to study the transition from acute to chronic pain at epidemiologic and basic science levels. Strategic, coordinated, multidisciplinary research efforts targeting mechanisms of pain chronification can to help minimize or eliminate persistent postsurgical pain.***

Key words: *Acute postoperative pain, persistent postsurgical pain, pain chronification, epidemiology, neurophysiology.*

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Address reprint requests to C. Richard Chapman, PhD, Pain Research Center, Department of Anesthesiology, University of Utah, 615 Arapeen Dr, Suite 200, Salt Lake City, UT 84108. E-mail: Richard.Chapman@hsc.utah.edu

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Chronic pain is a pressing medical and socioeconomic problem in the United States. Approximately 100 million adults are living with some form of chronic pain. Consequently, the number of Americans with chronic pain exceeds the total of Americans suffering from cancer, diabetes, and heart disease combined. The cost to American society for all forms of chronic pain is approximately $635 billion a year.[120]

This includes expense for medical treatment and also lost work productivity.

In response to the 2010 Patient Protection and Affordable Care Act, the Institute of Medicine prepared a report titled "Relieving Chronic Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." This report called for a strategically guided cultural transformation in how American society and medicine deals with the problem of chronic pain. Key steps in this transformation are recognizing chronic pain in its various forms, identifying the mechanisms of chronic pain development, and formulating steps for its prevention.

The first step in identifying the mechanisms of chronic pain development is to investigate the acute pain from which it arises. Examination of injuries that generate acute pain, and the acute pain process itself, may reveal potential risk factors for the development of chronic pain. Similarly, demographic, medical, and psychosocial patient characteristics are plausible risk factors for pain chronicity. Identified risk factors can provide clues about possible underlying mechanisms of pain chronification. An integration of studies that define the nature of chronic pain development in a specific patient population with research directed at potential mechanisms represents a sound strategic basis for engaging the problem of chronic pain.

Implementation of this strategy requires large scale, comprehensive studies of painful conditions that progress from acute to chronic pain. Postoperative pain is an excellent place to begin such work because acute postoperative pain occurs with high frequency and in controlled conditions. From the viewpoint of epidemiology, it represents a natural experiment that addresses the transition of acute pain to chronic pain.

This article has 3 primary goals. The first is to review current knowledge and hypotheses on the transition from acute to persistent pain after surgery. To this end, we briefly summarize literature in the following areas: 1) clinical epidemiology studies of persistent postsurgical pain (PPSP) development; 2) basic neurobiological studies targeting mechanisms in the periphery; 3) basic neurobiological studies targeting mechanisms at the spinal cord and cerebral targets of spinal projection; 4) studies of descending pathways involved in inhibitory and facilitatory modulation of noxious signaling at the spinal cord; and 5) functional and structural brain imaging studies that examine changes in higher brain structures and functions associated with pain chronification. We attempt to provide a conceptual map of research in this emerging field.

The second goal is to integrate the information and causal reasoning in areas of relevant literature. Numerous models now exist in basic neurobiolgy and in the area of neuroimmune interactions, and they guide research at all levels of the neuraxis. We have tried to identify conceptual elements behind the various models, bring them forward, and assemble a relatively coherent picture of the collective thinking behind the work.

The third goal is to identify barriers to progress in the field, including the absence of work in certain key areas. A review of opportunities for advancing the field complements the assessment of barriers and shortcomings. Finally, we evaluate the potential value of building lines of communication across researchers working at different levels of the neuraxis and coordinating work in clinical epidemiology with basic science research.

The literature review in this article is selective rather than exhaustive. Because the primary goal is to provide a conceptual map of the field, we have focused on the areas of investigation and the reasoning behind the work rather than on the body of knowledge accumulated to date. A thorough review of each of the areas included in this cross-disciplinary article would prove infeasible for a single article. Our broad objectives are to characterize the emergence of this important but diversified field of research, to articulate the Zeitgeist that surrounds it, to identify barriers to progress, and to point out opportunities for advancing progress in this line of research.

Definitions

The field has reached only partial consensus on key definitions. Therefore, we provide here definitions for the fundamental phenomena that his article addresses. Other definitions appear in context as needed.

Pain

The International Association for the Study of Pain (IASP) defines pain as "…an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Psychophysiologically, in addition to its subjective, or phenomenal, aspect, pain involves underlying physiological processes that involve sensory and autonomic nervous systems, circulating catecholamines and other stress-response hormones, and immune system responses to the autonomic and hormonal signaling.[61] Clinically, pain states may be either acute or chronic.

Acute Pain

Acute pain is an unpleasant, complex, dynamic psychophysiological response to tissue trauma and related acute inflammatory processes. Normally, acute pain is self-limiting and confined to a given period of time. It arises in response to tissue injury, disease, or inflammation. Acute pain serves a protective biological function that minimizes behaviors that incur risk and fosters tissue healing. Although in a primitive environment, acute pain promotes survival, in medical settings such as recovery from surgery, the physiological processes that accompany acute pain, if uncontrolled, can exert deleterious influences on health. Although the severity of acute postoperative pain is important, the rate at which acute pain resolves is also one of its key features.[60]

Chronic Pain

Pain has become chronic when it lasts beyond the healing of injured tissue and the related inflammatory processes. Many chronic pain conditions last indefinitely. A

chronic pain syndrome is a constellation of chronic pain symptoms that do not respond to the medical model of care. A chronic pain syndrome affects the patient adversely by inducing depressed mood, fatigue, reducing activity and libido, promoting physical deconditioning, and leading to disability out of proportion to documented impairment and pathophysiology. There are many chronic pain syndromes, and some may result from more than 1 etiology.

PPSP

Fortuitously, a large-scale natural experiment is available to help us engage the problem of chronic pain. Elective surgeries are acutely painful events that can lead to chronic pain. Patients undergo surgery for a wide range of conditions, and an estimated 10 to 50% of them develop PPSP.[160,172,219,339] Therefore, PPSP, a major problem in its own right, provides a natural experiment for the investigation of how chronic pain develops from acute pain.

PPSP encompasses a family of chronic pain syndromes that originated with surgical trauma. In some cases, the subjective features of PPSP may bear little resemblance to the acute postoperative pain from which it stems but relate nonetheless to the surgery (eg, phantom limb pain). Acute postoperative pain normally resolves within 2 to 10 days after surgery. Merskey and Bogduk,[243] in the IASP's classification system for chronic pain syndromes, describe PPSP as "a persistent pain state apparent two or more months' postoperatively that cannot be explained by other causes." Some contend that this definition is overly simplistic and is purely arbitrary, but the criterion of 2-month duration provides a practical basis for defining the onset of chronicity.[171] Presumably, peripheral and central neuroplastic changes can take place and sustain pain that should disappear with healing. Macrae[219] proposed a 4-point definition of PPSP. Postoperative pain qualifies as chronic if: 1) the pain has emerged as a consequence of surgery, 2) its duration is at least 2 months, 3) no other explanation exists for the pain, and 4) the pain is not a continuation of a preexisting chronic pain condition for which the surgery was performed. The IASP established a task force charged with developing a classification for chronic pain that would fit within the upcoming 11th revision of the World Health Organization's international classification of diseases.[360] The task force identified 7 diagnoses for chronic pain including among them "chronic postsurgical and posttraumatic pain." This is a pain that develops after a surgical procedure or tissue injury and persists for ≥3 months.

Research on Persistent Postoperative Pain

Scope of the Problem

In 2004, 187.2 to 281.2 million patients underwent surgery worldwide. This translates to approximately 1 surgery per every 25 persons.[403] In 2010 in the United States, more than 51 million inpatient surgeries took place.[366] A classic survey[12] revealed that approximately 80% of randomly selected postsurgical patients reported having experienced acute postoperative pain. Of these, 86% had moderate, severe, or extreme pain, with more patients experiencing pain after discharge than before.

Although most postoperative pain disappears with healing, surgery leaves a surprising number of patients with PPSP. The magnitude of the PPSP problem is substantial.[79,85] Johansen and colleagues conducted a large-scale survey of the general population in Norway.[160] In the preceding 3 years, 24% of respondents had undergone 1 or more surgical procedures. Of these, 40.4% reported chronic pain in the area of the surgery and 18.3% had moderate or severe chronic pain. Kehlet et al estimated that overall the incidence of chronic pain after surgery ranged from 10 to 50% with 2 to 10% of patients enduring severe chronic pain.[172] If this holds for the 48 million annual inpatient surgeries in the United States, chronic postsurgical pain will develop each year in 4.8 to 24 million patients, and it will be severe in 960,000 to 4.8 million cases.

Numerous studies have examined the incidence of PPSP related to specific surgeries. Phantom limb pain after amputation is perhaps the most readily recognized and best described persistent postsurgical chronic pain syndrome.[265] Reported incidence of chronic phantom limb pain varies from 30 to 81%.[281] PPSP after breast cancer surgery is also a major clinical problem, with reported incidences ranging from 25 to 60%. In a large, nationwide study, 47% of women experienced chronic pain after breast surgery, and of these, 13% reported that it was severe.[119,292] At least 5.9% of patients experienced chronic pain after Cesarean section,[264] and after vasectomy chronic pain occurs in up to 15% of men.[18] Studies of PPSP 4 months after inguinal hernia surgery estimate that pain persists in 39.5% of patients.[295,296] Studies of post-thoracotomy pain revealed that it becomes chronic in 25 to 60% of cases.[290] Other procedures studied for chronic pain after surgery include laparoscopic cholecystectomy,[34] hysterectomy,[41] and radical prostatectomy.[125] Reviews of PPSP in these and other procedures appear in Katz and Seltzer[171] and Kehlet et al.[172]

Research Approaches

Research on the acute postoperative pain to PPSP transition falls into 2 domains or paradigms: 1) clinical epidemiology, and 2) basic mechanisms. Clinical epidemiology seeks to identify patient features and medical variables that are risk factors for the development of chronic pain after surgery.[126] These studies can reveal mechanisms if they are prospective and identify the timing of certain influences. Basic research encompasses studies on potential mechanisms in the periphery and maladaptive neuroplastic changes in spinal cord and brain function and structure that are associated with effects on pain. These studies depend on appropriate assessments of pain intensity and/or pain sensitivity.

Clinical Epidemiology of Postsurgical Pain

Clinical epidemiology is the application of the science of epidemiology in a clinical setting. Its focus is a specific, medically defined population. The clinical epidemiologist attempts to determine who is at risk for a particular problem, in this case PPSP, and a goal has been to optimize postoperative pain control. This line of inquiry has done little to reveal mechanisms of pain chronification because of limitations associated with infrequent data acquisition via questionnaire, variations in anesthetic regimens, and sparse information on pain persistence for different kinds of pain. However, collection of pain report data over months or years after surgery permits approximate estimations of chronic pain persistence curves and influences on them. The chronic pain persistence curve concept, as we use it here, is a simple adaptation of the conventional survival curve. It depicts the proportion of patients reporting pain across multiple points of time after a specific event such as a particular type of surgery. Three key features of the chronic pain persistence curve are pain intensity, duration to an end point (0 pain or a plateau), and rate of change in incidence.

Here, we summarize results and insights from clinical studies of an intensively investigated surgical procedure. Unlike mega reviews that address limited questions on data combined from investigations that meet stringent methodological criteria, we consider studies individually with the goal of identifying factors that consistently influence chronic pain despite variations in experimental paradigms.

Thoracotomy

Chronic postoperative pain is common among patients who have undergone surgery accessing the heart, lungs, or esophagus. Rib retraction injures somatic and visceral tissues and traumatizes intercostal nerves. Fundamental research questions in this area address the intensity and maximal duration of pain after thoracotomy. In most studies of chronic post thoracotomy pain, the primary measure is the percent of patients who report pain when queried at set time points extending for months or years after surgery. The estimated pain persistence curve for thoracotomy is a gradual decline from a universal pain presence within the first week to 1 year, when the average incidence across 5 studies[80,169,221,283,290] was 55.6% (range = 52–61%), to 7 years, when 21% of 600 respondents reported pain.[221] The overall rate of decline over 7 years was 17% per year.

Generalized chronic pain persistence curves are deceptive in some respects, because of numerous factors that can increase individual variation. Research to date reveals the following:

- The proportion of patients reporting pain over an extended period of time is greater for younger patients[129,221,267,290,347] and women.[128,129,267] Other risk factors for pain chronicity include: pain intensity in the first postoperative week[128,129,169,172,196,283,284] and the extent of surgery.[284,290,347]
- The method and duration of early postoperative pain management can determine the incidence and intensity of chronic postoperative pain.[129,163,325,353]
- Postsurgical pain for individual patients can onset early or late, can be continuous or intermittent, and can fluctuate up or down over time.[128]
- The spatial distribution of pain, including allodynia and hyperalgesia in relation to the incision, can vary over time.[342]
- Different types of postoperative pain may have distinct chronic pain persistence curves.[135,221]

Pain Trajectories

Averaging chronic pain persistence curves across all surgical patients does not represent important differences between individuals. For example, one thoracotomy study describes 2 patient populations, each with distinctly different chronic pain persistence curves. Mean pain ratings (0–10) increased from 2.8 to 3.5 over postoperative weeks 4 to 48 for patients who developed chronic pain, compared with a decrease of 2.2 to 0 over the same period for patients who did not report pain at 48 weeks.[129] An approach that accounts for such differences is necessary. For example, a popular hypothesis is that neuropathic pain is responsible for long-duration pain trajectories.[27,127,135,169,172] Investigations that have compared neuropathic with non-neuropathic pain have reported that neuropathic pain is more severe, requires more analgesic medication, and interferes with daily activities to a greater extent.[27,135,221,347] However, the mechanism for chronic neuropathic pain is not certain and may or may not be attributable only to nerve injury, which likely occurs during all thoracotomies.[135,308,347] Also, clear evidence has not yet emerged that neuropathic pain resolves more slowly or less frequently than non-neuropathic pain after thoracotomy, in part because characterizing chronic pain as neuropathic after it has developed proves difficult. Some investigators attempt to do this by identifying the unique subjective qualities of neuropathic pain, and work is under way to develop and fully validate neuropathic pain questionnaires.[157,364] In a sample of 204 patients who received thoracotomies, 42% of patients reported pain at nearly 2 postoperative years, 23% of those with pain qualified as definitely neuropathic, 30% with pain qualified as possibly neuropathic (meeting some but not all criteria), and 47% were definitely not neuropathic.[347] Thus, this study included at least 3 varieties of chronic pain, possibly with different pain trajectories.

Prevention of Chronic Surgical Pain

An apparent long-term effect of pain control in the first week after thoracotomy suggests a possible approach to preventing chronic postsurgical pain. Because acute pain intensity is a risk factor for chronicity, clinical investigators have attempted to control acute postoperative pain aggressively. Typically, this involves the administration of a systemic opioid and a

nonsteroidal anti-inflammatory drug, along with delivery of a local anesthetic to peripheral afferents supplying the surgical field (eg, epidural or paravertebral injection for thoracotomy). Critical factors in the efficacy of this approach to preventing chronic pain appear to be the amount and duration of local anesthetic treatment. A systematic review examining the use of regional anesthesia to prevent PPSP reported that epidural anesthesia can prevent the development of PPSP in approximately 1 of every 4 to 5 patients.[11]

Examples of chronic pain prevention by analgesic medication during thoracotomy and subsequent hours or days are: 1) patients who received epidural morphine and ropivacaine for 48 postoperative hours had a reduced incidence of pain at 3 and 4 postoperative months, compared with patients who received intravenous (i.v.) fentanyl for 48 hours[217]; 2) paravertebral intercostal nerve block with nonsteroidal anti-inflammatory drug administration prevented chronic pain beyond 2 months[314]; 3) epidural bupivacaine and morphine self-administration for 72 hours significantly reduced chronic allodynia and improved performance of daily activities at 6 and 12 months, compared with subjects who received cryoanalgesia of intercostal nerves[163]; 4) at six postoperative months, the incidence of chronic pain was 45% for patients who received epidural bupivacaine and morphine during surgery and for 48 subsequent hours, compared with an incidence of 78% for patients who received i.v. morphine[325]; and 5) in a survey of pain intensity rather than incidence, subjects received epidural ropivacaine and morphine infusion for 48 hours postsurgically and i.v. ketamine or saline for 72 postoperative hours. Significantly lower mean pain intensities at 1 and 3 months, but not at 6 months, were obtained for subjects receiving ketamine.[353] The inclusion of ketamine provided a test for the hypothesis that central sensitization is a factor in development of chronic postoperative pain. A systematic review examining the efficacy of systematic drugs for the prevention of PPSP reported 14 randomized controlled trials using ketamine.[58] Meta-analysis revealed a modest reduction in the incidence of chronic pain after surgery. However, most of the trials had small samples sizes, thus increasing the risk of overestimation of effect.

Attenuation of chronic post-thoracotomy pain by aggressive early analgesic medication is consistent with identification of early pain intensity as a risk factor for chronic pain, and it suggests that the development and/or maintenance of chronic pain depends on a sensitizing influence of the high pain intensity that occurs early after surgery. Neuropathic pain draws suspicion as a sensitizing influence because of its typically high-intensity. These observations call for thorough prospective investigations of the time course of acute neuropathic and non-neuropathic pain attenuation after administration of specific analgesic protocols, compared with conventional pain management. Such studies would require documentation of the effectiveness of analgesic treatment of chronic postoperative pain for individual subjects characterized as neuropathic or non-neuropathic. In a study of total knee arthroplasty patients, daily treatment for 2 weeks with pregabalin (300 mg) reduced pain and opioid consumption immediately during hospitalization compared with placebo control participants.[50] It also improved range of motion in the first 30 days of rehabilitation. At 3 and 6 months postoperatively, patients who received pregabalin had a lower incidence of neuropathic pain than did placebo control participants.

Surgical Neuropathy

Pain is neuropathic when it stems from a primary lesion or dysfunction in the nervous system.[335,336] Many clinicians and investigators hold that neuropathy is a major cause of PPSP,[141,160,171] resulting from iatrogenic damage to sensory nerves. Some degree of nerve injury is inevitable with surgery.[39]

Nerve trauma during surgery mostly involves partial damage to peripheral axons through blunt trauma, including crush, stretching, perineural inflammation, compression, and scar formation, with entrapment of sensory fibers and/or neuroma formation. Regional anesthesia techniques can also damage peripheral nerves, producing neurogenic postoperative pain.[46,193,413] In general, partial damage to sensory axons during surgery leads to spontaneous activity and a lowered threshold for activation, along with increased responses to a normal stimulus. Hyperesthesia can be attributed to increased sensitivity of uninterrupted but injured axons that develop increased densities of abnormal sodium channels, and this condition sets the stage for spontaneous ectopic discharges. An iatrogenically damaged nerve can develop ectopic neuronal pacemakers at various sites along its length. Also, expression of receptors along its axons can be altered, which makes it more sensitive to algogenic substances, and it may even respond to substances to which it is normally unresponsive.[401] The inflammatory response associated with surgery can alter gene expression at the dorsal root ganglion, and this increases synthesis of peripheral receptors that sensitize the nociceptors.

During surgery nerve transection is unavoidable. A fully severed or axotomized nerve typically undergoes Wallerian degeneration.[94] Regenerating nerves can produce traumatic neuromas at their severed ends due to unregulated nerve degeneration, often near a scar.[116] These bulbous swellings are made up of abnormal sprouting axons that can respond to catecholamines. Neuromas can accumulate abnormal sodium channels that contribute to their sensitivity and activation. Similarly, dorsal root ganglion neurons produce ectopic discharges that can generate pain as well as paresthesias.

Assessment of neuropathy in PPSP is challenging, and the literature to date lacks uniformity in reporting the prevalence and sensory characteristics of PPSP.[141] Qualitative features of neuropathic pain arising from peripheral sensory nerve injury include sensations of prickling, tingling, burning, pins and needles, or electrical shock-like sensations. True neuropathic pain after surgery should have an anatomical as well as a temporal

relationship to the surgery and manifest associated sensory disturbances with features that correspond to criteria used in neuropathic pain-specific questionnaires. Johansen et al[160] queried survey respondents about sensory abnormalities associated with the site of past surgery and reported them to be strongly associated with the severity of PPSP.

Overview of Risk Factors

The risk factors identified for chronic pain after thoracotomy, as reviewed previously, plus those listed in this section, have been confirmed in numerous studies of a variety of surgical procedures, strongly reinforcing their validity. Risk factors for PPSP can be either surgery-specific or patient-specific. Surgery-specific factors further break down into preoperative, intraoperative, and postoperative factors, depending on their relationship to the surgical procedure. A combination of surgery-specific and patient-specific factors offers the best risk assessment.[1]

Preoperative Factors

These are patient-specific factors that comprise existing conditions or traits that the patient brings into the surgical setting. Preoperative factors can be constitutional such as gender, age, and genetic predisposition, or psychological such as depression and a tendency to catastrophize. Medical history variables such as preexisting pain or comorbidities are also preoperative factors.

Preexisting pain. Patients may have pain related to the pathology that the surgery is addressing, or the pain may stem from unrelated chronic pain conditions. For example, a patient with a painful arthritic knee might undergo surgery for hernia repair. Regardless of the origin of the preexisting chronic pain, it predisposes patients to a slower rate of postoperative pain resolution. Radical prostatectomy patients with preoperative chronic pain reported more severe acute postoperative pain, which could subsequently progress to PPSP.[125] The severity of preoperative pain has emerged in many studies as a factor contributing to the development of persistent postoperative pain.[1,171,195,263,265,417] Fibromyalgia syndrome (FMS) also increases risk for PPSP. Increasing score on a fibromyalgia questionnaire is associated with increasing PPSP risk after lower extremity arthroplasty.[47]

Demographic factors. Basic demographic factors have proven useful for establishing risk for PPSP. Over the past decade, clinical as well as epidemiologic findings indicate that women are at increased risk of developing chronic pain conditions, and they report high levels of acute procedural pain.[55,107,233] Increasing age reduces the risk of chronic pain in breast surgeries, hernia repairs, and laparoscopic cholecystectomy.[34,219,295,337,356] A progressive loss of cerebral cholinergic neurons with age may be related to the reduced reactivity to pain with age.[387]

Psychosocial factors. A systematic review of psychosocial predictors of PPSP revealed that psychological vulnerability, particularly depression, and traits such as neuroticism and anxiety are equally important postsurgical factors, increasing the risk of PPSP.[144,172] Some patients have a tendency to regard an aversive or challenging situation as if it were utterly disastrous. This tendency, termed catastrophizing, is a risk factor for the development of PPSP, and it also predicts the severity of acute postoperative pain.[278,280,352] Preoperative neuroticism emerged as an independent risk factor for early postoperative pain after laparoscopic cholecystectomy in a multivariate analysis model.[34] Reviews of psychological and psychosocial factors as predictors of postoperative pain intensity and PPSP are available elsewhere.[171,265]

Presurgical pain sensitivity and pain modulation. Patients who come to the surgical encounter with abnormal sensitivity to painful events seem to be at greater risk for PPSP.[277,407] For example, postherniotomy patients who had a high pain response to a standardized heat stimulus preoperatively had greater risk for PPSP.[1]

Preoperative sensory testing of elective surgery patients can help identify individuals who are at risk for PPSP.[97,410,423] Quantitative sensory testing methods can evaluate the integrity of large and small fiber function, including allodynia and hyperalgesia. Preoperative hyperalgesia and poor inhibitory modulation appear to increase vulnerability for subsequent chronic pain. Low, or inefficient, conditioned pain modulation (CPM; described in the Conditioned Pain Modulation section) is a risk factor for chronic pain in general and for the development of chronic pain after surgery.[370,422]

Pain genetics. Several reports provide a review of findings on the genetics of pain susceptibility.[108,171,175,252,361] Pain genetics is a young, rapidly developing field. It promises to account for trait variance in chronic pain states as well as vulnerability to developing chronic pain. Individual differences are high in almost all chronic pain syndromes. Strong interindividual variation characterizes the sensitivity of pain-free volunteers to experimental pain stimuli, the rates at which patients develop chronic pain after undergoing common surgical procedures, the severity of the chronic pain syndromes patients report, and the pain relief patients report in response to standard analgesic interventions such as opioid medications. Such marked individual differences may derive from genetic variation in pain sensitivity, differences in endogenous pain modulation, varied environment influences, or gene by environment interactions, including epigenetics. This line of inquiry in the PPSP domain attempts to identify who is most at risk for developing chronic pain after surgery, and it indicates that postoperative pain should be managed on a case by case basis rather than a standard ward protocol. The long-range goals of such research include improved diagnosis of PPSP conditions and, ultimately, gene therapy.

Max and Stewart[234] identified 2 types of pain genetics investigations. The first attempts to identify polymorphisms that alter vulnerability for developing a structural lesion that causes pain, such as a herniated disk. They labeled such polymorphisms as disease genes related to

painful conditions. The second type of study seeks to identify polymorphisms that code for molecules that affect the neural processing that underlies chronic pain. For example, many patients undergoing surgery suffer nerve injury, but only a few develop chronic neuropathic pain as a result. This line of research endeavors to identify which polymorphisms increase vulnerability to chronic pain and, conversely, which are protective. One hypothesis is that chronic pain is more likely to emerge in surgical patients whose genetic makeup causes them to have higher than normal pain sensitivity or an exaggerated pain response.[89] Other hypotheses target genetically determined molecular mechanisms in the periphery or in the central nervous system (CNS) that could sustain sensitized transduction or transmission of noxious signals. Still others pursue polymorphisms that could cause the failure of key inhibitory processes that modulate the transmission of noxious signaling. A problem common to these and related studies is determining and quantifying the pain trait that defines chronic postsurgical pain.[171] Chronic pain syndromes have many features, and different polymorphisms may well determine different features. The lack of consensus on what constitutes a multivariate phenotype for PPSP is a major barrier to progress in this field.

Katz and Seltzer[171] point out that, although there are numerous links between different polymorphisms and features of various chronic pain syndromes, there is, as yet no identified genetic basis for the risk of developing chronic pain after surgery. Mogil[252] provides a comprehensive review of the current state of knowledge in Mendelian genetics related to pain. The scope of this review included acute pain, inflammatory pain, back pain, musculoskeletal pain, neuropathic pain, cancer pain, visceral pain, experimental pain, widespread pain, and idiopathic (functional) pain. Mogil clearly articulates the dilemma that investigators face: "…if one does find a gene variant with broad effects on chronic pain, is it more likely that the gene participates in pain physiology per se, or in the physiology of psychological modulators of pain (eg, anxiety, depression, anger, or catastrophizing)?" This conundrum underscores the importance of rigorously defining a multivariate phenotype for PPSP.

Much of the enthusiasm for progress in pain genetics derives from the hope that new discoveries will lead to new drug development. Mogil[252] concludes that the challenge of work in this area is enormous because the extent of the problem is much larger than initially anticipated. "At the present time, I am not optimistic about pain geneticists explaining enough trait variance in clinical pain states or analgesic response to serve as a guide to individualized pain therapy any time soon."

Pain epigenetics. Epigenetics is the study of heritable changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence, namely DNA methylation and histone modification that bring about chromatin remodeling. Epigenetics explains how heritable phenotypes can occur in response to changes in gene expression that the environment has caused without concomitant alteration in the DNA sequence. The fundamental principle is that experience, whether one's own or that of one's progenitors, can turn off or turn on the expression of specific genes through chromatin remodeling. Thus, epigenetics bridges the once presumed separate influences of genes and environment. Notably, in addition to explaining the influence of traumatic childhood experience on adult pain sensitivity, this field accounts for how the effects of parents' experiences pass down to the child and to subsequent generations. Conceivably, the acute to chronic pain transition might depend on the priming influences of changes in chromatin structure.

To date, the inchoate field of pain epigenetics has yielded only a modest volume of pain-relevant literature. There is, however, a substantial literature on epigenetic regulation of memory and neuroplasticity, which is relevant to pain processing.[83] Epigenetic mechanisms may silence the expression of pro- or antinociceptive genes, and they may modulate the pharmacology of analgesic drugs.[91] Denk and McMahon[88] posited that epigenetic mechanisms contribute to the development of chronic pain states in 3 main areas: 1) regulation of peripheral inflammation, 2) gene expression in nociceptive processing, and 3) neuroplasticity and cortical pain processing. This field is promising but very challenging, because epigenetic changes related to chronic pain syndromes probably involve multiple genes, and epigenetic influences may be uneven across cell types. Major advances await the development of additional technology. A fascinating aspect of this work is that it bridges the traditional mind-body problem of how early childhood experience and trauma can set the stage for chronic pain development. Unlike genetic determinants, epigenetic influences are potentially reversible through psychotherapy, pharmacotherapy, and other environmental influences.

Intraoperative Factors

Intraoperative factors are surgery-specific. An early article by Crombie and colleagues[77] identified surgical trauma and nerve injury as major risk factors in the development of chronic pain, and later studies support these observations.[1,411] Several other intraoperative factors have attracted the attention of researchers. These include anesthetic technique,[34,41,64,264,291] extent of surgery,[290,292] and anatomical site, especially ear, nose, and throat surgery.[340] Additional intraoperative factors associated with the development of PPSP include increased duration of surgery, whether the surgery takes place in a low- versus high-volume surgical unit; and whether the operation is open versus laparoscopic in approach.[171]

Postoperative Factors

Strong correlation exists between the severity of acute postoperative pain and its transition to PPSP.[162,290,292] More severe acute postoperative pain increases the likelihood of chronic pain development. Accordingly, the quality of effective perioperative pain control is related to the development of PPSP.[408] Also, postoperative treatments related to a preoperative condition can

be expected to enhance PPSP.[337] For example, radiotherapy treatments can extend for months after the procedure. Radiation to the axilla may cause brachial plexopathy and consequent neuropathic pain. Andersen et al[9] examined the development of chronic pain in women who had undergone breast cancer surgery and identified radiation therapy as a risk factor for more intense chronic pain 2 months after surgery. Poleshuck et al[292] replicated this observation.

Quality of postoperative pain management appears to influence pain chronicity.[255] In a study of orthopedic surgery patients, intervention patients receiving physical therapy and more aggressive analgesic treatment during hospitalization had less pain and better function than control participants, who received standard care. At 6 months postsurgery the intervention patients reported less pain with walking and were less likely to use analgesic medications.

Postdischarge pain management is an understudied postoperative factor. It is common practice to ignore postoperative pain management after surgical patients leave the hospital. Apfelbaum et al[12] reported that patients experienced more postoperative pain after going home. Joshi and Ogunnaike[162] reviewed literature that showed the following: 1) Many studies report increased incidence of pain at home, 2) Pain is one of the most common causes for readmission after outpatient surgery, 3) Pain delays return to daily living functions, and 4) Pain is the most frequent reason for postsurgical patients to contact their general practitioner after discharge from a hospital. Few studies have addressed postoperative pain in patients discharged from the hospital, although this could prove informative for the question of how acute postoperative pain becomes chronic.

Chapman et al[59] tracked postoperative pain for 6 days after elective surgery, creating a postoperative pain trajectory for each patient. The pain trajectory is a linear fit of pain intensity across time with 2 features: 1) the intercept or initial level of postoperative pain, and 2) the slope or rate of change in pain over days. Of the 502 patients studied, 63% showed the expected pattern of gradual pain resolution over days after surgery, but 25% of the sample showed a flat trajectory over 6 days with no meaningful change in the intensity of the pain they reported initially. The remaining 12% of the patients reported steadily increasing pain over 6 days. Thus, approximately 37% of the patients went home after discharge with pain that was not resolving or was worsening. The postoperative pain trajectory quantifies not only the level of each patient's postoperative pain but also the rate at which the patient resolves that pain. This approach provides a potentially valuable tool for studying risk associated with postoperative pain management in patients who could go on to develop chronic pain.

Summary of Risk Factors

A fundamental underlying assumption in clinical epidemiology research is that risk accumulates; as a given patient facing surgery accrues more and more risk factors, his or her risk of developing PPSP increases additively.[1] Some investigators have sought to form preoperative prediction rules that will allow them to identify who is at high risk for the development of chronic pain before the surgery takes place.[166]

Table 1 provides a list of preoperative, intraoperative, and postoperative risk factors associated with the incidence or severity of chronic postsurgical pain. Some of these are generic in nature, applying to all procedures, whereas others are specific to certain types of surgeries, and they apply to some patients but not others.[153,296,339] The existing literature on PPSP presents replications of significant risk factor effects across numerous studies of many surgical procedures. However, a better appreciation of risks would exist if PPSP studies had followed the pain trajectories of individual patients, providing estimates of pain intensity or probability over time when a given risk is a factor. On the basis of currently available probabilities that a variety of risks can influence chronic pain, there is no consensus concerning recommended clinical approaches when certain risks or combinations of risks are present for individual surgical patients.

Table 1. Risk Factors for the Development of Chronic Postoperative Pain

Risk Factors
Preoperative
Demographic factors
Gender
Age
Preexisting pain
Response to experimental pain assessment
Pain genetics
Pain epigenetics
Psychosocial factors
Depression
Anxiety
Neuroticism
Catastrophizing
Poor coping strategies
Low sense of control
Poor social support
Illness preoccupation
Negative expectations
Stress
Intraoperative
Anesthetic technique
Extent of surgery
Anatomical site of surgery
Duration of surgery
Low- or high-volume surgical unit
Open versus laparoscopic surgical technique
Hernia repair technique
Pericostal versus intracostal stitches
Intraoperative nerve damage or a surgical approach that risks nerve damage
Postoperative
Severity of acute postoperative pain
Perioperative pain management
Radiotherapy associated with breast cancer surgery

Candidate Mechanisms for Pain Chronification

Presumably, all patients who develop chronic postsurgical pain initially experience acute surgical pain. Potential mechanisms exist at peripheral as well as central levels for the transition from acute to chronic pain.[22] Most investigators concerned with central mechanisms target neuroplastic changes at the dorsal horn of the spinal cord, but recently investigations have focused on higher brain structures, including changes in white matter connectivity or the volume of neural networks activated by pain or affective reactions to pain. Another approach targets the loss or dysregulation of endogenous pain modulation. Whether pain chronification involves a relatively sudden change in state—that is, a distinct transition—or a gradual change in pathophysiology remains uncertain.[200] If the former, then when this occurs is of critical importance. If the progression to chronicity is gradual, then the trajectory of this progression and the time at which it is complete are of paramount importance.

Models of Increased Nociceptive Sensitivity

Surgical models of tissue injury in laboratory animals are available, with or without nerve injury, that closely mimic human pain-generating injuries. Investigations using animal models avoid the complexities associated with psychosocial factors, personality variables, comorbidities, and genetic variation, allowing investigators to focus clearly on basic mechanisms. Animal models are excellent for studying peripheral pathophysiology related to neurotrophins, prostaglandins, kinins, and neuroinflammation after tissue or nerve injuries of various sorts. They are well suited for studying inhibitory and facilitatory modulation. Animal laboratory models offer the advantages of statistically adequate sample sizes, precise control of surgical trauma, extensive repeated measurement, and quantification of central neuroplastic changes associated with chronic hyperalgesia.

Animal models permit rigorous testing of hypotheses about mechanisms for pain chronification that would be infeasible or impossible in humans. It should be possible to define normal recovery from surgical tissue injury and contrast this with the persistence of enhanced pain sensitivity in animals subjected to additional factors such as specific nerve injuries. Laboratory animal models should provide insights into the question of why some individuals have no PPSP, some have persistent PPSP that eventually resolves, and others develop PPSP of indefinite duration after tissue or nerve injury. However, valid answers to these questions will not be forthcoming if basic scientists continue to use the methods of behavioral testing that have dominated laboratory animal investigations intended to reveal effects of experimental treatments on pain.

Most laboratory animal studies of nociception have evaluated spinal flexion/withdrawal reflexes, despite the inability of reflex tests to assess pain sensitivity. Because multiple reviews address the inherent failings of reflex tests to reveal pain,[372-374,379,381,382,386] we need not do that in this article. Put simply, reflex tests assess spinal processing of nociceptive input to spinal interneurons within reflex circuits that output directly to motoneurons to evoke responses that occur before or long after pain sensations occur, depending on the stimulus.[386] Spinal circuits subserving flexion/withdrawal reflexes are not components of spinothalamocortical projection systems for nociceptive input but are integral to motor systems that control balance and locomotion.[44,96,132,155,238,310] Of critical importance, reflex tests produce results that are often incompatible with the pain sensitivity of humans, in contrast to comparable results obtained with operant escape and human psychophysical tests of pain sensitivity.[232,386] Valid animal models of pain must mimic human pain conditions and also must be as similar as possible to human tests of pain sensitivity. The psychophysical methods used for human pain testing rely on conscious perception and reporting of pain, not on reflex responding. Therefore, the optimal strategy for evaluation of pain in laboratory animals is to train them to escape nociceptive stimulation consciously. Learning to evaluate evoked sensations and respond accordingly brings into play the entirety of the peripheral to cerebral cortical systems that participate in the encoding of perceived pain and the emotional and motivational reactions that elaborate and act on pain.

Because few animal laboratory pain studies have used escape procedures, we often are left to discuss neurobiological findings obtained with procedures presumed to produce acute or chronic pain in laboratory animals but with little or no behavioral evidence for abnormal pain sensitivity.

Peripheral Mechanisms of Chronic Pain

Nociceptors are free nerve endings that detect tissue trauma and generate signals that transmit this information to the spinal cord, with relays to the brainstem and subsequently the cerebrum. There are 2 classes of nociceptors, each with subtypes defined according to their sensory functions.[388] C-fiber polymodal nociceptors are unmyelinated, slowly conducting fibers with free nerve endings that respond to mechanical, thermal and chemical stimuli. A-δ nociceptors are rapidly conducting, medium diameter, myelinated fibers that respond to mechanothermal but not chemical stimuli, and they have larger receptive fields than C-fibers. Although unimodal nociceptors exist, most are polymodal. A sensitized polymodal (eg, mechanical and thermal) nociceptor exhibits a lower threshold for activation in all of its modalities. Neuropathic pain can be attributed to abnormal activity among nociceptors.[319]

Inflammation

Surgical trauma initiates a wound repair process characterized by 3 overlapping phases: inflammation,

proliferation, and tissue remodeling.[207] The protective inflammatory response is a major part of the innate immune reaction to bodily injury, and it is a necessary step in bringing about wound repair and restoration of function. The familiar cardinal signs of inflammation are pain, redness, swelling, heat, and loss of function. The pain associated with the acute inflammatory reaction results largely from the release of proinflammatory peptides substance P, calcitonin gene-related peptide, and neurokinin A from C-fibers in the area of injury. These are messenger substances in the nervous system that participate in neuroplasticity.[61,305] For example, after inflammatory injury, A-β-fibers that normally transduce touch and proprioception can be induced to synthesize receptors that normally exist in C-fiber polymodal nociceptors. This occasions a phenotype shift in which A-β-fibers take on C-fiber characteristics and activate nociceptive spinal neurons that are similarly sensitized by inflammation.[260] This is a peripheral mechanism behind allodynia, or touch-induced pain.

Damaged cells release bradykinin (BK), potassium ions, hydrogen ions, nerve growth factor (NGF), and adenosine triphosphate (ATP). At the same time, chemotaxis draws in leukocytes, mast cells, eosinophils, and macrophages that release proinflammatory cytokines and NGF at the site of injury.[305] The presence of the proinflammatory cytokines, interleukin 1-β and tumor necrosis factor α, increase NGF expression and affect nearby afferents. Fibroblasts, keratinocytes, and Schwann cells also produce NGF. Collectively, these processes produce an inflammatory "soup" that also contains prostaglandins, histamine, nitric oxide, and serotonin.[22,93] Moreover, sympathetic nerve terminals participate in the process of peripheral sensitization by releasing norepinephrine and prostanoids.[154,282] Eventually sympathetic efferents become able to activate nociceptive fibers through α-adrenoceptors.[394]

Acute surgical wounds can be severely painful and hyperalgesic, but normally this pain should resolve steadily with wound healing. The acute inflammatory response duration varies with the wound and the patient and may last from 24 hours to approximately 2 weeks. However, chronic inflammation can persist indefinitely without the cardinal signs of acute inflammation. Li et al[207] state that this can occur when necrotic tissue seals a wound, pathogen contamination occurs, or a foreign material exists at the site. Chronic inflammation often accompanies a failed wound repair process. Persisting low-grade inflammation after surgery can, in principle, cause PPSP.

Neurotrophic Factors

After surgery, NGF becomes an important part of the inflammatory soup. NGF belongs to a neurotrophic factor subset, neurotrophins, that promote the growth of neurons and the regrowing of damaged neurons. Neurotrophic factors bind to various tropomyosin-related kinase (Trk) receptors, and TrkA preferentially binds NGF. Most A-δ and C-fibers express TrkA receptors, making these nociceptive fibers sensitive to NGF. The actions of NGF on TrkA receptors upregulate, stimulate, and maintain sodium channels in injured nerves, prolonging the period of increased wound sensitivity. England et al observed that pain levels from neuromas correlate positively with the density of sodium channels.[104] Also, NGF plays a crucial role in the development of chronic wound pain,[130,299,418] as indicated by blockade of sodium channels, which produces pain relief in neuropathic as well as in inflammatory pain states.

In addition to acting on C-fiber nociceptors through TrkA receptors to produce hypersensitivity, NGF is synthesized by satellite glial cells in dorsal root ganglia, supplying it to sensory neurons when initial NGF levels decline because of healing.[333] Also, trauma to a nerve can induce NGF expression, with growth (sprouting) of TrkA-positive nociceptive fibers.[223] Levels of NGF are elevated in many acute and chronic pain conditions, and NGF has become a therapeutic target for pain control.[401] Mantyh and colleagues[223] stated that "…the NGF-TrkA axis appears to play a pivotal role in the early, intermediate, and long-term generation and maintenance of several types of acute and chronic pain." Another neurotrophin, brain-derived neurotrophic factor (BDNF) plays a role in activity-dependent synaptic plasticity related to learning and memory, peripherally as well as centrally.[306] BDNF binds to the tyrosine kinase receptor B (TrkB). Nociceptor-derived BDNF-TrkB signaling appears to play a significant role in inflammatory pain but not neuropathic pain.[429]

Kinins

The kinins, including BK, are a family of polypeptides produced at the site of tissue damage or inflammation.[285,392] They contribute to the regulation of pain and hyperalgesia after surgical insult by activating 1 of 2 G-protein coupled receptors: kinin B1 and kinin B2. BK is a well studied inflammatory mediator that increases noxious signaling and vascular responses and upregulates B1 in response to injury. The B1 receptor is upregulated within 3 hours after oral surgery in humans, and B1 plays a role in sustaining inflammation in chronic pain states.[140] Moreover, proinflammatory cytokines appear to upregulate B1 expression. This suggests that patients who come to surgery with a preexisting inflammatory condition may be at risk for an exaggerated B1-mediated postsurgical inflammatory response and peripheral sensitization. In light of the mechanisms described previously, this could initiate a chain of central sensitizing events that culminate in chronic pain.

Immune Mechanisms and Peripheral Nerves

The interaction between the nervous and immune systems is an essential element for the development and perpetuation of pain.[10,61,84,305,348] In the past decade, the role of the immune system in generating sensitization at the dorsal horn of the spinal cord has attracted a great deal of attention. Also, nociceptors

control the behavior of circulating immune cells through the release of proinflammatory peptides.

Ren and Dubner[305] provide a thorough review of the interactions of immune cells and nociceptors. The onset of an inflammatory response causes granulated resident mast cells located close to primary afferent terminals to degranulate, releasing BK, histamine, and other products that foster vasodilation.[202] Mast cells help sensitize nociceptors and, although the major responsible substances are still uncertain, BK is the prime suspect. Circulating macrophages, after chemotaxis, increase at the site of tissue trauma and supply proinflammatory cytokines to the chemical surround of nociceptors. Neutrophil leukocytes also migrate to the wound, passing through the vascular endothelium to accumulate at the site of injury. Finally, components of the complement system contribute to sensitization of nociceptors.[305]

Nociceptors have their cell bodies in the dorsal root ganglion or the trigeminal ganglion, and small glial cells (SGCs) surround these cell bodies. The SGCs connect by gap junctions to the neural cells and support them by supplying nutrients and other products. Resident macrophages in this vicinity also move in if the nerve sustains damage. Although there is no gap junction coupling in the absence of injury and noxious signaling, induced inflammation increases gap junction coupling. The interaction of the SGCs and the neurons during noxious signaling boosts neuronal excitability and nociceptive input, and this can spread, resulting in pain outside of the involved dermatome. The model becomes more complicated as we consider nociceptor sensitizing positive feedback loops and the accumulation of pro- and anti-inflammatory cytokines. The nociception-generated interactions between SGCs and neurons can fail to resolve itself and transition from acute to chronic noxious signaling, by unknown mechanisms. The peripheral immune and nervous system interactions involving the dorsal root ganglia and the SGCs merit examination in the search for mechanisms of acute to chronic pain transition.

Peripheral Neuropathic Pain

Approximately 2.4% of all nerve injuries result in neuropathic pain that is sustained over time. Pain from peripheral neuropathy clearly is caused by insult to a nerve sufficient to form a neuroma or otherwise induce damaged axons to chronically generate action potentials. The abnormal discharge is mechanistically critical, as indicated by application of local anesthetic to the damaged portion of the nerve, which eliminates neuropathic pain.[15,131,186,311] Other means of chronically silencing spontaneous activity among injured axons, without eliminating normal transmission and the associated sensory and motor functions of a nerve, have not been developed. Additional nociceptor and CNS plasticity could be addressed. Responses to nerve injury include alterations in structure, neurotransmitter changes, and variations in molecular transduction mechanisms.[388] However, resolution of abnormal activity among nociceptors at the site of nerve injury should prevent or reverse changes in dorsal root ganglia, the spinal cord, and brain that contribute to the maintenance of neuropathic pain.[348]

Models of Nerve Injury Pain

Unilateral constriction of a peripheral nerve (CCI) produces edema, ischemia, and axonal damage with changing patterns of degeneration and regeneration of the constricted nerve.[136] Early histological examinations of ligated nerves have reported a distal loss of large myelinated afferents[24,164] and disruptions of A-δ and C afferents.[24,70,122,136,164] Coincident with anatomical changes distal to nerve injury, abnormal discharge among afferents occurs proximal to the injury, including spontaneous activity.[164]

Animal models of chronic neuropathic pain typically observe spontaneous behaviors (eg, guarding the affected limb[17] or decreased thresholds or latencies for reflex responses to stimulation within or near the innervation territory of an injured nerve.[29] The effect of CCI on innate reflex behaviors lasts approximately 40 days before returning to control levels, summarized by Vierck et al.[373] The temporary effects of CCI may be a methodological artifact of comparing ipsilateral and contralateral responses after unilateral injury. This experimental strategy brings the lateralized organization of spinal reflex organization into play. In addition, interruption of motor axons produces a visible motor deficit and abnormal posture of the ipsilateral foot, eliminating experimenter blinding. Most important, weakness and spontaneous behaviors involving the injured limb do not reflect altered sensations,[257] and they resolve at approximately the same time as the return of reflex sensitivity to normal levels.[178] The temporary ipsilateral hyper-reflexia for cold and heat stimulation after unilateral CCI[30] does not correspond to effects of nerve injury on pain sensitivity for humans.

Bilateral nerve injury eliminates the influences of lateral asymmetry on behavioral tests of nociceptive sensitivity, and the use of operant tests bypasses the deficiencies of reflex testing.[381] In investigations using operant escape from painful thermal stimulation, bilateral CCI of the sciatic nerves and bilateral L5 spinal nerve ligation have resulted in hyperalgesia for cold stimulation that is stable for 80 to 100 days.[376,425] Increased operant escape from nociceptive cold stimulation after bilateral nerve damage is consistent with symptoms of neuropathic pain in humans.[131,152,161,198]

Four models of reflex hypersensitivity produce different patterns of axonal injury, compared with loose constriction of the sciatic nerve (CCI). Sciatic cryoneurolysis[87,222,391] is a model of whole nerve injury that involves some recovery of axonal damage with regeneration over time, similar to CCI. CCI and sciatic cryoneurolysis can produce autotomy,[30,87] which is an ethical concern and can result in sacrifice of some animals before abnormal nociceptive sensitivity would become chronic. Partial nerve injury (ligating a portion of the sciatic nerve),[324] sciatic nerve injury (sparing the sural branch of the sciatic nerve),[84] and spinal nerve ligation (ligation of the L5 and

L6 spinal nerves)[257] model partial transection of a nerve's input to the CNS with little or no regeneration over time. Effects of partial nerve injury and sciatic nerve injury on operant escape from nociceptive stimulation are needed.

Regardless of the injury method chosen, investigators must use valid measures of pain sensitivity, and it will be important to compare them with the time course of abnormal input to the CNS from the injured nerve.[150,164] A key determination for long-term studies of chronic pain is whether the central effects of nerve injury become independent of peripheral driving over time. Unilateral nerve injuries provide optimal models because such injuries are the preponderant cause of neuropathic pain in humans. However, contralateral stimulation cannot serve as a viable control because of reports of mirror image hyperalgesia/pain for humans.[161,192,198,298] Also, sham surgery can produce long-term hyperalgesia[376] necessitating an experimental focus on long-term changes in the escape performance of individual animals after nerve injury, with comparisons of neurobiological effects for animals with and without evidence of hyperalgesia/allodynia.[198]

Fig 1 summarizes the major hypotheses about the origins of pain chronicity in the periphery. These mechanisms are not mutually exclusive. In some cases, inflammatory processes may interact with nerve injury.

Central Mechanisms

The CNS does not simply receive and relay noxious signals from the periphery to the brain. It engages in bottom-up as well as top-down modulation of noxious signals from the periphery by either enhancing or dampening transmission through multiple mechanisms. Fig 2 provides an overview of research approaches addressing potential central mechanisms for the development of chronic pain after surgery.

Ascending Noxious Signal Modulation

Central Sensitization

Enhanced central transmission of noxious signaling and miscoding of normally non-noxious signals to noxious signals constitute central sensitization. Woolf[416] defines the term central sensitization as "a set of phenomena that involve amplification of noxious signaling within the central nervous system to elicit dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation." Theoretically, chronic pain after surgery could result from central sensitization.

Injury such as surgical insult activates C-fiber and A-δ fiber nociceptors with ensuing release of glutamate, the major excitatory neurotransmitter in the CNS, at their central terminals. Glutamate acts on 2 classes of receptors to influence noxious signal transmission: ligand-gated ionotropic glutamate (iGlu) receptors and G-protein coupled metabotropic glutamate (mGlu) receptors. Long-lasting changes in synaptic excitability result when glutamate activates the following iGlu receptors: N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, and kainic acid.[63,246,272] Repeated nociceptive messaging from the periphery strengthens the synaptic connections between nociceptive afferents and the spinal cord neurons that engage in noxious signaling, and the

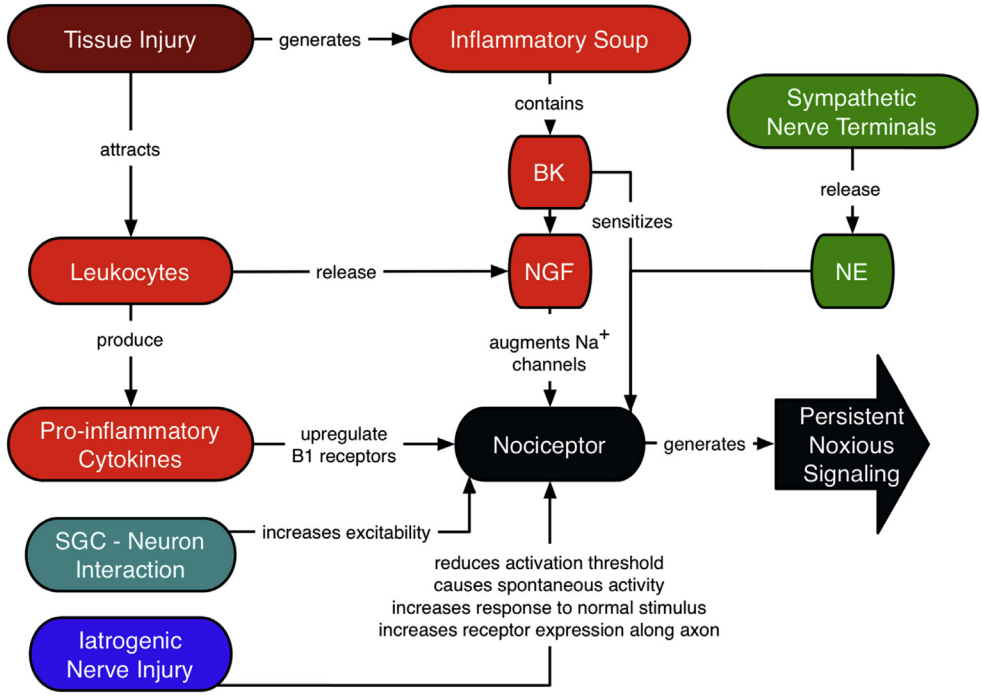

Figure 1. Potential mechanisms for the development of chronic postoperative pain in the periphery. Leukocytes include neutrophils, lymphocytes, monocytes, and macrophages. Abbreviation: NE, norepinephrine.

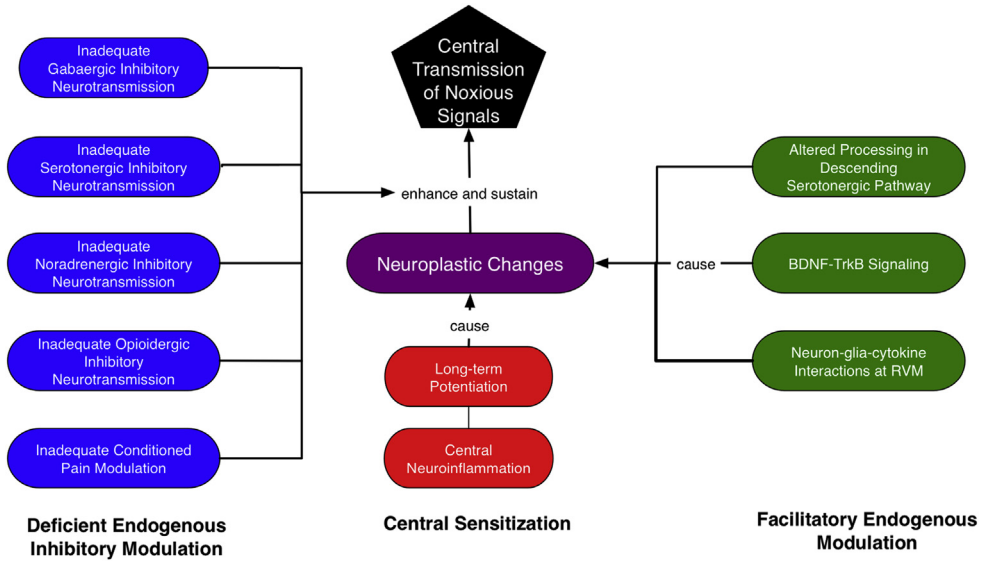

Figure 2. Mechanisms under study for the development of chronic postoperative pain at the spinal cord. The mechanisms are not independent, but they represent hypotheses that investigators usually study independently.

result is hyperalgesia. Accordingly, Mendell and Wall[240] observed that repetitive stimulation of C-fibers at a constant stimulus intensity caused activation of spinal dorsal horn neurons to increase progressively in magnitude as well as in duration. This change, termed wind-up, generates hyperexcitability in wide dynamic range neurons of the spinal cord and increases the receptive fields of these neurons.

Because in vivo recording from dorsal horn neurons in humans ethically is impossible, investigators must use other methods to demonstrate a phenomenon similar to wind-up in humans. In normal human subjects, delivery of repetitive, noxious stimulation at a constant intensity produces a phenomenon closely resembling wind-up, called slow temporal summation. For example, an investigator might deliver brief heat pulses to the skin at the rate of 1 pulse per 2 to 5 seconds and track changes in sensation according to pain intensity ratings.[188,378] Slow temporal summation of pain has become a part of the quantitative sensory testing battery for evaluation of central sensitization in chronic pain patients, particularly those with neuropathic pain.[98,286,309,343] However, slow temporal summation depends on activation of C nociceptors, which can be abnormally sensitive in chronic pain patients. It is misleading to regard temporal summation as a mechanism for chronic pain if it is entirely dependent on peripheral sensitization, but discrimination between peripheral and central sensitization is difficult.

Temporal summation of pain reflects an NMDA-sensitive wind-up of spinal[414] and cortical[359] neuronal activation. It depends on the intensity of cutaneous stimulation, occurs within a narrow range of slow frequencies, and decays rapidly when the rate of stimulation decreases.[378] To show that temporal summation is enhanced in association with chronic pain, it should be established at a higher rate (slope) for a frequency and intensity of stimulation. However, the criterion of an enhanced rate of pain increase in association with chronic pain has rarely been met. Rather, increased pain ratings of the first stimulus in a repetitive series are commonly observed for patients with chronic pain, compared with normal control participants.[345] This effect represents allodynia, and it is often followed by normal temporal summation of pain magnitudes for subsequent stimuli in a series.

When established, temporal summation can be maintained at a slower-than-normal stimulation rate for pain patients, compared with normal subjects.[346] This effect likely represents more prolonged central discharge in response to individual stimuli, without enhanced temporal summation. Thus, repetitive stimulation in a wind-up paradigm reveals abnormalities of pain perception that do not represent enhanced temporal summation. Accordingly, patients in investigations of chronic pain are not more sensitive than normal subjects to attenuation of temporal summation by the potent NMDA antagonist dextromethorphan.[345] Stringent tests of NMDA-sensitive temporal summation rates have not been conducted for other pain conditions. For example, it is critical to establish that subjects rate only second pain, but some methods of nociceptive stimulation, such as ramp-and-hold heat from a contact thermode, activate A-δ and C nociceptors.[383]

Multiple subtypes of mGlu receptors play important roles in learning, memory, and emotion as well as pain. They exist presynaptically on primary afferents,[246] postsynaptically in the spinal cord, and also supraspinally. Glutamate activation of mGlu receptors initiates slower but more persistent modulatory neurotransmission than iGlu activation occasions. Several subtypes of mGlu receptors contribute to the development and maintenance of long-lasting nociceptive sensitization. Astrocytes and microglia (discussed in the Glia section) also express mGlu receptors.[40] Because of their greater role in modulating pain, as contrasted with NMDA and

α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, mGlu receptors may be more likely to play a role in chronic pain.[63]

Long-term potentiation. Stimulating 2 neurons synchronously produces a long-lasting enhancement in signal transmission between them, strengthening the synaptic connection. Synaptic strength varies according to neurotransmitter release or uptake. This synaptic strengthening is long-term potentiation (LTP), and it is a well studied mechanism of memory and learning, especially at the hippocampus. LTP is a cellular mechanism of central sensitization and could be a cause of intense acute postoperative pain.[159,180,313,317] Noxious stimulation with a pattern that induces LTP in animals causes hyperalgesia in humans, and LTP may explain many forms of hyperalgesia in patients. Conventional theory holds that LTP should decline naturally over time, and pain conditions resulting from it should resolve spontaneously. However, Ruscheweyh and colleagues propose that decreased endogenous antinociceptive processing might maintain it.[313] Pfau et al[287] reported that a subset of subjects experiencing LTP demonstrated abnormally long times to recovery, suggesting that LTP could be a factor in the development of persisting pain.

Long-term depression. Long-term depression (LTD) is an opponent process to LTP. It is an activity-dependent reduction in the strength of a synapse, or synaptic weakening.[37,179] Although less well studied than LTP, it appears to occur in response to repetitive weak and/or low-frequency stimulation. LTP as well as LTD take place at glutamatergic synapses and therefore can modify the excitatory aspects of noxious signal transmission. However, LTP and LTD can also affect inhibitory synapses.[220] Therefore, although specific conditions that favor these opponent processes for noxious signal transmission are still lacking, the literature suggests that activity-dependent neuroplasticity can either strengthen or weaken synapses that are either excitatory or inhibitory within the dorsal horn of the spinal cord.

Neuroimmune Interactions

A number of investigators have focused on interactions of the immune and CNS during the postinjury inflammatory cascade.[118,138,225,305,307,334,398,406] After tissue injury, circulating bone marrow-derived immune cells follow chemical signals to the wound, but the blood-brain barrier prevents them from entering the CNS. Instead, microglia residing within the CNS take on the role of immune surveillance.[5]

Glia

Glial cells exist throughout the CNS, and there are 3 main types: microglia, astrocytes, and oligodendrocytes. Microglia are essentially resident macrophages and as such provide the first line of immune defense in the CNS. They routinely exist in a ramified or resting form but activate into a phagocytic state in response to chemical stimulation. Activated microglia can migrate, engulf offending material, secrete proinflammatory substances, and proliferate. They are the main source of inflammatory mediators in the CNS.[362] If activated, microglia do not return to a ramified state but instead remain "primed"[261]; they may contribute to the acute to chronic pain transition by perpetuating central sensitization.

Astrocytes are star-shaped glial cells that envelope synapses, and they generate extensive networks with themselves. Astrocytes secrete or absorb neurotransmitters, help maintain the blood-brain barrier, and provide metabolic support to neurons, among other functions. They may interact with mast cells in generating an inflammatory response that contributes to central sensitization.[334] Astrocytes also activate in response to systemic inflammation or nerve injury, but they normally become active after microglial activation and sustain their activated state for a longer duration. Astrocyte production of chemokines and proinflammatory cytokines increases excitation and decreases inhibition of nociceptive traffic in spinal cord pathways, thus sustaining neuroinflammation. A number of investigators have implicated microglia and astrocytes, the promotors and sustainers of neuroinflammation, in the development of chronic pain after acute injury.[118,300,320,334,362]

Work targeting the interactions of the nervous and immune systems suggests that central sensitization does not depend solely on glutamate-mediated synaptic plasticity at the synapse between the primary afferent terminals and the second-order neurons. Clearly, glial cells and other immune cells contribute inflammatory mediators that include proinflammatory cytokines, chemokines, prostaglandins, histamine, nitric oxide, and growth factors. These products facilitate excitatory nociceptive transmission in dorsal horn neurons.

Chemokines

A chemokine is a type of small cytokine that functions primarily as a chemoattractant to guide migrating or patrolling monocytes. Whereas some have homeostatic functions, others are proinflammatory and play a sensitizing role in neuroimmune interactions.[118] In addition to attracting circulating monocytes, these substances can act on glial cells and also neurons. The chemokine fractalkine, cleaved from neurons after neural injury at the periphery, can activate microglia that, in turn, initiate an inflammatory cascade. The chemokine C-Cmotif, ligand 2 (CCL2) is involved in glia-to-neuron signaling after nerve injury.[2] CCL2 induces central sensitization by increasing the activity of NMDA receptors.

Toll-Like Receptors

When neural structures undergo injury, stressed or necrotic cells release danger-associated molecular patterns or "alarmins,"[146,228] and these activate Toll-like receptors (TLRs). TLRs are pattern recognition receptors of the immune system that sense the presence of injury and respond by producing signals that neurons and other immune cells can receive.[212,247,261,355,399] TLR4 in turn activates glial cells through a proinflammatory signaling cascade. Nicotra et al[261] suggest that TLR4 upregulation may be a marker for primed microglia, a

potential central sensitization mechanism, for the transition from acute to chronic pain.

Functional Significance of Central Inflammatory Regulation

The effect of central inflammatory reactions on chronic pain resulting from peripheral tissue and/or nerve injury is highly suggestive but is unknown. The substantial literature that describes central glial and inflammatory reactions to nerve injury[400] has used spinal reflex measures of nociceptive sensitivity. Also, the reflex effects and central inflammatory correlates of nerve injury have been described only at several postoperative weeks. Difficulties with this approach are: 1) when abnormal pain sensitivity and/or spontaneous pain results from nerve injury, it typically is chronic; 2) spinal reflex effects of nerve injury can normalize within 2 months, reflecting neuroplastic adaptations of spinal reflex circuits that do not represent changes in supraspinal encoding of pain,[376] 3) reflex sensitivity does not represent pain sensitivity,[386] and 4) analysis of central glial and inflammatory reactions has used group comparisons of nerve injury versus sham surgery, but chronic pain does not develop for all recipients of nerve injury. Therefore, the remarkably thorough and informative literature on spinal glial and inflammatory adaptations to nerve injury has not shown relevance to chronic pain. If spinal glial and inflammatory reactions abate acutely after nerve injury, and if they do not persist beyond this period for subjects with chronic pain, then they are relevant to spinal reorganization of reflex control but not to chronic pain.

Gamma-Aminobutyric Acid and Glycine

Gamma-aminobutyric acid (GABA) and glycine are the main inhibitory neurotransmitters in the CNS, including the spinal cord.[427] These interneurons provide an inhibitory counterbalance to glutamatergic excitatory processes. For example, electrical stimulation of a peripheral nerve (eg, transcutaneous electrical nerve stimulation) activates GABAergic and glycinergic neurons, inhibiting spinal input from unmyelinated nociceptors and ameliorating clinical pain. Examples of transcutaneous electrical nerve stimulation efficacy are a short-term attenuation of: experimental pain,[65] postoperative pain during movement,[302] the spontaneous, ongoing pain of multiple sclerosis,[318] and surgical pain.[35] However, peripheral nerve damage with tonic abnormal discharge can result in a loss of GABAergic and glycinergic inhibition,[427] and a sustained loss of inhibitory neurotransmission could be a mechanism of chronic pain.[428]

Recordings from spinal, lamina I neurons have shown that peripheral nerve injury renders nociceptive-specific (NS) neurons abnormally sensitive to brushing or punctate tactile stimulation of Aβ afferents (allodynia). There is an increased sensitivity to nociceptive stimulation, afterdischarge, and abnormal spontaneous activity.[173] The relevance of these findings for neuropathic pain is enhanced considerably by recordings from spinal neurons backfired using intrathalamic stimulation.[201] After nerve injury, a new class of spinothalamic neuron appears, in addition to the normal complement of wide dynamic range neurons and a reduced distribution of NS-spinothalamic neurons without sensitivity to touch. The new subgroup of spinothalamic neurons exhibits levels of spontaneous discharge not normally seen, along with sensitivity to non-nociceptive stimulation and enhanced responses to nociceptive stimulation. Each of these effects on spinothalamic neuronal discharge occurs during weakened inhibition by disruption of spinal chloride transport or after pharmacological antagonism of $GABA_A$ or glycine receptors.[75,173,201] Thus, disinhibition from $GABA_A$ and glycine interneurons can account for the effects of nerve injury on NS-spinothalamic projection neurons. Accordingly, blocking GABAergic inhibition increases pain and allodynia.[183]

Inhibition of NS spinal neurons by activation of $GABA_A$ or glycine receptors on spinal interneurons depends on a hyperpolarizing influx of chloride ions that is counteracted by a depolarizing efflux of bicarbonate. Normally, chloride is maintained at a low level within the interneurons by a chloride potassium symporter 5 (KCC2) cotransporter that links Cl^- and K^+ efflux. However, if chloride accumulates intracellularly, as a consequence of a high rate of afferent input to the $GABA_A$/glycine interneurons, or if KCC2 extrusion of Cl^- fails, disinhibition of NS neurons results.[297] Furthermore, nerve injury upregulates protein kinase C $(PKC)_\gamma$ in the superficial dorsal horn,[224] and PKC_γ enhances central sensitization by removing the Mg^+ block of NMDA receptor channels.[62] A local PKC_γ/NMDA-dependent circuit normally is inhibited by glycine interneurons but is disinhibited after glycine dysfunction from nerve injury or application of the glycine antagonist strychnine. Accordingly, selective antagonism of PKC_γ or NMDA prevents activation of NS neurons by low-threshold tactile stimulation after spinal application of strychnine.[248]

GABA disinhibition contributes to development of allodynia by mechanisms similar to those of glycine. Nerve injury reduces markers of GABA cells glutamic acid decarboxylate 67 (GAD67) and parvalbumin in the medullary dorsal horn,[90] and this increases responsivity of medullary dorsal horn neurons to low-threshold tactile stimulation.[229] Similarly, administration of the $GABA_A$ antagonist bicuculline releases responsivity of superficial spinal neurons to Aβ afferent input.[19] Reduction of GABA degradation by administration of the GABA transaminase inhibitor vigabatrin (increasing GABA availability) restores the expression of GABA cell markers and decreases PKC_γ expression in the medullary dorsal horn.[90] Thus, nerve injury induces GABA and glycine disinhibition, with activation of PKC interneurons, resulting in allodynia. In the absence of contradictory evidence, it appears that $GABA_A$/glycine disinhibition and allodynia depend on chronic abnormal discharge from an injured nerve.

Blocking conduction of Aβ afferents from glabrous skin can eliminate allodynia for humans with neuropathic pain.[52] However, neuropathic allodynia is not limited to glabrous skin and is not always attenuated

by blocking conduction in Aβ afferents.[69] Hairy (but not glabrous) skin is supplied by C afferents that respond to slow stroking or brushing of the skin,[209,323] which can be a potent stimulus for neuropathic allodynia.[222,304,316] C-tactile afferents innervate the superficial dorsal horn,[316] with subsequent projection to the thalamus and then the insula.[7,36,76,322] Normally, slow brush stimulation of C-tactile afferents evokes sensations of pleasure,[209] but in conditions of GABA and glycine disinhibition (eg, nerve injury), lamina I NS neurons are converted into wide dynamic range neurons.[76] Thus, slow brush stimulation exacerbates neuropathic pain by a mechanism that provides access of C-tactile afferents to a nociceptive projection pathway.

Spinal lamina I (NS) neurons that are excited by C nociceptors are inhibited/disinhibited first by nociceptive input to GABAergic interneurons in the superficial dorsal horn and then again within the primary somatosensory cortex (SI). Normally, areas 3b/1 and 3a within the SI are mutually inhibitory via intracortical connections that terminate on $GABA_A$ interneurons. Cytoarchitectural areas 3b/1 receive medial lemniscal and lateral spinothalamic input originating from Aβ (touch) and A-δ (pain and temperature) afferents, and cytoarchitectural area 3a receives spinothalamic input originating from C afferents (pain and temperature).[385] However, cerebral cortical $GABA_A$ inhibition is activity-dependent, on the basis of chloride transport,[204] as described previously for the conversion of spinal inhibition to disinhibition. If C afferent drive to area 3a is strong and prolonged so that KCC2-mediated outward transport is insufficient to maintain Cl^- homeostasis, GABA-mediated hyperpolarization (inhibition) switches to depolarization (excitation). In terms of intracortical dynamics within SI, strong nociceptor drive to areas 3b/1 can disinhibit responses in area 3a to thermal stimulation of unmyelinated afferents.

At low and/or high levels of the CNS, negative feedback circuits reduce the intensity of tactile and pain sensations in response to brief stimulation. However, inhibitory modulation by GABA and glycine is time-limited, with important implications for chronic pain; it is activity-dependent and can switch to facilitation, resulting in allodynia, hyperalgesia, and spontaneous pain. The CNS does not protect against an abnormal prolongation of pain.

Mu Opioids

Mu opioid receptors are present throughout the neuraxis, and systemic administration of mu opioid agonists such as morphine affects attention, pain sensitivity, and autonomic control over body temperature, defecation, and respiration. Mu opioid inhibition of pain is indubitable and has earned a reputation for morphine as the prototypical analgesic agent. The clinical effectiveness of morphine conflicts with much of the laboratory animal literature on mechanisms of morphine action. Very high systemic doses (often 5–10 mg/kg) are required to produce hyporeflexia. Nociceptive reflexes, as tested behaviorally, require input from Aβ or A-δ afferents, and morphine attenuates input from myelinated nociceptors only at doses that produce a profound sedation.[73,424] In contrast, escape by rats or monkeys and pain for humans in response to C nociceptor input is powerfully attenuated by low doses in the therapeutic range for humans (<.5 mg/kg).[74,377,424] By inference, clinical pain conditions that benefit from mu opioid therapy must involve considerable input from C nociceptors.

A critical issue concerning opioid therapy pertains to the chronicity of pain. Mu opioid administration is undoubtedly effective for acute pain that arises from activation of C nociceptors, but sustained use of these compounds for control of chronic pain is highly questionable, albeit common. If mu opioid use by chronic pain patients is to be continued, the extent to which these compounds are efficacious over time must be determined, with consideration of numerous and complex actions throughout the nervous system and adverse effects, including an increased sensitivity to pain.[14,145,237]

Descending Control Over Spinal Nociceptive Transmission

Descending Inhibitory Modulation

Spinal nociceptive systems operate in conditions of continuous descending inhibition that normally constrains the excitability of dorsal horn neurons involved in nociceptive transmission.[95,197] Presumably, variations in the potency of descending inhibition can determine individual differences in sensitivity to noxious events. Loss of tonic descending inhibition may cause the hyperalgesia and allodynia which are features of many chronic pain states.[427]

The periaqueductal gray (PAG) and the nucleus raphe magnus emerged early on as key midbrain structures in opioid-related endogenous pain modulation. Electrical stimulation of the PAG in animals inhibits spinal nociceptive processing, and microinjection of opioids disinhibits inhibitory neurons in the PAG, accentuating descending antinociception.[23] The descending inhibitory pathways involved in these phenomena involve spinal serotonin as well as α_2 adrenoceptors, implicating serotonin and noradrenaline in endogenous pain modulation as well as endogenous opioids.[51,419,420] Other structures implicated in endogenous pain modulation are the noradrenergic locus coeruleus, the parabrachial nucleus, the lateral reticular nucleus, nucleus paragigantocelluaris, and the solitary nucleus. Also, recent evidence links endocannabinoids to endogenous analgesia.[92,148,269,276] Descending endogenous modulation probably assists survival by helping assure that severe pain during an emergency will not impede fight or flight.

Cognitive and emotional processes influence descending modulation of noxious signaling. Ossipov et al[273] usefully linked bulbospinal pain modulation pathways to higher brain centers, including interactions between prefrontal cortex and the amygdala that play a major role in cognition, anxiety, and negative emotion. Corticofugal projections to the PAG and hypothalamus are

well known,[271] but until recently their importance has been unclear. Brain imaging studies of human subjects confirm the existence of links from higher brain structures involved in emotion and cognition to descending modulatory pathways. Stein et al[350] have shown that individual placebo analgesia is associated with increased mean fractional anisotropy (white matter integrity) in the right dorsolateral prefrontal cortex, left rostral anterior cingulate cortex (ACC), and the PAG. The same group has shown that placebo analgesia involves endogenous opioid circuitry and is naloxone-reversible.[99]

Descending Facilitatory Modulation

After decades of regarding descending control of spinal nociceptive processing as inhibitory, neurophysiological recordings from the nucleus raphe magnus in the rostral ventral medulla (RVM) have revealed inhibitory as well as facilitatory influences.[106] Recent findings reveal that the RVM descending serotonergic pathway is not solely inhibitory.[6,301,358,402] It can enable facilitatory modulation of noxious signaling in response to pronociceptive RVM (on-cell) activation. In facilitatory mode, the RVM descending serotonergic pathway increases neuronal excitability at the spinal dorsal horn by upregulating glutamate receptors, and this, in turn, heightens behavioral hypersensitivity. Evidence from neuropathic as well as inflammatory pain models supports the existence of descending facilitation via pathways from the RVM to the spinal cord dorsal horn. This mechanism most likely contributes to pain chronification in clinical conditions involving persistent inflammation such as osteoarthritis or when the pain is neuropathic in origin. Descending facilitatory mechanisms function as secondary contributors to injury-related hyperalgesia.[124,369] The nocebo effect, an exacerbation of pain in someone holding negative beliefs or expectations, uses higher cortical (eg, prefrontal) control over descending pathways from the RVM to facilitate nociceptive processing.

The BDNF-TrkB signaling system may enhance and/or sustain descending facilitation. BDNF-TrkB is widely expressed throughout the CNS, including the descending pathways that link the PAG, the RVM, and the spinal cord. After injury, this signaling system activates rapidly.[306] BDNF-containing neurons in the PAG project to the RVM where they release BDNF, and this contributes to facilitation of noxious signal transmission. Guo et al[137] showed that microinjection of BDNF into the RVM induced descending nociceptive facilitation, mediated by NMDA receptors. Peripheral inflammation enhanced the process. Neuron-glia-cytokine interactions may also play a role in descending facilitation related to nerve injury via the chemokine CCL2 and its receptor, CCR2, in RVM astrocytes. RVM-related facilitation occurs when inflammation is present, and neurokinin 1 receptors are involved.[42]

Balance of Descending Inhibition and Facilitation

The prefrontal and ACC and the amygdala, with projections to the PAG, coordinate inhibitory and facilitatory influences of the RVM on spinal nociceptive processing.[185,250,274] Expectations act through this system to influence the magnitude of pain, accounting for nocebo facilitation and placebo inhibition of pain intensity in response to suggestion.[16,187,326] Also, the PAG serves as a comparator of nociceptive signals from the periphery[121] against expectations that have been generated on the basis of previous nociceptive input to the prefrontal cortex via the insula.[312] Accordingly, anticipation affects pain intensity bidirectionally when experimentally-induced thermal pain sets up expectancies of increasing and decreasing stimulus intensities.[415]

In a psychophysical paradigm with alternating series of ascending and descending intensities that reverse when pain ratings reach a set point, changes in direction are not immediately matched by a reversal in pain ratings. After the last stimulus in ascending series, subjects continue to sense increasing pain according to expectations, although stimulus intensity is decreasing. After descending series, decreasing pain is sensed until the discrepancy between expectation and sensation intensity is substantial. Exaggerated oscillations in pain ratings occur normally, but aging magnifies them.[258,384] The warning effect of the ascending series is increased, and the safety signal during the descending series is enhanced. This increase in pain variability likely results from engagement of descending systems for facilitation and inhibition, and it shows that testing for only facilitation or inhibition can be misleading. Bidirectional enhancement of pain intensity ratings represents an endogenous mechanism for oscillations in pain intensity that individuals with chronic pain often report.[259]

Conditioned Pain Modulation

Research on diffuse noxious inhibitory control (DNIC) has extended the model of descending inhibition. DNIC refers to a spinal-medullary-spinal mechanism by which harmless but noxious stimuli (such as heat, high pressure, or electrical stimulation), may inhibit the responsiveness of dorsal horn wide dynamic range neurons to noxious stimulation delivered at a separate location. Lesions of the RVM or the PAG do not block DNIC. DNIC integration appears to occur at the level of the dorsal reticular nucleus, which projects to the spinal cord. The dorsal reticular nucleus also receives projections from cortical sites.[273]

The "pain inhibits pain" model, when applied to humans, is termed CPM.[206] CPM, a psychophysical marker of endogenous analgesia, is impaired in many chronic pain states, and speculation exists that reduced CPM in surgical patients awaiting surgery may predict the transition of acute to PPSP. Lewis et al[206] conducted a systematic review using meta-analysis to determine whether CPM is dysfunctional in patient populations with chronic pain and concluded that this is the case. The effectiveness of conditioning stimulation in CPM is termed efficiency. Yarnitsky et al[423] assessed CPM efficiency before surgery and followed patients at 6 and 12 months after surgery. CPM efficiency predicted lower levels of PPSP, although it could not predict acute postoperative pain intensity.

Psychophysical pain evaluation typically pairs CPM with temporal summation, because the 2 reflect opponent processes. In some cases involving healthy subjects, the inhibitory influence of CPM appears to attenuate the excitatory influence of temporal summation.[344] A combination of intact temporal summation and inefficient or absent CPM, a pronociceptive state,[422] would presumably predispose a patient to develop chronic pain after a surgical or other trauma that generates acute pain.

Fig 2 summarizes the major hypothesized spinal mechanisms of PPSP. As is the case with peripheral mechanisms, they are not mutually exclusive.

Brain Mechanisms

One can argue that chronification of pain after surgery takes place at the periphery and through interactions of peripheral and spinal cord processes, but the extent to which sustained input from an injury is crucial to the development and maintenance of chronic pain remains to be determined. This issue needs resolution. Ultimately, pain, whether acute or chronic, is a complex subjective experience that engages the brain. Hence, it is a mistake to regard the brain as an unaffected, passive recipient of noxious signaling generated and modulated at lower levels of the nervous system. For example, sensory, emotional, and cognitive processes involving interactions across mesencephalic, limbic, and cortical structures take place before pain emerges as a conscious experience for the patient. Accordingly, clinical epidemiologic studies indicate that factors such as psychological stress, catastrophizing, and brain illness such as depression are risk factors for chronic pain. Also, the presence of preoperative pain (pain memory) increases the incidence of PPSP[20] and influences the referred sensations experienced.[170]

Stress-Induced Analgesia or Hyperalgesia?

The stress response provoked by tissue trauma activates the locus coeruleus noradrenergic system, the sympathoadrenomedullary axis, and the hypothalamo-pituitary-adrenocortical (HPA) axis.[61,228] When activated by hormonal and neural signals of injury, the hypothalamic periventricular nucleus of the HPA induces release of the precursor polypeptide pro-opiomelanocortin at the anterior pituitary. Pro-opiomelanocortin cleaves into several active peptides, including the endogenous opioid peptide neurotransmitter β-endorphin, which exerts analgesic effects by binding at μ receptors. Viewed broadly, the 3 classical endogenous peptides related to modulation of noxious signaling are β-endorphin, the met- and leu-enkephalins, and the dynorphins. They modulate noxious signaling by acting, respectively, on μ, δ, or κ opioid receptors, all of which have multiple subtypes.[149] An understanding of the differential effects of μ, δ, or κ opioid agonists on pain sensitivity in laboratory animals has been negated by the use of reflex measures of nociceptive sensitivity.

Endogenous opioid peptides dampen neuronal excitability by inhibiting voltage-gated $Ca2^{+}$ channels and/or opening K^{+} channels. Endogenous opioid modulation can occur in the periphery,[149,205,349] but it takes place principally at the dorsal horn of the spinal cord, the mesencephalic PAG, and the RVM. Endogenous inhibition of noxious signaling is activated as part of the injury-induced stress response, where significant threat (fear) exists. In these situations, antinociception can come on suddenly,[49] fostering survival in emergency situations. Stress-induced hypoalgesia is likely time-limited to the duration and immediate aftermath of intense stress. At such times, behavioral pain sensitivity is difficult to evaluate, because it would be strongly influenced by distraction.

Stress-induced analgesia has been claimed to follow an acute stressful experience for an undetermined period of time. This impression has been artificially established by numerous laboratory animal demonstrations of nociceptive reflex attenuation after psychological stress.[38] However, reflex modulation does not represent (often differs from) pain modulation. When operant escape from nociceptive thermal stimulation is tested after acute psychological stress, hyperalgesia for thermal stimulation is observed.[176,177,227] Thus, the effect of a brief stress experience appears to transition from hypo- to hyperalgesia over an undefined but short period of time (minutes).

Chronic Stress and Chronic Pain

The prefrontal and ACC cortex construct emotions of fear and anxiety from traumatic events and their memories.[45,185,194,250,256,331] The prefrontal cortex, ACC, amygdala, hippocampus, insula, and hypothalamus manage psychological stress, with activation of the HPA and the sympathetic nervous system.[117,147,181,185,203,251,315,332,354,430] Of particular relevance to development of pain trajectories, repetitive activation of the central stress circuitry by memories of traumatic events can establish posttraumatic stress disorder, which often is associated with pain.[43,151,250,256,321,331,395,421]

Not only can chronic fear and anxiety be sufficient to create a pain condition, as shown by posttraumatic stress disorder, but these emotions are elicited by pain, which is a powerful stressor.[194,380] Muscular pain is particularly susceptible to enhancement by chronic nociceptive input to the central stress circuitry, with tonic activation of the sympathetic nervous system.[109,275,371,375] Stress is an important consideration for understanding chronic pain trajectories and a change in the character of pain over time (eg, pain from a local inflammatory injury to generalized muscular pain).

Sympathetic Dysregulation and Peripheral Ischemia

Stress activates the sympathetic nervous system, producing tonic peripheral vasoconstriction, which results in muscular ischemia when chronic, with pain and hyperalgesia.[21,28,31,32,102,103,158,199,218,241,367,368,412] Ischemia is

a potent generator of muscle pain,[242] particularly for women, who are prone to experience excessive sympathetic vasoconstriction of peripheral vasculature[53,71,72,105,226] and are especially susceptible to the deep muscular pain of fibromyalgia.[214]

FMS is characterized by pain that is widely distributed within deep tissues and is commonly associated with a more localized pain condition such as temporomandibular/myofascial,[289] whiplash,[48] repetitive strain,[210] headache,[25] interstitial cystitis,[68] irritable bowel syndrome,[409] back pain,[199] or inflammatory pain.[211] These and other sources of psychological stress, can result in FMS pain when chronic.[30,31,82,102,110,158,199,218,230,231,268,275,371,375,393,426] Detection of stress-induced, widespread, ischemic pain can be accomplished with sustained or repetitive muscular compression or intramuscular electrical stimulation or infusion of hypertonic saline. These procedures evoke greater and more sustained pain for FMS patients compared with pain-free subjects.[26,191,245,341,344] Thus, it could be instructive to track the transition from acute to chronic postoperative pain with psychophysical evaluation of pain intensity during and after sustained or repetitive muscular stimulation.

FMS pain often coexpresses with symptoms other than pain. For example, pain can be accompanied by chronic fatigue syndrome (CFS) or not, and CFS can exist without FMS. These conditions share abnormal expression of peripheral receptors (acid-sensing ion channel 3, purinergic P2X and nociceptive vanilloid receptor 1 receptors) responsive to a cocktail of muscle metabolites (protons, lactate, and ATP).[8] This is revealed by a definitive experiment.[293] Infusion of a small amount of protons, lactate, and ATP into the interstitial fluid of a thumb muscle of human subjects (at a concentration present during moderate to intense aerobic exercise) evokes a sensation of fatigue. Pain results from infusion of concentrations of the metabolite mixture present during ischemia. This and related experiments reveal peripheral mechanisms for CFS and FMS.

Fibromyalgia is a complex, multisystem disorder that differs between individuals.[363] A variety of central mechanisms have been proposed to account for the different symptoms of FMS, but it is likely that central correlates of FMS pain are secondary consequences of autonomic dysregulation and abnormal peripheral input from ischemic muscles. Thus, it seems prudent to thoroughly explore therapeutic options for attenuation of stress and tonic peripheral vasoconstriction as potentially prime mechanisms for FMS pain and for chronic postoperative muscular pain.[371]

Central Neuroplasticity and Neuropathic Pain

An indeterminate incidence and extent of nerve injury makes it difficult to identify a mechanism for PPSP after surgery. PPSP is not always associated with nonpainful phantom sensations, which occur reliably after limb amputation and are presumed to result from deafferentation-induced spontaneous central activity.[239,266] Even after limb amputation, which invariably transects major nerve trunks, neuropathic pain does not always develop; reports of phantom pain range from 51 to 85%.[112,143,262] However, heightened sensitivity of and/or abnormal discharge from the stump region appears to be a mechanistic factor for triggering of neuropathic pain.[54,168,189,266,327,328,330] Excitatory influences on stump neuromas (eg, noradrenalin) induce phantom pain,[56,57,168,327] and the intensity of phantom pain is related positively to pain in the stump or residual limb.[279,329,330] Phantom limb pain often is associated with some phasic event (eg, movement of a limb or its phantom, pressure on the intact portion of the limb or adjacent regions, stimulation of the stump, or spontaneous stump pain[143]). Accordingly, anesthesia of the stump has been shown to eliminate current phantom limb pain in some subjects (3 of 6).[33]

In addition to peripheral factors, some forms of central neuroplasticity that vary between individuals likely contribute to neuropathic PPSP. For example, new cortical connections (eg, sprouts from innervated to deafferented cells in SI)[244,294] may be responsible for referral of pain to a deafferented region.[3,4,78,101,133,139,303] When these connections have formed, stimulation of the stump or the residual limb could synchronize and increase the activity of newly connected, previously deafferented cortical cells, with referral of pain to their original receptive fields.[254,330] In this respect, particularly important observations after amputation are that the magnitude of phantom limb pain is directly related to the amount of cortical reorganization, substantially increasing the number of neurons that, when activated by stimulation of intact receptive fields, could refer sensations to the amputated portion of a limb.[100,114,134,167,213] Similarly, there is a strong correlation between the amount of cortical organization after amputation and the percentage of body sites that refer sensations to a phantom limb during painful stimulation.[134,184]

The formation of new cortical connections after nerve transection is use-dependent, changing over time depending on patterns of input.[139,184] For example, functional changes in cortical receptive fields similar to those seen after nerve section occur for normal monkeys after conditioned (active) receipt of structured tactile stimulation of several digits throughout test days.[156] Conversely, disuse (or deafferentation) results in a reduction in cortical representation in proportion to minimal (or lost) input.[404,405] Thus, cortical reorganization occurs after limb amputation, and its influence on pain depends on some combination of active use of intact structures (eg, the residual limb), abnormal sensory input from the stump, and the extent of deafferentation. The use-dependency of cortical organization underlies demonstrations that chronic postoperative phantom limb pain can be alleviated by training procedures that dictate patterns of cortical plasticity.

Phantom limb pain decreases after training to control a mechanical hand from contractions of arm muscles

accessed at amputation stumps[404] or after feedback-guided sensory training to discriminate between different locations or frequencies of nonpainful electrical stimulation.[113] Cortical reorganization is noted for trained patients, but not for control participants, on the basis of neuroelectric source imaging of responses to tactile stimulation of the lip. Also, strong reinforcement for the functional efficacy of training with intent to reorganize spatial cortical maps has been provided by studies of patients with motoric loss after strokes. Restraint of the unimpaired arm and rehabilitative training of the impaired arm results in remission of motor deficits and recovery of normal cortical organization, as shown by focused magnetic stimulation.[208]

Investigations that have shown functional recovery and cortical reorganization after nerve injury clearly demonstrate that central neuroplasticity can be misguided by deafferentation, resulting in chronic pain and adding a cerebral cortical mechanism to a peripheral one. Directing new cortical connections by training has shown therapeutic potential and should be investigated until fully understood. Does cortical reorganization work because connections from entirely afferented to deafferented cells drop out? What is the optimum training regimen and the necessary maintenance schedule?

Pain-Specific Brain Activation Patterns

The hypothesis that pain chronification involves maladaptive brain neuroplasticity raises the question of whether gross changes in brain morphology or connectivity (other than reinnervation of deafferented cells) occur over time in association with PPSP. Observing neocortical, limbic, and mesencephalic structures associated with the processing of noxious stimulation or with the reported experience of pain in humans has become straightforward. More than 2 decades of work on brain imaging and pain are behind us, and the literature contains more than 1,000 reports and reviews. Many examine brain responses to a noxious stimulus using functional magnetic resonance imaging (MRI), which measures blood oxygen levels, or arterial spin labeling perfusion MRI, to assess brain responses to a painful perceptual experience, or functional MRI, to study functional connectivity (temporal correlations) among brain areas. Structural MRI studies examine the volume and thickness of cortical gray matter as well as midbrain gray matter, and there are also studies of white matter integrity and possible brain neuroinflammation, on the basis of diffusion tensor imaging, as well as studies of white matter connectivity among brain areas. Apkarian et al[13] and Davis and Moayedi[81] provide excellent reviews of this area.

Identifying pain chronification within the brain is straightforward if cortical activation during pain is specific to certain brain structures. Early neurophysiological pain research relied heavily on line-labeling approaches that traced the transmission of noxious signals from the periphery to the thalamus and somatosensory cortices. However, identification of polymodal nociceptors and findings that wide dynamic range neurons respond to innocuous as well as noxious stimuli support the importance of signal transmission patterns. Thus, the specificity of cortical projections is complicated by patterns of activity in specific regions. Some investigators subtract activation patterns associated with non-noxious stimuli from those associated with similar noxious stimuli in an attempt to identify a single structure or set of structures that respond differentially to noxious signaling. Nonetheless, others contend that distinct patterns of brain activation are specific to subjective experience and reports of pain rather than to the nature of the stimuli-generating activation. This approach makes sense for studies of chronic pain states in which the link between a peripheral stimulus and a central response is abnormal or absent altogether.

Cortical processing of pain involves at least the activation of limbic and frontocortical areas as well as somatosensory cortex. Cognitive experiences modify pain and add affective components to its representation in the brain. Thus, the term, "pain matrix" appears frequently in the literature.[115] Loosely, it refers to a set of structures that activate in response to noxious stimulation and the related intensity and unpleasantness of pain. A typical report[236] describes the pain matrix as comprising primary and secondary somatosensory cortices, specific areas within the insula, ACC, amygdala, and prefrontal cortices, along with the thalamus, but there are variations. Identification of a structure or pattern of activation across structures that is specific to pain is the holy grail of the field.

Wager and colleagues[390] delivered warm and painfully hot stimuli to the forearms of healthy subjects undergoing functional MRI scans in an attempt to find a neural signature in brain activity unique to pain. They succeeded in identifying patterns of brain activation that distinguished pain from warmth with 93% accuracy. Administration of remifentanil selectively affected the pain but not the warmth response pattern. This demonstration of a neurologic signature for pain is a major advance in identifying a unique brain response to pain, but the study of response to a heat stimulus in normal volunteers is very different than the study of chronic pain in patients. Ultimately, this approach may lead to the discovery of an objective biomarker of clinical pain.

Imaging Chronic Versus Acute Pain

Functional brain imaging has yet to engage the problem of acute to chronic pain transition in surgical patients. However, it has shown that the patterns of brain activation associated with chronic pain differ from those that characterize acute pain, suggesting that chronic pain is the product of higher-order maladaptive CNS plasticity.[142] Neuroinflammation, essentially the same processes described previously, may be the root cause of brain structural changes.[81] Volumetric MRI studies indicate that chronic pain patients tend to have decreased gray matter volume in structures related to chronic pain activation.[235] Gray matter may age abnormally for pain patients.[249] Emerging findings in several areas indicate that chronic pain conditions are associated

with abnormal connections in white matter tracts.[81] Relief of chronic pain is generally associated with normalization of brain activation and structural patterns. Potentially, this area of research can identify brain activity and structural changes associated with the processing of noxious signals, activity reflecting antinociceptive processes, the balance of the two and, in principle, any existing pronociceptive imbalance in brain function and structure that occurs as acute pain transitions to chronic pain.

Qualifying Concerns

Pain is not unique in altering brain structure. Several psychiatric conditions are associated with abnormal gray matter volume and white matter alterations. Patients with major depressive disorder show substantial gray matter volume reductions and white matter abnormalities,[190,357,397,431] whereas panic disorder patients show increased cortical gray matter volume[365] and increased midbrain gray matter volume including the PAG.[86] Also, gray matter volumetric abnormalities tend to exist in patients who have a helplessness trait, defined according to the Pain Catastrophizing Scale.[81] Thus, altered brain structure in patients who have developed PPSP, if observed, could reflect comorbidities as well as the chronic pain state. These considerations also suggest that gray and white matter abnormalities associated with preexisting pain or with psychopathology may identify factors for the development of PPSP in patients enduring acute pain. Although still inceptive, the emerging body of research on gray matter volume and white matter integrity in patients with psychiatric disorders suggests that patients with these conditions who come to surgery may have maladaptive brain alterations in structure and function that put them at risk for abnormal processing and failed resolution of acute postoperative pain.

Fig 3 depicts hypotheses about how changes in brain function and structure might sustain PPSP. These alterations depend on abnormal noxious signaling in the periphery and/or abnormal processing and transmission of noxious signaling at and above the spinal cord. Emotional and mood disorders probably contribute to abnormalities in brain properties associated with pain.

Normal Versus Postinjury Somatosensory Processing

Mammalian sensory systems have evolved and developed for attention to and processing of phasic events. Somatosensory receptors fail to respond to sustained stimulation unless there are temporal variations in stimulus contact or magnitude. Adaptation and habituation reduce the sensitivity of peripheral receptors and their central projections to constant or repetitive stimulation.[182,225,253,396] Thus, chronic pain is associated with abnormally extended neuronal activity.[165,189,216,270,389] Similarly, endogenous inhibitory modulation of nociceptive input is designed for attenuation of acute pain, as evidenced by failed chronic administration of exogenous opiates and by reversal of GABA and glycine inhibition to facilitation with prolonged painful stimulation. Additionally, throughout the CNS, opponent control systems (eg, facilitation/inhibition, sympathetic/parasympathetic) achieve set point balance by back-and-forth (phasic) adjustments. Chronic sympathetic dominance is problematic, and chronic pain probably would not develop if endogenous inhibition of nociception could be sustained indefinitely at a level that can occur phasically. To the extent that neuroplastic adaptations to neural injury have evolved, they enhance sensation (restoring lost or impaired vision, hearing, or touch), and these otherwise adaptive processes can magnify pain. Inhibition can be reduced and/or facilitation increased, accounting for enhanced responses to phasic stimulation (allodynia and hyperalgesia).

Conceptual Map of Research Approaches

The potential causes of PPSP are not mutually exclusive, and they differ mostly because they focus on different levels of the neuraxis. Each approach has its champions who assert that their lines of inquiry will yield the key to understanding and ultimately preventing the development of PPSP. Fig 4 provides a schematic representation of these hypothetical mechanisms, depicting them, somewhat artificially, as 5 independent

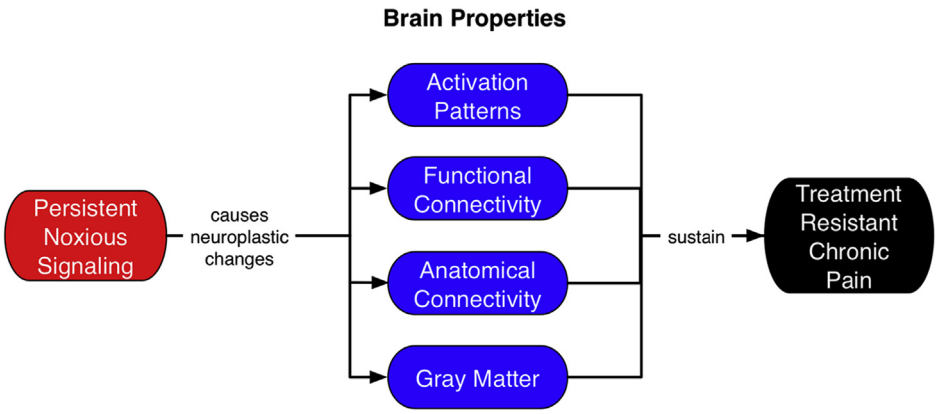

Figure 3. Potential mechanisms for persistence of chronic postoperative pain in the brain.

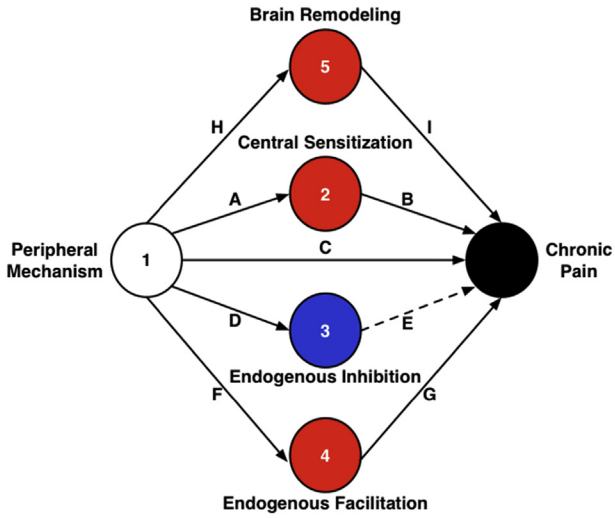

Figure 4. Five families of hypotheses accounting for the transition of acute postoperative pain to chronic postoperative pain (PPSP). Hypothesis 1 holds that PPSP results from persistent noxious signaling **(C)** from the periphery, as might occur with iatrogenic nerve injury or chronic inflammation. Hypothesis 2, the central sensitization hypothesis, focuses on the dorsal horn of the spinal cord. Persisting noxious signaling **(A)** may cause excitatory neuroplastic changes in noxious signal transmission **(B)** at the dorsal horn that persist after **(A)** disappears. Hypothesis 3 addresses endogenous bulbospinal inhibitory modulation of noxious signaling. Noxious signaling **(D)** initiates this process, but for various reasons descending inhibitory modulation becomes compromised or lost **(E)**. PPSP results from the loss of descending inhibition of noxious signaling. Hypothesis 4 attributes the development of PPSP to the establishment of descending endogenous facilitation of noxious signaling over time. Persisting noxious signaling **(F)** eventually causes enhanced bulbospinal neurotransmission of noxious messages **(G)**. Finally, Hypothesis 5 proposes that PPSP occurs because noxious signaling **(H)** has brought about maladaptive brain remodeling in function, structure and connectivity **(I)**. The brain has become optimally reorganized over time to generate and sustain PPSP, even when **(H)** has disappeared.

approaches, each with its own basic assumption(s). Of course, some combination of the 5, or all of them together, could be at work in a single case.

The first approach hypothesizes that PPSP originates with, and is sustained by, pathophysiology in the periphery. Although central changes may occur in response to peripheral pathophysiology and modulate a painful condition, the fundamental mechanism is a peripheral driver. As noted previously, many investigators assume that peripheral nerve injury or inflammation or the combination of these factors can generate repetitive bursts of primary afferent activity that initiate activity-dependent plastic changes in glutamatergic neurotransmission in dorsal horn neurons, including LTP, and ultimately these changes lead to a chronic pain condition. Pathophysiology in the periphery can take many forms: preexisting or unresolved inflammation, nerve injury, neurotrophin dysregulation, kinin dysregulation, and abnormal glial cell contributions to peripheral neuroinflammation and sensitization. The nociceptive drivers in the periphery are not mutually exclusive as potential mechanisms. For example, inflammation may foster NGF dysregulation and adhesion formation that causes nerve injury, and kinins play a role in sustaining tissue inflammation.

In Fig 4, pathway C represents this approach. Examples include nerve damage, the formation of scar tissue that compresses, entraps, or irritates nociceptive fibers, adhesive capsulitis, and painful keloid formation. In Fig 4, pathways AB and FG may exacerbate the severity of the pain and alter its features, but the root problem is pathway C. The PPSP depends on the driver in the periphery and removal of that driver terminates the chronic pain.

The second approach presumes that PPSP results from maladaptive central neuroplasticity that occurs because of excessive noxious signaling in the periphery or nerve injury that causes abnormal, persistent nociceptive firing patterns. This approach differs from the first in that it assumes maladaptive neuroplastic central changes can become permanent and exist indefinitely in the absence of noxious signaling in the periphery. Thus, inflammation and related healing processes may eventually resolve but leave behind dysregulated modulation processes at the dorsal horn of the spinal cord or above that produce and enhance noxious signal transmission. In addition to LTP and synaptic strengthening, central neuroinflammation processes involving glial cells and TLRs could play a role in sustaining the maladaptive central neuroplasticity that results in PPSP. In Fig 4, the second approach follows the AB pathway. Over time, as tissues heal, A may disappear, leaving B as the sole mechanism driving PPSP. The key to preventing or alleviating PPSP is the control of maladaptive neuroplastic changes. A test of the independence of B with chronicity is the same as for the first approach—removal of the peripheral driver.

The third approach asserts that PPSP develops because of compromised or lost inhibitory modulation of noxious signaling in medullary-spinal pathways. The literature currently provides one body of information on stress-related modulation that engages endogenous opioids and another body of information on CPM. Whether these systems are independent inhibitory mechanisms or different aspects of a single process is at issue. Either way, this approach postulates that PPSP and other chronic pain states develop because patients have compromised or lost their endogenous mechanisms for modulating noxious signaling. The mechanisms behind the dysregulation of endogenous modulation remain largely a mystery, but evidence suggests that the use of exogenous opioids for chronic pain can make patients hyperalgesic.[66] Many investigators assert that this occurs because exogenous opioids resemble β-endorphin and confuse negative feedback loops in the hypothalamo-pituitary-axis and elsewhere,[215] but the role of endogenous opioids is controversial. Chu et al[67] showed that opioid-induced hyperalgesia after remifentanil hypoalgesia did not change with naloxone administration, indicating that the endogenous opioid system did not determine opioid-induced hyperalgesia. In Fig 4, the DE pathway represents this approach. The inhibitory influence at E appears to be weakened. However, a psychophysical

demonstration of increased pain sensitivity cannot distinguish between mechanisms of reduced inhibition or enhanced facilitation (sensitization).

The fourth approach posits that PPSP is the product of descending facilitatory modulation. Recent evidence reveals that under certain conditions RVM modulation of noxious signaling can convert from inhibitory to facilitatory. This process involves spinal serotonergic and noradrenergic pathways that normally play a role in tonic inhibitory modulation, or it could result from a reversal of GABA/glycine inhibition to sensitization. A shift from inhibitory to facilitatory modulation in these bidirectional pathways may come about with nerve injury or in response to inflammation. In Fig 4, the FG pathway represents facilitatory modulation, essentially a reversal of the DE pathway. It follows that such a shift in the bidirectional modulation pathway involves on the one hand a loss of tonic inhibition of noxious signaling (third approach) and on the other hand a facilitation of noxious signaling (fourth approach). Thus, this is a possible mechanism for the conversion of acute postoperative pain to PPSP, particularly in cases in which nerve damage has occurred. For this approach, the fundamental mechanism of PPSP is facilitatory modulation.

The fifth approach holds that acute pain becomes chronic because over time changes occur in brain function, including structural volume and functional connectivity. Various chronic pain syndromes manifest such changes.[142] The MRI and other imaging literature shows that chronic pain is associated with altered patterns in brain processing of noxious signaling and losses in brain gray matter volume. Concomitantly, abnormal connections occur in white matter tracts.[13,81] These abnormalities in the brain, the organ of perception, suggest that maladaptive brain changes in structure and function occur in response to a peripheral or lower-level central driver so that the brain over time becomes optimally organized to generate and sustain the experience of pain. If the original driver disappears, the brain changes may remain, leaving the patient with a brain remodeled to generate pain indefinitely, or they may normalize. Phantom limb pain is perhaps the best example of this concept. However, 3 observations (discussed previously) constrain this hypothesis: 1) a specific pattern of brain activation for pain still eludes us, 2) similar brain remodeling changes occur with depression and other chronic conditions, and 3) removal of the peripheral driver for the pain can often reverse changes in the brain. In Fig 4, pathway HI represents maladaptive structural and functional changes in the brain, or brain remodeling.

Finally, the purpose of Fig 4 is simply to map broadly the thinking in the literature about the possible mechanisms behind PPSP. Many combinations of these approaches are possible. The time frame for the processes depicted extends from 2 months to approximately 1 year. Fig 4 calls attention to the need for strategic planning and integration of approaches in the pursuit of causes of PPSP.

Barriers to Progress and Opportunities

Clinical Epidemiology

Definition of Persistent Postoperative Pain

With a few exceptions, investigators have sought to predict the simple presence of a pain condition or its severity at various times after surgery. For example, Johansen et al[160] used numerical rating scale responses to determine the percentage of PPSP respondents with no, mild, moderate, or severe pain. Unidimensional approaches such as this are limiting. Chronic pain has other key features that include affective distress, interference with sleep, interference with daily activities, and effect on quality of life. Qualitative descriptors of the pain and abnormal sensations in the area of the surgical wound are important because they provide information about the likelihood of unhealed nerve injury. Furthermore, not all PPSP is constant. Some pain conditions are silent until the patient engages in certain types of activities; some pains emerge at night, and others come on spontaneously, seemingly at random, from time to time. Overall, the proportion of patients who report PPSP is higher at 3 months than at 6 months, and this proportion is even lower at 9 months and 1 year. However, many patients will have PPSP for the rest of their lives. A need exists for a systematic way of assessing and gauging PPSP according to its multifactorial nature. A critical consideration in this regard is the consistent finding that some individuals develop chronic pain and others do not, after all types of surgery, and the reasons for this are unknown.

The Need for Longitudinal Measurement

The severity of acute postoperative pain is one of the risk factors for PPSP. Most investigators gauge this by obtaining a pain intensity report on the first postoperative day, using a cross-sectional study design. Unfortunately, the practice of measuring acute pain as a point estimate (single measure, cross-sectional design) rather than a process playing out over time is a barrier to progress. Point estimates of acute pain are weak on 2 counts. The first is that the standard error of measurement is quite high for single numerical rating scale reports of acute pain, and so the precision of a single measurement is poor.[59] Second, the assumption that acute postoperative pain is at its worst on the first day after surgery is untenable. As described previously, we found that fully 37% of postoperative patients either reported pain at the same level for 6 days after surgery or gave increasingly worse ratings of pain over the 6 days. Using the linear pain trajectory to quantify acute postoperative pain, we recorded not only the intensity of pain immediately after surgery but also the rate of change in the pain over the 6 days including the direction of the change—whether it diminished or intensified. The pain trajectory yielded summary measures that were much more precise than single pain reports. Patients with worsening pain or nonresolving pain in the first week after surgery may be

more likely to develop PPSP. Therefore, repeated measures of pain are valuable for defining this risk factor because it increases substantially the precision of the pain measurement and it provides more information. In addition to initial pain intensity, the assessment yields the direction and rate of pain resolution and an estimate of the duration of the acute postoperative pain.

Repeated measurements of the characteristics of chronic pain, including intensity, also will be necessary for an adequate understanding of mechanisms for PPSP. Simply reporting the incidence of pain at different points in time for all postsurgical patients does not generate a pain trajectory, which applies only to individuals with chronic pain. Individuals who receive surgery but do not experience chronic pain can be used as control subjects, but they distort the time course of pain development or decay. Similarly, mechanistic considerations are only relevant to individuals who report pain at some time(s) beyond 2 postinjury months. Statistics for the pain characteristics of these individuals will be particularly useful if on the basis of subgroups with common PPSP characteristics—for example: acute pain that declines beyond 2 months postinjury; acute pain that becomes chronic and does not remit; postinjury pain that appears late; neuropathic pain; surgical incision pain; nonneuropathic, nonincisional pain; generalized muscular pain; oscillations in PPSP intensity over time; or high-intensity pain. It is likely that different risk factors will apply differentially to these and other possible profiles/characteristics of chronic pain.

The previously mentioned recommendations for thorough prospective study of PPSP are a tall order, because large numbers of patients with different pain profiles will be helpful, if not necessary, to understand relationships of risk factors (and associated mechanisms) with different types and trajectories of chronic pain. Multiinstitutional observations with coordination of protocols and repeated measures, long-term, are needed to improve on the existing literature involving numerous studies of a variety of surgical procedures without commonalities that permit meaningful combination of the data.

The Lack of an Adequate Definition for Iatrogenic Neuropathy

The lack of a methodology for identifying neuropathic features of PPSP (or neuropathic varieties of PPSP) is a barrier to progress in assessing the contribution of nerve injury to the different profiles/characteristics of PPSP. Substantial research exists on the subjective features of painful neuropathy, but there is not a consensus on assessment tools for neuropathic pain.

Individual Risk Profiles

The possibility of determining which patients come to surgery with high risk for developing PPSP represents a promising opportunity. The PPSP risk profile of every surgical patient is drawn from a domain of all possible preoperative, intraoperative, and immediate postoperative risks. This domain encompasses patient-specific as well as surgery-specific variables. Patient-specific variables include demographic characteristics such as age and gender, genetic and epigenetic predispositions, and environmental and psychosocial features. The latter comprise vocational adjustments, family functioning, economic well-being, and personality traits, including the tendency to catastrophize. The risk profile for a patient also incorporates preexisting medical and behavioral comorbidities such as diabetes and depression. Among the medical comorbidities is CPM dysregulation, which might stem from genetic predispositions or from the patient's psychological state.

Surgery-specific risks break down into preoperative, intraoperative, and postoperative groups. Preoperative factors encompass the patient's medical history including the diagnosis, whether the patient has an existing chronic or acute pain condition, hyperalgesia, and preoperative medications. Intraoperative factors include anatomical site, extent and duration of surgery, surgical approach, nerve damage, and anesthetic technique. Postoperative factors comprise the severity and trajectory of the acute postoperative pain over days after the surgery, medications, and adequacy of postoperative pain management.

Research continues to uncover and evaluate new risk factors and to pursue the relative risk of established risk factors. Although additive risk assessment models are a useful beginning, a need exists for statistical modeling approaches that identify the correlations and interactions among the risk factors and take them into account. Ultimately, an opportunity will exist to create risk profile assessment for individual surgical patients and associated adjustments in pain management that will prevent most PPSP.

Effect Size Estimation

The search for clinically meaningful PPSP risk factors typically involves large sample sizes, and the excessive statistical power associated with large samples is likely to reveal clinically meaningless, yet statistically significant, predictors of chronic pain unless investigators make use of effect size statistics.[174,351] An effect size is an index of the quantitative relation between variables (ie, the effect that one variable exerts upon another). Statistical significance, in contrast, simply indicates how likely it is that an observed effect is exactly 0. Effect size estimation complements significance testing by quantifying the magnitude of observed effects. Finding that a difference is statistically significant in a large sample does not mean that the difference is large, nor does it mean that the difference is important from either a clinical or research point of view. More than 70 indices of effect size exist, and they vary with the nature of the data and the statistical test used. Most provide classifications of outcomes into small, medium, and large effects. Common effect size indices include Cohen d, the standardized mean difference between 2 groups, R^2, a gauge of the amount of variance in one variable for which the other variable can account, and Cramér V, the strength of association between 2

categorical values in a contingency table. The odds ratio is useful when the research question focuses on the degree of association between 2 binary variables such as gender and the presence or absence of PPSP at, say, 3 months after surgery.

It is appropriate to report confidence intervals with effect sizes. As sample sizes increase, confidence intervals narrow. Careful attention to the effect sizes of variables that predict PPSP will eliminate trivial predictors and facilitate the development of a risk profile model for individual surgical patients.

Lack of Veterinary Epidemiology Studies

Large and small animals undergo surgery in everyday veterinary practice, and some suffer pain.[111,123] Veterinary epidemiology can address problems of this sort[288] and has means to engage the problems of acute postoperative pain and the development of PPSP in animal populations. Although animals cannot generate patient-reported outcomes, they express uncomfortable or painful conditions through abnormal vocalization with movement or palpation, licking or biting a dysesthetic area, reduced activity levels, changes in personality, altered posture or ambulation, piloerection, excessive salivation or oculonasal discharge, altered bowel function, or teeth grinding.[338] Veterinary clinicians diagnose abnormal sensory or sensorimotor conditions using a combination of these features rather than one alone, and patterns vary markedly across species. Although these measures cannot define and validate pain, they indicate the presence of sensorimotor dysfunctions that could include pain. Determining and evaluating risk factors for such patients would be similar to that performed in human clinical epidemiology studies. In such investigations, operant escape from nociceptive stimulation can be used to simulate the psychophysical tests that document allodynia or hyperalgesia in humans with PPSP.[386]

Veterinary studies help fill the gap between animal laboratory models and human patient studies. Animal patients are psychosocially less complex than their human counterparts, and physiological risk factors under study in humans should apply to animals. More importantly, veterinary models for PPSP should allow us to test hypotheses derived from theory. Veterinary epidemiologic studies of PPSP could provide an additional line of evidence about how acute postoperative pain becomes chronic.

Integrating Clinical Epidemiology with Basic Science

Finally, in light of the hypotheses represented in Fig 4, an opportunity exists for clinical epidemiologists to assist basic science researchers by undertaking retrospective studies. Investigations of patients living with PPSP, and matched control participants, could reveal which patients have which hypothetical mechanisms or combinations of mechanisms. For example, a retrospective study of PPSP patients could determine whether each patient has: 1) evidence of a peripheral driver for nerve injury, 2) persisting low-grade or other inflammation, 3) evidence of central sensitization, 4) abnormal descending modulation of noxious signaling, and 5) evidence of pain-related alterations in brain function, structure, or connectivity. The outcomes could guide future prospective clinical epidemiology studies and help clarify research priorities for basic scientists.

Neuroimmune Mechanisms

Neuroimmune interactions are emerging as potential mechanisms of PPSP in the periphery, at the spinal cord, and in the brain where glia-induced neuroinflammation may be the root cause of structural changes related to chronic pain. To date, they have received less attention for human chronic pain than they merit, and an opportunity exists for expanding insights into their role in the transition from acute pain to PPSP. These mechanisms are most likely to activate with nerve injury when injured neural tissues release danger-associated molecular patterns. SGCs at the dorsal root ganglion, glial cells at the spinal cord, and brain glial cells may, or may not, operate via a proinflammatory signaling cascade to induce long-term sensitization and plasticity. They may or may not generate TLR signaling or invoke the same processes that ultimately result in proinflammatory cytokine release. Whether glia-mediated neuroinflammatory processes are mechanisms uniquely associated with neuropathic PPSP is uncertain and merits investigation. No evidence exists to answer the question of whether these processes at different levels of the neuraxis are a chronic manifestation of a common underlying mechanism for acute pain. Direct comparisons of patients who have received a given surgical procedure and do or do not have PPSP will be beneficial.

The Need for Integrated Theory to Guide Models

Although there are 5 lines of basic scientific inquiry into the cause(s) of PPSP, there are as yet no attempts to combine all or some of them into more comprehensive mechanistic hypotheses. Conceivably, the process of pain chronification might progress in stages. Initially, persisting peripheral mechanisms could generate central neuroplastic changes at the dorsal horn of the spinal cord. A shift from inhibitory to facilitatory modulation could occur but eventually disappear, if the lower-level drivers no longer exist. All the while, neuroplastic changes in brain function and structure could facilitate the pain experience. The literature is clear that these changes can sometimes reverse when a peripheral driver is removed, but the possibility remains that some higher-level central changes do not reverse. This appears to be the case with phantom pain and may perhaps occur in other cases in which central representation of specific body areas is compromised through denervation. The essential point is that pain chronification may entail neurophysiologically definable stages. It may be more useful to consider the 5 approaches to PPSP as potentially compatible mechanisms operating at different levels of

the neuraxis, and perhaps at different stages in time, than as competing explanations.

Conclusions

Clinical epidemiology has made progress in defining the nature and scope of the PPSP problem. Clearly, PPSP can result from a wide variety of injuries and surgical interventions, regardless of the extent of the insult. Procedures that damage nerves such as radical mastectomy, thoracotomy, and limb amputation incur a higher risk of PPSP, but the problem also occurs with surgeries that entail minimal risk of nerve trauma. Inflammation is a mechanism that can interact with nerve injury. Broadly, this work shows that PPSP has multiple and varied manifestations, and is unlikely to be the product of a single mechanism. Moreover, the risk of developing PPSP depends on characteristics of the patient as well as on features of the surgical procedure.

Chronic pain is a major clinical problem in the United States and worldwide that merits urgent attention. A concerted, strategic effort directed at integrating clinical epidemiology studies, basic science research, and current theory about pain mechanisms for the study of chronic pain would greatly increase progress in understanding and open new avenues for prevention, management, and perhaps cure of many pain syndromes.

The search for the mechanisms is vitally important to the pain research field. Although at its present stage PPSP research is neither systematic nor strategic, the body of work reviewed in this article is the beginning of a concerted effort to address the fundamental and overarching question of how chronic pain develops and persists. Progress at the basic science level will lead to innovative interventions that help prevent PPSP and many types of posttraumatic chronic pain.

The large-scale natural experiment that PPSP represents remains an overlooked opportunity. At present, research on PPSP is nascent, with relatively few investigators in multiple areas working mostly without coordination. A need exists for an interdisciplinary PPSP forum for the exchange of ideas, the development of consensus on key definitions and models, and bidirectional exchanges between clinical epidemiologists and basic scientists. Without this, the field is likely to evolve slowly with fragmented progress in multiple fields.

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