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Pain Treatment in the Perioperative Period

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Pain Treatment in the Perioperative Period

At first glance, it seems a curious fact that acute pain in the perioperative period continues to be a major clinical problem. Opioid analgesics have been in continuous use by Western civilization for more than 450 years; remarkable advances in biomedical research have provided new insights into the basic neurophysiologic features of pain; a diverse array of pain treatment therapies are available; and patients, physicians, and regulatory agencies have urged that greater attention and more resources be focused on the treatment of acute pain. A desire for pain relief by the patient and the desire of the physician to relieve pain and suffering are among the principal motivating factors behind most clinical encounters. Still, severe pain is prevalent in the perioperative period. A significant decrease in the prevalence and severity of acute perioperative pain will be possible only if physicians who care for individuals with acute pain understand more clearly and consistently the medical problem that is clinical pain.

The International Association for the Study of Pain defines *pain* as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”¹ Perioperative pain is most often associated with tissue injury, but neither tissue injury nor threatened injury is a prerequisite for pain. Nerve injury or disease is a common problem that may cause pain long after the acute injury resolves. Pain is always an emotional experience and always unpleasant. A patient’s pain experience always will be influenced by associated emotional and cognitive factors, and pain will be reflected in the patient’s behavior. Pain is subjective; in the overwhelming majority of clinical scenarios, the patient is (by far) the most reliable reporter of pain.

A common clinical experience is one in which the clinician is faced with a patient whose pain behaviors appear to be “out of proportion” to what is expected, given the observed extent of injury and disease. Faulty clinician expectations, based on outmoded theories of nervous system functioning, are at the foundation of this troubling scenario. In the past, the nervous system was often described in terms of static, hard-wired electrical circuits, with implied assumptions about the reliability and reproducibility of signal transmission. It is now clear, at least with regard to signals related

to tissue injury and pain, that neural transmission is an active process that involves integration/interpretation of signals at many levels. The processes of tissue injury and of the transmission of pain signal facilitate the transmission of pain signals and alter the nervous system. Understanding the factors that influence the pathophysiologic features of pain may lead to insightful clinical pain treatment.

Pathophysiologic Features of Pain

Nociception: Neuroanatomy, Physiologic Features

Nociceptor Physiology: The Detection of Noxious Stimuli. Although pain is always unpleasant, the ability to detect actual and potential tissue injury is essential for survival. It has been recognized since the early 1900s that detection of various tissue-threatening or noxious stimuli is dependent on specialized neurons and that activity in those neurons is associated with pain sensation.² These specialized neurons, known as nociceptors, respond to stimuli that are of specific types (eg, chemical, thermal, or mechanical) and are of sufficient intensity (high-intensity threshold for activation) to be associated with potential tissue injury. Although the major function of nociceptors is to transmit to the spinal cord impulses that reflect peripheral noxious stimuli, nociceptors are not passive “hard-wired” conduits for signal transmission. The transduction and integration of noxious stimuli are active processes that reflect complex interactions between the peripheral tissues, nociceptors, and the central nervous system (CNS). Understanding the factors that influence peripheral nociceptor function is an important step towards improved clinical pain treatment.

Peripheral cutaneous nociceptors are the most prevalent type of primary afferent sensory neuron. Most peripheral, small-diameter afferent neurons (in humans and several other species) are nociceptors, with only a small number (less than 10%) dedicated to the detection of nonnoxious thermal sensation. Cutaneous nociceptors, whether small lightly myelinated A δ fibers or small unmyelinated polynodal (C-fiber) nociceptors, terminate in peripheral tissues with unencapsulated free nerve endings. These nerve endings branch widely in the peripheral tissues, resulting in dense innervation. Nociceptors, by definition, have a high threshold for activation but respond to high-intensity stimuli of mechanical, thermal, or chemical nature. Nociceptors that respond to virtually any combination of these stimuli have been identified, but most are polymodal nociceptors, which can respond to any of these noxious stimuli.^{2,3} The prevalence of peripheral nociceptors, the density of cutaneous innervation by nociceptors, and the overlapping redundancy of nociceptor stimulus modality sensitivity bespeak the importance of nociceptor function.

The mystery of how nociceptors transduce various noxious stimuli into nerve impulses has resulted in an intense research effort. Searching to understand noxious chemical stimulus transduction, investigators successfully cloned the receptor for capsaicin, the active ingredient in hot chili peppers. The cloned receptor is a nonselective cation channel with high Ca^{2+} permeability and considerable structural homologic features with other membrane proteins that are involved with calcium homeostasis. Not only responsive to applied capsaicin, these cloned receptors are also responsible for a rapid calcium influx that occurs when transfected cells are exposed to a rapid temperature increase. Additional research has led to the identification of a homologous receptor-channel that does not respond to capsaicin but has an even higher temperature threshold to activation. Detection of noxious heat may involve several "heat-gated" ion channels, with a range of activation thresholds. Other research has begun to yield insight into neural transduction of mechanical stimuli through the identification of mechanically-sensitive ion channels.² It is hoped that basic research developments such as these will eventually lead to the development of analgesic therapies that specifically target peripheral nociceptors, which are the source of pain stimuli after tissue injury.

During embryonal development, the survival of peripheral neurons depends on connections with the appropriate peripheral target tissue, which serves as a source of neurotrophins and other growth factors. For virtually all nociceptors, nerve growth factor (NGF) is the principal neurotrophin required in development; it is also clear that NGF continues to play important regulatory functions in most nociceptors in adult animals.² Peripheral levels of NGF appear to regulate the responsiveness of nociceptors to noxious stimuli such that decreased NGF results in reduced nociceptor sensitivity. Increased NGF levels, found in settings of peripheral inflammation, result in the altered regulation of receptor proteins and neural transmitters, which enhance nociceptor signal transduction and transmission. Other neurotrophins appear to have regulatory influence on those few nociceptors that are unresponsive to NGF.

One class of nociceptors is referred to as "silent nociceptors" because they are generally unresponsive to noxious mechanical or thermal stimuli. It is estimated that as many as 30% to 40% of nociceptors (both $\text{A}\delta$ and C-fiber nociceptors) are silent nociceptors and do not respond to the noninjurious application of noxious stimuli. After tissue injury and/or peripheral inflammation, however, these silent nociceptors become responsive to subsequent noxious stimuli. The process of tissue injury and inflammation activates these otherwise "silent" nociceptors, resulting in an increased number of nociceptors that are available to transmit signals of noxious stimuli to the CNS.⁴

Recruitment of “silent” nociceptors is only one of the mechanisms in the peripheral nervous system that lead to the amplification or facilitation of pain signaling after tissue injury.

Simple activation of nociceptors, without tissue injury, is a useful research tool; however, at least in the postsurgical period, clinically significant pain is generally associated with tissue injury and varying degrees of inflammation. Tissue injury and inflammation have profound effects on nociceptor function, which in turn cause profound changes in CNS responsiveness to pain signals. Therefore, clinical pain (associated with tissue injury) is not based on the simple activation of nociceptors but is due to nociceptor activity that is facilitated by injury-induced inflammation and other mechanisms of facilitation of nociception. The dynamic fluctuations of responsiveness in each of the various receptors are integrated by the nociceptors into patterns of electrical signals that are delivered to the CNS.⁵ That peripheral neural activity is then integrated and interpreted by the CNS as noxious input.

Tissue Injury and Peripheral Inflammation. Tissue damage and the resultant inflammatory response cause marked changes in nociceptor responsiveness: the thresholds for activation of A δ and C-fiber are lowered; “silent” nociceptors are activated, and peripheral nociceptors become more metabolically active. Synthesis and the transport of neurotransmitters and ion channels are upregulated, which further enhances neuronal excitability. Postganglionic sympathetic neuronal activity directly enhances peripheral inflammation⁶ and is also required to produce some of the effects of proinflammatory mediators. Nociceptor activity contributes to the neurogenic component of inflammation, which further facilitates nociception.

Tissue injury triggers a complex cascade of events, including many that facilitate peripheral nociceptor activity (Fig 1).^{7,8} Direct tissue damage causes the release of intracellular contents, including protons and adenosine triphosphate (ATP). Inflammatory cells are activated and release inflammatory mediators. Mast cells release 5-hydroxy-tryptamine, histamine, and arachidonic acid metabolites/prostaglandins. Macrophages release interleukins (IL-1 β , IL-6) and tumor necrosis factor-alpha (TNF α), cytokines that induce the production of neurotrophins (eg, NGF and leukemia-inhibiting factor). NGF has direct and indirect effects, which enhance inflammation and facilitate nociception. Bradykinin is produced from plasma α_2 -globulins by circulating kallikreins that are activated at sites of tissue injury. Neural transmission in the primary nociceptors causes antidromic depolarization of peripheral nerve terminals, which results in peripheral release of neurotransmitters (such as substance P and calcitonin gene-related peptide). This neurogenic inflammation triggers

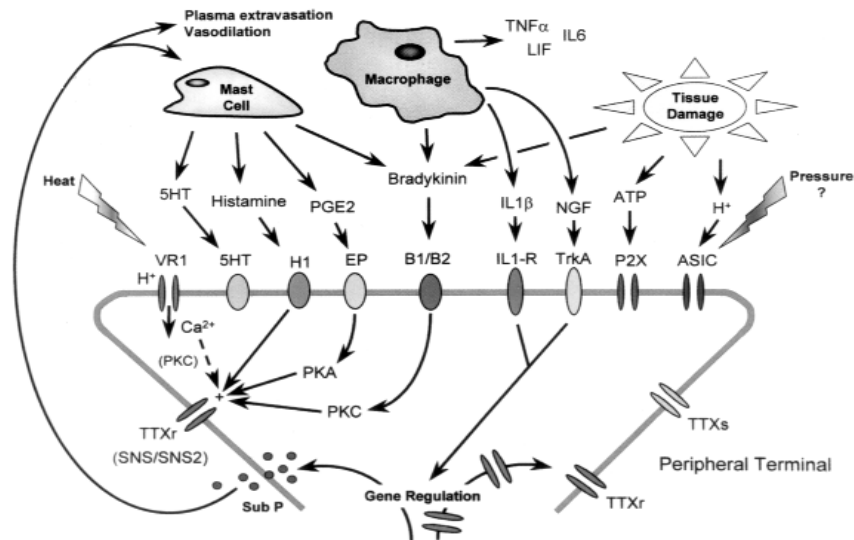


FIG 1. Modulation of the primary afferent nociceptor by inflammation. Multiple inflammatory mediators released from inflammatory and noninflammatory cells at the site of injury act on the peripheral nerve terminal to initiate changes that sensitize the nociceptor. Heat and pressure can act directly on their respective transducer proteins: vanilloid receptor (VR-1) channel protein acts as a heat transducer; the mechanotransducer to detect noxious pressure is unknown but is likely to have similar structural properties to the acid-sensing sodium ion channels (ASICs). Mast cells, macrophages, and cells that are damaged by injury release multiple neuroactive mediators, which lower the threshold of activation of the neuron by protein kinase A (PKA)- and PKC-mediated phosphorylation of tetrodotoxin-resistant (TTXr) sodium channels. Upregulation of substance P and TTXr sodium channels also occurs by activation of the tyrosine kinase (*TrkA*) receptors of nerve growth factor (NGF) and interleukin-1 β (IL1 β). Substance P (*Sub P*), when released from the peripheral terminal, initiates plasma extravasation; increased TTXr sodium channel levels increase the cell's capacity to be depolarized. Other inflammatory mediators include tumor necrosis factor α (TNF α), leukemia inhibitory factor (LIF), 5-hydroxytryptamine (5HT), prostaglandin (PGE2), adenosine triphosphate (ATP), and hydrogen ion (H⁺). Receptors include H1, histamine; EP, prostaglandin E₂; B1/B2, bradykinin; P2X, ATP-activated purinoreceptor; SNA/SNS2, sensory neuron-specific; TTXr, tetrodotoxin-resistant. (From Costigan M, Woolf CJ. Pain: molecular mechanisms. *J Pain* 2000;1 (suppl):35-44. Reproduced by permission.)

vasodilatation, plasma extravasation, and further release of inflammatory mediators from the peripheral tissues.⁹ The end result of injury and associated inflammation is that the peripheral nociceptor nerve endings are bathed in a sensitizing soup of inflammatory mediators, which markedly facilitate nociceptive transduction and transmission.

Inflammatory mediator facilitation of nociception occurs by both indirect and direct mechanisms.⁷ ATP and protons activate specific receptor-mediated ion channels that lead to nociceptor depolarization. Protons also enhance the responsiveness of heat-sensitive receptors to noxious heat. 5-hydroxytryptamine, histamine, prostaglandin E₂, and bradykinin effects are mediated through specific receptors that are linked to facilitatory trans-

membrane G-proteins. Activation of these receptors triggers the production of intracellular second messengers, which leads to phosphorylation/activation of some cation channels, which causes increased nociceptor neuronal membrane responsiveness and a lowered threshold for activation.

NGF, made in the cells of peripheral tissues (especially fibroblasts), is significantly increased in inflamed tissues. TrkA, a membrane-bound tyrosine-kinase-linked receptor that is highly selective for NGF, is found on inflammatory cells (eg, mast cells), postganglionic sympathetic neurons, and approximately 50% of primary afferent nociceptors. NGF binding to mast cells is a potent stimulus for mast cell degranulation. NGF binding to peripheral sympathetic postganglionic fibers triggers the release of prostaglandins. These NGF-mediated effects appear to mediate much of the rapid-onset hyperalgesia that has been noted in some animal models of inflammatory pain.⁶ When NGF binds to TrkA receptors on peripheral nociceptors, the NGF-TrkA complex is internalized and transported to the nociceptor cell body, triggering gene transcription, which enhances nociceptor responsiveness.⁷

“Wind-Up” and Spinal Sensitization. The complex and variable processes by which peripheral nociceptors integrate noxious stimuli result in the transmission of neuronal signals to the synapses with spinal cord neurons. It is through the patterns of signals generated by peripheral nociceptors⁵ that the CNS detects actual or potential tissue injury. Although the complexity of the CNS response to nociceptor input is only beginning to be understood, it is evident that there is marked CNS response plasticity; the CNS response to nociceptor input is altered by nociceptor input. Furthermore, not only does the CNS integrate and modify the transmitted nociceptive signals, but also the CNS itself is altered, sometimes fundamentally, by that signal processing.

Peripheral A δ and C-fiber nociceptors synapse, in the dorsal horn of the spinal grey matter, with nociceptive-specific neurons and with wide-dynamic-range (WDR) neurons. WDR neurons, which are the most common target of peripheral nociceptor central projections, are so named to indicate the graded response these neurons have to a wide range of non-noxious and noxious sensory input. WDR neurons respond maximally to high-intensity/noxious stimuli, have relatively wide receptive fields, and frequently have inputs from skin, muscle, and/or viscera. The wide range of stimulus type and intensity received allows WDR neurons to integrate stimulus intensity, regardless of the stimulus modality.⁴

Spinal neurons, and especially WDR neurons, demonstrate remarkable plasticity in their response to peripheral input. At low rates of C-fiber stim-

ulation, spinal neurons generally have a fixed stimulus-dependent response; the spinal neuronal response is proportional to the afferent neuronal input. However, with higher rates of C-fiber stimulation, some spinal neurons (especially WDR neurons) respond with intense bursts of activity, which persist beyond the termination of the afferent input. This exaggerated or “wind-up” response is out of proportion to what is expected. Wind-up response has been studied extensively in animals and humans and has been found to correlate with the increased sensitivity to noxious stimuli (hyperalgesia) present after tissue injury.

The phenomenon of “wind-up” and some other mechanisms of spinal sensitization are dependent on the activation of the N-methyl-D-aspartate (NMDA) receptors that are linked to high-capacity calcium channels on spinal cord neurons (Fig 2). At normal resting (spinal) neuronal membrane conditions, the calcium channel linked to the NMDA receptor is blocked with a magnesium ion so that the activation of the NMDA receptor does not result in calcium influx. If the spinal neuron is “primed” or partially depolarized as a result of activation of other (non-NMDA) excitatory receptors from nociceptor release of neural transmitters, the magnesium ion blockade is removed and subsequent activation of the NMDA receptor results in marked calcium influx into the cell. This increased intracellular calcium results in persistent, partial depolarization of the neuron, leading to a lowered threshold for subsequent activation and the sustained neuronal firing of wind-up. Furthermore, this increase in intracellular calcium and membrane depolarization results in a far-reaching alteration of neuronal excitability, gene expression, and metabolic regulation.⁸

With increased activity in the spinal neuron, several intracellular signaling cascades are activated, including release of intracellular calcium stores and activation of protein kinase C (PKC). PKC-mediated phosphorylation affects various aspects of cellular regulation, including NMDA receptor calcium channels. After PKC phosphorylation, NMDA receptors no longer have the previously described membrane-voltage-dependent magnesium block and also have altered ion-channel kinetics, which increase calcium influx into the cell. Therefore, without further need for “priming” depolarization, PKC-mediated modification of NMDA-calcium channels results in further increases in calcium influx, prolonged membrane depolarization, and increased neuronal responsiveness. Through this and other mechanisms of cell regulation, existing cellular structures are altered (posttranslational modification) and subsequently facilitate nociceptive transmission.

In addition to posttranslational modification of cellular membrane structures, alterations of spinal neuronal gene regulation are important compo-

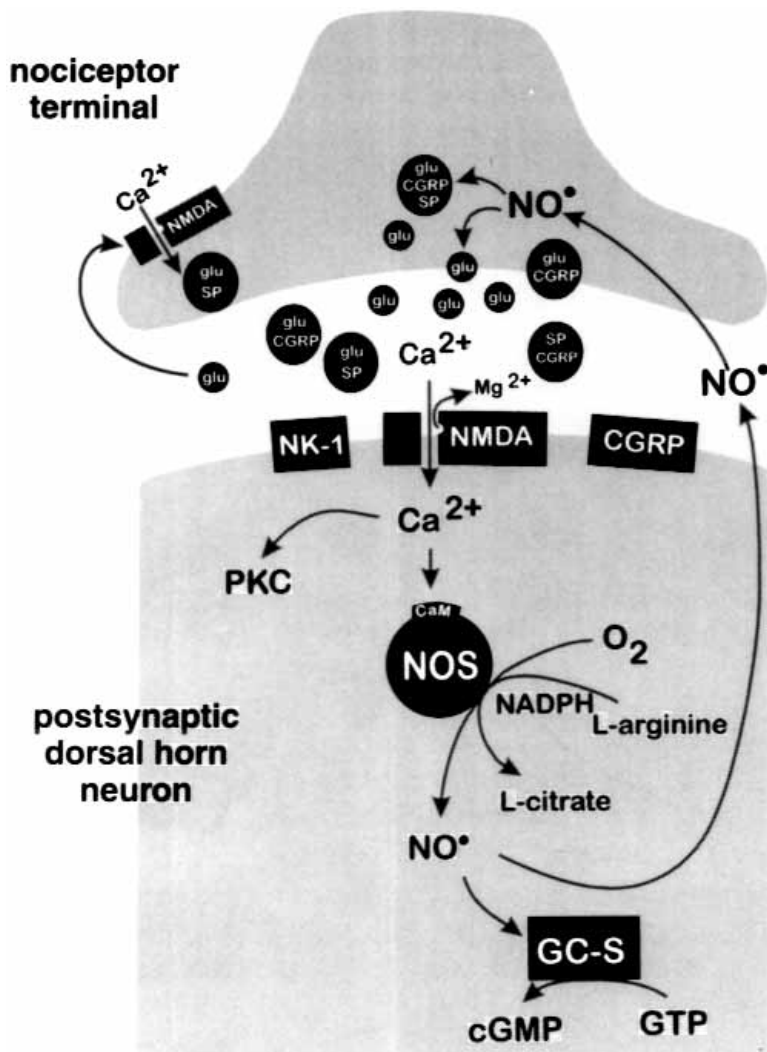


FIG 2. Neurotransmitters contained in vesicles and released from the central terminals of nociceptors: calcitonin gene-related peptide (CGRP), glutamate (glu), and substance P (SP). When released by depolarization of the nociceptor, these transmitters act at their respective receptors (neurokinin [NK-1]) for substance P and N-methyl-D-aspartate [NMDA] for glutamate) contained on spinal dorsal horn neurons. Among many consequences of receptor activation, calcium is shown here to activate protein kinase C (PKC) and nitric oxide synthase (NOS), which leads to the synthesis of nitric oxide (NO) and activation of soluble guanylate cyclase (GC-S) and the production of another messenger, cyclic guanosine monophosphate (cGMP). Note that both glutamate and nitric oxide also can affect the nociceptor terminal and lead to further release of glutamate. The N-methyl-D-aspartate receptor and the production of nitric oxide are considered critical to development of central sensitization and hyperalgesia. CaM, calmodulin; NADPH, reduced nicotinamide adenine dinucleotide phosphate; GTP, guanosine triphosphate. (From Urban MO, Gebhart GF. Central mechanisms in pain. *Med Clin North Am* 1999;83:585-96. Reproduced by permission.)

nents of observed central sensitization. For example, increased intracellular calcium concentration and the production of second messengers in spinal neurons leads to increased cellular production (translation) of nociceptive facilitatory receptors. The upregulation of nociceptive receptors results in the long-lasting enhancement of neuronal excitability.⁷ Processes to activate these NMDA-mediated and other mechanisms of CNS sensitization are initiated after only a few seconds of noxious input, but the resultant facilitation of spinal neuronal response can persist for prolonged periods.

Supraspinal Modulation of Pain Signaling. Activation of spinal dorsal horn interneurons may lead to spinal-level reflex activation of motor neurons, whereas other spinal neurons transmit the nociceptive signals to higher neural centers in the brainstem and brain. The predominant central projections of spinal nociceptive neurons cross over to the contralateral anterolateral portion of the spinal cord and extend toward brainstem nuclei, the thalamus, the limbic system, and cerebral cortex through the spinothalamic tract. The spinothalamic tract and the ascending tracts in the anterolateral funiculus of the spinal cord are the major afferent pain pathways in the spinal cord (Fig 3). Other afferent tracts are also involved in pain signaling, especially in chronic pain and in cases of nervous system injury.¹⁰ It is clear that powerful mechanisms for the modulation of pain signaling exist in the CNS and are based on activity in descending neural pathways from brainstem structures. Classic studies in experimental animals and clinical experience in humans have led to an awareness of the involvement of portions of the thalamus and cerebral cortex in pain perception, but recent functional imaging studies have suggested (not surprisingly) that central neural mechanisms in the brain regarding pain are quite complex.

Descending inputs from supraspinal sites potentially have a marked inhibitory effect on spinal processing of nociceptive signals. The periaqueductal gray (PAG) area of the midbrain is an important center for inhibition of nociceptive signaling. Electrical stimulation of the PAG produces profound analgesia in experimental animals and humans. PAG stimulation-produced analgesia is reduced by the administration of naloxone, which indicates the involvement of endogenous opioid peptides in supraspinal and spinal mechanisms of nociceptive inhibition, but several other neural transmitters and pathways are also involved.¹¹ The PAG integrates descending neural inputs from the limbic system, cerebral cortex, and thalamus together with ascending spinal inputs (Fig 4).

Stress, cognition, and pain are factors known to activate the descending inhibition of nociception in experimental animals and humans. Stress-induced analgesia, which is produced by exposure to aversive environ-

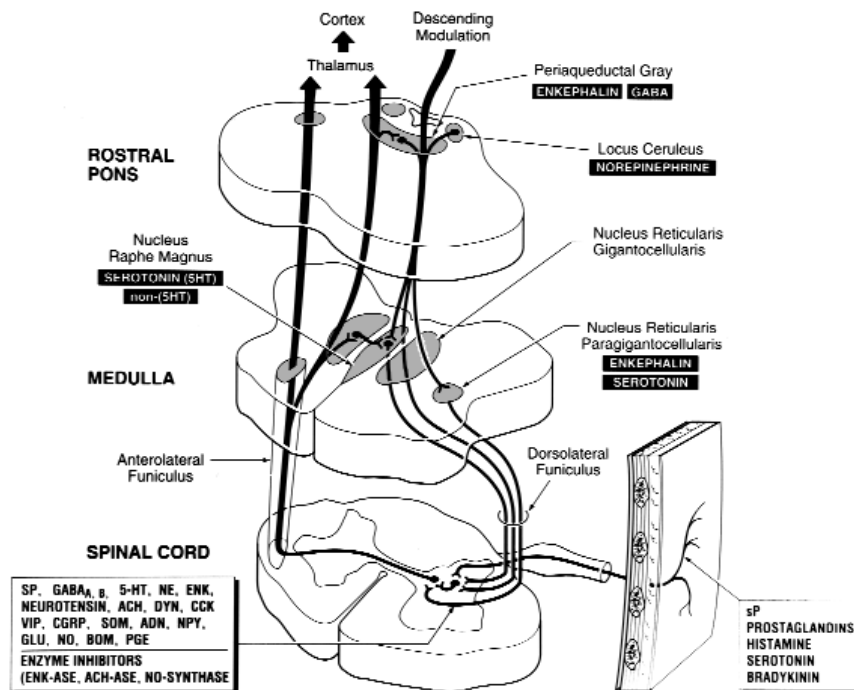


FIG 3. Simplified schema of afferent sensory pathways (**left**) and descending modulatory pathways (**right**). Stimulation of nociceptors in the skin surface leads to impulse generation in the primary afferent. Concomitant with this impulse generation, increased levels of various endogenous algogenic agents (eg, substance P, prostaglandins, histamine, serotonin, bradykinin) are detected near the area of stimulation in the periphery. Primary afferent nociceptors relay to projection neurons in the dorsal horn, which ascend in the anterolateral funiculus to terminate in the thalamus. En route, collaterals of the projection neurons activate multiple higher centers, including the nucleus reticularis gigantocellularis. Neurons for the nucleus reticularis gigantocellularis project to the thalamus and also activate the nucleus raphe magnus and periaqueductal gray (PAG) of the midbrain. Descending fibers from the PAG project to the nucleus raphe magnus and reticular formation adjacent to the nucleus raphe magnus. These neurons activate descending inhibitory neurons, which are located in these regions and travel by way of the dorsolateral funiculus to terminate in the dorsal horn of the spinal cord. Descending projections also arise from several brainstem sites that include the locus ceruleus. Several neurotransmitters are released by afferent fibers, descending terminations, or local interneurons in the dorsal horn and modulate peripheral nociceptive input. These include substance P (SP), gamma aminobutyric acid (GABA), serotonin (5-HT), norepinephrine (NE), enkephalin (ENK), neurotensin, acetylcholine (ACH), dynorphin (DYN), cholecystokinin (CCK), vasoactive intestinal peptide (VIP), calcitonin-gene-related peptide (CGRP), somatostatin (SOM), adenosine (AND), neuropeptide Y (NPY), glutamate (GLU), nitric oxide (NO), bombesin (BOM), and prostaglandins (PGE). Inhibitors of enzymes such as enkephalinase (ENK-ASE), acetylcholinesterase (ACH-ASE), and nitric oxide synthase (NO-SYNTASE) may act to modify the action of these neurotransmitters. (From Siddall PJ, Cousins MJ. Introduction to pain mechanisms: implications for neural blockade. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and management of pain. 3rd ed. Philadelphia: Lippincott-Raven; 1998. p. 675-99. Reproduced by permission.)

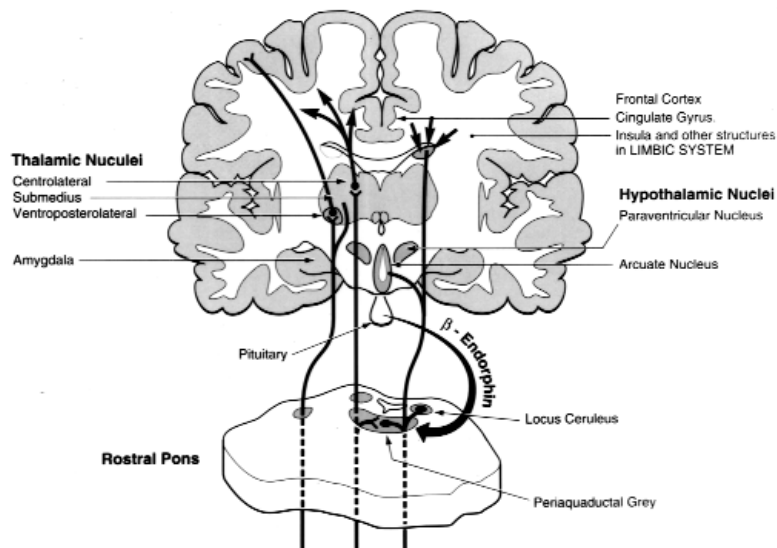


FIG 4. Rostral projections of nociceptive processing. Ascending projections (**left**) that travel in the anterolateral funiculus and projections from the medulla, pons, and midbrain terminate in the thalamic nuclear complex. The ventroposterolateral, centrolateral, and submedian nuclei receive nociceptive information. The ventroposterolateral projects to the somatosensory cortex. The centromedian nucleus projects more diffusely, including projections to regions of the limbic system. The descending fibers (**right**) inhibit the transmission of nociceptive information between primary afferents and projection neurons in the dorsal horn. The periaqueductal gray receives projections from several brain regions that include the amygdala, the frontal and insular cortex, and the hypothalamus. In addition to direct neural connections, endorphins that are synthesized in the pituitary are released into the cerebrospinal fluid and blood, where they can exert an inhibitory effect at multiple centers, which includes the periaqueductal gray. (From Siddall PJ, Cousins MJ. Introduction to pain mechanisms: implications for neural blockade. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and management of pain. 3rd ed. Philadelphia: Lippincott-Raven; 1998. p. 675-99. Reproduced by permission.)

mental stimuli or signals that predict such aversive events, is mediated in part by the hypothalamic-triggered release of endogenous opioid into the PAG, which activates descending inhibitory pathways.¹² At least in experimental settings, noxious-stimulation-induced analgesia has been demonstrated in humans.⁴ Such pain-mediated analgesia does not exhibit somatotopy; noxious input from one area results in descending inhibition that affects the whole body. Diffuse pain-induced analgesia, together with hyperalgesia at the site of tissue injury might serve to focus an animal's attention on a significant injury and minimize attention to more modest noxious stimuli.

Electrical stimulation of the PAG or the rostral ventromedial medulla results in inhibition of pain signaling, but the application of lower intensity

electrical stimulation to the rostral ventromedial medulla has also been shown to result in facilitation of spinal nociceptive transmission. Descending facilitation involves subpopulations of neurons within nociceptive bulbospinal pathways and is neuropharmacologically based on the action of distinct neurotransmitters. Descending facilitation is thought to be involved especially in the mediation of secondary hyperalgesia, the increased sensitivity that is present in tissues that are distant to the injury.¹²

The Pathophysiologic Features of Neuropathic Pain

In the immediate postoperative period, the pain most patients experience is due to tissue injury and inflammation, but surgical intervention generally involves nerve injury, which can result in severe chronic pain. Nerve injury results from the transection of small cutaneous nerves (eg, simple cutaneous incision), the intentional transection of a major nerve (eg, extremity amputation), or other intended/unintended tissue manipulation. Fortunately, the vast majority of surgical interventions heal without the development of chronic pain, but chronic neuropathic pain is a potential complication of most surgical procedures (ilioinguinal neuralgia after inguinal herniorrhaphy and intercostal neuralgia after thoracotomy are two examples¹³).

Neuropathic pain, caused by nerve injury (eg, trauma or surgery) or disease (eg, diabetic neuropathy or postherpetic neuralgia), may be confusing to patients and health care professionals whose understanding of pain is limited to acute nociceptive pain.^{13,14} Neuropathic pain is often described differently (“burning pain,” “episodic shooting pain”) than nociceptive pain, may be associated with increased sensitivity to normally non-noxious stimuli (allodynia), and may cause increased sensitivity to normally noxious stimuli (hyperalgesia) in the absence of acute tissue injury. Furthermore, these pain sensations may originate from or around areas of decreased sensitivity or numbness. Nerve-injury pain may persist long after wound healing is complete and may last indefinitely. Neuropathic pain may exhibit decreased responsiveness to opioid analgesics compared with tissue-injury pain.¹⁵

Despite increased recognition of neuropathic pain as a potential complication of trauma or surgery,^{13,16} it is still true that some patients who experience this complication are told that their well-healed incisions/wounds could not be causing pain, with the stated or implied suggestion that the pain “is not real” and that it originates from psychopathologic factors. Hopefully, wider appreciation of the pathophysiologic features of neuropathic pain will result in improved patient care now, and future research developments will translate into better therapies for the treatment and prevention of neuropathic pain.

Nerve injury results in several structural and functional changes that potentially contribute to the development of chronic pain. In the past decade, extensive research in animal models of partial and complete nerve injury^{14,17} has allowed significantly improved understanding of the pathophysiologic features of nerve injury and their effect on pain transmission. Animal studies have included both investigations into the cellular pathophysiologic features of nerve injury and the correlation of such changes with alteration in behavioral responses to noxious stimuli, allowing insight into clinical neuropathic pain. Based on animal and clinical research, neural injury can result in alteration of the peripheral,^{14,17} central,¹⁷ and sympathetic nervous systems,¹⁸ with each potentially contributing to the development of neuropathic pain.

Peripheral Mechanisms of Neuropathic Pain. Peripheral nerve injury, especially nerve transection, may result in Wallerian axonal degeneration, a process that involves macrophage activation with the release of inflammatory mediators that contribute to hyperalgesia. If the neuron survives such an injury, axonal regeneration will follow.¹³ If the Schwann-cell support structure of the nerve is destroyed, regenerating axons will be unable to reach the target tissue, which will result in neuroma formation. Neuromas, regenerating axons, and neurons that have been subjected to demyelinating injuries have been shown to have abnormal numbers and distribution of voltage-gated sodium channels, which enhance neuronal excitability (eg, facilitate transmission of pain signals) and also give rise to ectopic (spontaneous) neuronal depolarizations.^{14,17} Such ectopic, spontaneous depolarizations may be the pathophysiologic basis of the episodic, shooting pains often reported in neuropathic pain (eg, phantom-limb pain). The analgesic efficacy of pharmacologic agents active at voltage-gated sodium channels (eg, systemically administered local anesthetic and carbamazepine) may be dependent, in part, on diminishing the activity of abnormal sodium channels in damaged neurons.

Another peripheral mechanism in the pathogenesis of neuropathic pain is the formation of abnormal or ephaptic connections between neurons. Under physiologic conditions, peripheral neurons, including unmyelinated neurons, are functionally isolated from each other by adjacent Schwann cells. Injury can result in disruption of these Schwann-cell sheaths so that abnormal or ephaptic interactions can take place between neighboring axons. Ephaptic connections between peripheral neurons can produce "cross-talk" between axons, which results in the abnormal spread of discharge patterns and ectopic impulse generation. In addition, it appears that, with nerve injury, afferent neuron cell bodies in the dorsal root ganglia may become functionally "connected," which results in abnormal

cross-depolarizations that could result in the enhanced stimulation of spinal neurons.¹⁴

One of the unusual features of many cases of nerve-injury pain is the presence of mechano-allodynia in the absence of acute tissue injury or inflammation. These abnormal pain sensations, often seen in postherpetic neuralgia and postincisional neuralgias, are precipitated by very mild mechanical stimulation to the skin (eg, light touch or vibration) of the sort that typically activate low-threshold mechanoreceptor neurons rather than high-threshold nociceptors. In an animal model of nerve injury, the apparent sprouting of low-threshold nerve terminals from their normal termination sites in deep layers of the spinal dorsal horn, into superficial dorsal horn layers, has been documented.^{3,14} The development of such abnormal spinal projections of low-threshold mechanoreceptors could result in “cross-talk” between nonnociceptive mechanoreceptors and nociceptive pain pathways and is a potential neural mechanism of mechano-allodynia.¹⁷

The Sympathetic Nervous System in Neuropathic Pain. The sympathetic nervous system appears to be involved in some clinical neuropathic pain problems and animal models of nerve-injury pain.¹⁸ Under physiologic conditions, afferent nociceptors do not respond to sympathetic nervous system activity or the exogenous administration of adrenergic agonists; however, after neural injury, sympathetic activation can result in enhanced nociceptor activity. Axotomized primary sensory afferent neurons develop functional adrenoceptors and can be excited by sympathetic stimulation. Sprouting of sympathetic neurons, to envelop dorsal root ganglia neuronal cell bodies, has been demonstrated in experimental animals after nerve injury. Although the functional significance of sympathetic neuronal sprouts is uncertain, it has been postulated that such abnormal anatomic connections between the sympathetic nervous system and primary afferent neurons may be part of the pathophysiologic basis of sympathetically maintained neuropathic pain.⁸

Central Mechanisms of Neuropathic Pain. CNS changes from peripheral nerve injury appear to result from enhanced neural input into spinal dorsal horn neurons, based on changes in the peripheral and sympathetic nervous systems. Increased peripheral neuron input to the spinal cord appears to result in NMDA-receptor-mediated central facilitation of neural transmission, similar to that seen in acute injury and inflammation.^{3,17} Certainly, many features of experimental neuropathic pain can be prevented or diminished subsequently with the administration of NMDA-receptor antagonists, but there are other important changes in the CNS that result from peripheral nerve injury. Such injury may result in a protracted stimulation of spinal dorsal horn neurons and cause a prolonged increase in

intracellular calcium because of NMDA-receptor activation. Persistent elevation of intracellular calcium triggers metabolic cascades that further increase neuronal excitability, including the activation of calcium-dependent PKC and nitric-oxide synthase. Phosphorylation of the NMDA-receptor by activated PKC results in a conformational change in the calcium channel, which facilitates NMDA-receptor-mediated calcium entry into the cell. PKC-mediated phosphorylation also affects the activity of several other cellular proteins, including membrane-bound opioid receptors. Phosphorylation of opioid receptor proteins has been suggested as one mechanism of opioid tolerance.¹⁹ Nitric oxide synthase activation results in production of nitric oxide, an important intra- and intercellular messenger. Nitric oxide readily diffuses out of the cell and can interact with peripheral nociceptor terminals to facilitate the further release of excitatory neurotransmitters.¹²

In addition to the facilitation of pain signaling, nerve injury also may be associated with the loss of normal inhibitory regulation of pain signaling. With extreme nerve injury-induced activation of some spinal pain neurons, normal metabolic processes may become deranged to the point of causing excitotoxic cell death. Nitric oxide synthase activation and nitric oxide production have been shown to be important steps in excitotoxicity of CNS neurons after peripheral nerve injury in animal models.²⁰ Similar animal models of neural injury show evidence of decreased spinal production and release of inhibitory neurotransmitters. One mechanism behind this apparent reduction in spinal inhibition of pain signaling may be the excitotoxic loss of spinal inhibitory interneurons.^{17,20} Similarly, it has been proposed that the loss of thalamic-level inhibition of pain signaling may be an important mechanism of so-called “deafferentation pain,” which may arise after major nerve injury causes the loss of peripheral sensory input to the CNS.²¹

Individuals with severe neuropathic pain have all too often been labeled as having a “functional” problem, presumably because pain is subjective and routine physical examination in such settings may reveal only moderate or no significant abnormality. Given the remarkable developments in our understanding of pathophysiologic mechanisms of disease in general, clinicians are understandably skeptical of the cause of “functional” illness and may tend to downplay the significance or severity of such patient problems. Ephaptic connections between damaged peripheral nociceptors, ephaptic connections between the sympathetic nervous system and nociceptive pathways, receptor modification, and excitotoxic loss of inhibitory neurons appear to be structural changes in the peripheral, sympathetic, and CNS that are induced by peripheral nerve injury. These structural

changes give a solid “organic” basis to many cases of clinical neuropathic pain.

In view of the expanding knowledge of the extensive changes in the peripheral, sympathetic, and central nervous systems brought on by nerve injury, it is little wonder that there has been so much research in recent years that has been focused on potential techniques for the treatment and/or prevention of neuropathic pain. One decade ago, there was optimism that the appreciation of the central role of NMDA-receptor activation in pain facilitation would lead directly to improved analgesic therapies, but clinical trials of NMDA antagonists have produced mixed results,^{22,23} and there is still concern about toxicity.^{8,24} Nonetheless, an improved knowledge of the pathophysiologic features of neuropathic pain is leading to a more rational use of available analgesic therapies¹⁵ and is helping to formulate the search for new analgesic strategies.²⁵

Pathophysiologic Features of Opioid Tolerance

Clinical experience reveals that tissue injury and/or nerve injury result in increased sensitivity to pain, but the same is true for opioid tolerance. It is a common clinical experience (although perhaps less commonly recognized as a specific, predictable clinical phenomenon) that a patient with chronic opioid use may have poor pain control after acute injury or operation. One might expect that the chronic dose of opioid would also control the new, acute pain, but the opposite is usually the case; the chronic opioid dose is often insufficient, and the new acute pain is often unusually difficult to treat. From the clinician’s perspective, it may appear that the opioid-tolerant patient “tolerates pain poorly.”

Over the last 10 years, it has become apparent that there are many similarities between the hyperalgesic state produced by nerve injury and that of opioid tolerance. Extensive animal research, with the use of models of opioid tolerance and partial nerve injury, indicate that NMDA-receptor-mediated facilitation and the loss of inhibitory regulation appear to result in enhanced pain signal transmission in both nerve injury and opioid tolerance. In other words, it appears that, although the pathophysiologic changes associated with nerve injury pain result in analgesic resistance to opioids, opioid tolerance induces alterations in CNS function and structure similar to those seen in neuropathic pain.¹⁹

Persistent stimulation of spinal-neuron NMDA receptors results in a marked increase in intracellular calcium and leads to activation of PKC. Persistent opioid activation of opioid receptors may also activate PKC. Once activated, by either injury or opioid mechanisms, PKC induces alteration in NMDA-receptor calcium channels (to facilitate further calcium

entry into the neuron) and opioid-receptor proteins (perhaps through uncoupling of receptor proteins^{19,26,27}). These PKC-mediated alterations in NMDA calcium channels and opioid receptors both serve to facilitate pain signaling and decrease efficacy of opioid analgesics. Persistent elevation of the intracellular calcium level leads to the activation of nitric oxide synthase and production of nitric oxide, which appear to be essential factors in the development of excitotoxic loss of spinal dorsal horn (possibly inhibitory) interneurons.¹⁹ In experiment animals, either nerve injury or opioid tolerance appears to be sufficient for PKC and nitric oxide synthase activation and initiation of mechanisms of CNS sensitization (Fig 5).

Tolerance develops very quickly in experimental animals,²⁸ but in the clinical treatment of either acute or chronic pain, the significance of opioid tolerance is less clear.²⁷ There is clinical evidence that suggests that opioid tolerance can develop rapidly during an opioid-based anesthetic, which results in postoperative hyperalgesia and increased opioid use.²⁹ However, other information indicates that opioid efficacy does not deteriorate through the perioperative period.³⁰ It has been suggested that the co-administration of NMDA receptor antagonists with opioid analgesics might provide improved pain relief and decrease the development of tolerance. Although there have been considerable research efforts in both acute and chronic pain settings,^{22,23,27} the role of NMDA receptor antagonist drugs as adjuvants to opioid therapy remains unclear.

The idea that opioid administration could lead to the facilitation of pain signaling and even excitotoxic loss of inhibitory spinal neurons is clearly of clinical concern.^{19,27} In particular, there is the concern that opioid administration for the treatment of neuropathic pain might enhance the pathophysiologic mechanisms that result in neuropathic pain. It is important to note that the evidence for opioid-tolerance induction of CNS sensitization comes from animal models of opioid tolerance. There may be considerable differences between administering fixed, high doses of opioid to animals without "pain" and the careful titration of opioid analgesics to the endpoint of pain relief to individuals with pain. Furthermore, the neurophysiologic response to chronic opioid administration may differ in different clinical pain syndromes (eg, acute, chronic, inflammatory, neuropathic). Opioid tolerance previously was thought to be based on the downregulation of opioid receptors; although downregulation may play a role in opioid tolerance, opioid tolerance now also appears to be related to the facilitation of pain signaling. Although our understanding of the mechanism has changed, opioid tolerance is the same clinical problem that clinicians have treated for centuries; a better understanding of the pathophysiologic mechanisms of opioid tolerance does not change the established

therapeutic safety of opioid analgesics. An improved understanding of the pathophysiologic mechanisms of neuropathic pain and opioid tolerance does present opportunities for the development of improved analgesic therapies through further research.

The Emotional, Cognitive Components of Pain

Injury, pain, and suffering are related but very different processes. Injury and nociception involve noxious stimuli and the induced neurophysiologic response to those stimuli. Pain indicates an awareness of noxious sensation in the mind's representation of self.³¹ Suffering may be induced by injury but can certainly exist without injury; furthermore, not all injuries necessarily lead to suffering. Suffering arises from perceived existent or impending damage to oneself or some essential component of oneself.³² It is evident that numerous cognitive, emotional, and psychologic factors will largely determine the interaction among injury, pain, suffering, and clinically observed pain behaviors (Fig 6).

Because awareness and interpretation of pain are subjective experiences and activity in nociceptive pathways cannot be directly measured except in complex research programs, it is through the interpretation of patients' pain behaviors that health care professionals become aware of clinical pain and, less directly, nociception. Pain behaviors include a wide range of responses: moaning, crying out, asking for pain medication, seeking medical attention, avoiding normal activities, and exhibiting other illness behaviors. Those behaviors can be rewarded (encouraged or discouraged) by the responses from family members, health care professionals, and environmental factors (operant conditioning).³³ Clinical pain behaviors generally reflect suffering more closely than nociception. Clinically observed pain behaviors therefore are heavily influenced by emotional, cognitive, and other psychologic factors that are involved in suffering.

Several clinical studies have demonstrated the lack of consistency between the apparent extent of acute injury or trauma and the reported pain. The initial absence of pain after serious injury has been documented in a significant proportion of soldiers who are wounded in battle³⁴ and in civilians who seek emergency room care.³⁵ The effect of attention on pain awareness has also been studied in experimental animals.³¹ In other settings, fear, anxiety, lack of control, and social and/or ethnic backgrounds have been shown to have a marked influence on reported pain intensity.^{13,36} In general, it appears that the state of the individual has as much or more to do with the resulting pain (behavior) than the precipitating injury or noxious stimulus.³¹

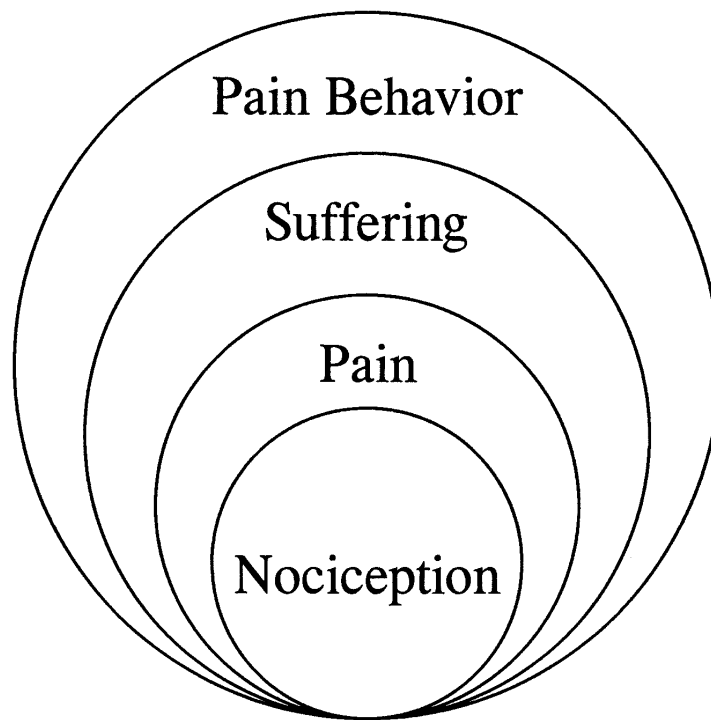


FIG 6. A conceptual model of the components of human pain. (From Loeser JD. Concepts of pain. In: Stanton-Hicks M, Boas R, editors. Chronic low back pain. New York: Raven; 1982. p.145-8. Reproduced by permission.)

The concept of “total pain,” derived in the context of hospice care for patients with terminal illness,³⁷ suggests that emotional, social, and spiritual factors contribute to a patient’s pain experience, in addition to physical factors. When a patient complains of pain, the responding health care professional should recognize the complaint as a pain behavior that reflects “total pain” or suffering and should determine which components of pain may be amenable to therapy. Similar pain components contribute to pain in all clinical settings, including the perioperative period.¹³ Perioperative treatment plans that include strategies to address the “total pain” or “total suffering” of patients may be more successful than those designed simply to optimize the administration of analgesics. Even within the realm of analgesic use, clinical research indicates that lower pain intensity ratings and the decreased use of opioids can be achieved with strategies that allay patient-related anxieties and empower patients to become active participants in their pain control and postoperative care.³⁸

Although human response to placebos is complex,³⁹ placebo analgesia appears to be a common factor that potentially confounds the interpretation of patient response to medical or surgical interventions.⁴⁰ In postoperative pain,⁴¹ placebo-mediated analgesia is often naloxone reversible, which strongly suggests that it is mediated by the release of endogenous opioids from the CNS.⁴² Placebo analgesia is enhanced by a patient's previous treatment with an effective analgesic therapy⁴³; in other words, patient expectations or cognitions result in real, physiologic activation of central mechanisms of pain modulation and influence spinal transmission of noxious stimuli. Placebo administration, which may trigger the release of endogenous opioid and produces profound analgesia, is not an inactive treatment. An analgesic response to placebo administration is not an indication that "the pain is not real." A patient's response to the intentional administration of ineffective treatment (placebo) can never be used to "diagnose" psychopathologic condition (in the patient).

"The pain is all in your head" is a "diagnosis" feared by many people with pain who are concerned that physicians and others will conclude that their experience of pain is somehow "imagined" and therefore not "real." In an anatomic sense, the pain is always in our heads, even though attempts at assigning aspects of pain perception to specific areas of the brain have been of only limited success. In general, spinal thalamic projections to the lateral thalamus seem to be involved with sensory-discriminative aspects of pain, whereas medial thalamic projections involve motivational-affective aspects.⁴⁴ The cingulate cortex, on the medial surface of each cerebral hemisphere, appears to be involved with affective components of pain. Indeed, surgical cingulotomy is a rarely performed neurodestructive procedure that potentially alleviates the suffering from intractable pain, although the detection of noxious stimuli remains intact. Recent studies that involved functional imaging of the brain seem to confirm the involvement of the cingulate cortex in the evaluation of the unpleasantness of noxious stimuli and areas of somatosensory cortex in sensory-discriminatory evaluation of noxious stimuli.⁴⁵ Despite the insights gained from these studies, there is much complexity and individual variation in the brain processing of pain signals that has precluded direct translation of this knowledge into useful clinical therapies for pain. At the very least, it is clear that emotional, effective components of the pain experience are an anatomic fact and should be expected in all clinical pain.

Pain That Is Out of Proportion to What Is Expected

The complaint of severe pain must be evaluated first as a sign of a significant underlying pathologic condition, but occasionally one encounters

a patient who is described as having pain that is “out of proportion to what is expected.” This description is meant to imply that the patient is exaggerating the report of pain, perhaps intentionally. The describing health care professional is stating that, based on experience and expectation, the patient’s report of the patient’s own experience of pain is incorrect. Patient self-reporting of pain has been compared with pain-intensity rating that is based on the health care professional’s observations in a variety of clinical settings,^{46,47} and significant discrepancies have been commonly identified. Clinicians should be hesitant to disregard the patient’s self-reporting of pain because a more reliable reporter of the patient’s experience will not be found. In those rare instances when a clinician’s considered impression is that a patient’s report of pain is unreliable, psychologic or psychiatric evaluation may be helpful in gaining insight into the factors that are contributing to the patient’s suspected unreliability.

Despite the advancements in understanding of the neurobiologic features of pain in the last 20 years, the common conceptual model of pain in health care continues to be that of “transient pain” or simple nociception (which is not associated with significant tissue injury, inflammation, or other mechanisms of pain facilitation).⁴⁸ It is clear that significant clinical pain almost always involves the facilitation of nociceptive signaling. When clinicians feel a given patient’s pain is “out of proportion,” a significant factor is often the clinician’s failure to recognize the clinical setting as one in which pain facilitation should have been anticipated. The translation of basic science research data into improved analgesic strategies for clinical practice has been slow, but clinicians should now be able to recognize the pathophysiologic components of complex pain problems and to initiate available therapies for the nociceptive, neuropathic, emotional, cognitive, and/or behavioral components of clinical pain. Rather than faulting patients for reporting pain when pain behaviors do not meet clinicians’ (perhaps flawed) expectations, clinicians should strive to anticipate when routine analgesic therapies are likely to prove insufficient and develop treatment strategies (care paths) to avoid or treat such pain problems.

Measurement of Pain

Measurement of pain is becoming increasingly important because it is recognized that pain is underestimated by health care providers and widely under treated.¹⁶ The current standards of the Joint Commission on Accreditation of Healthcare Organizations require that pain be assessed in each patient.⁴⁹ Therefore, a measure of pain intensity is becoming the “5th vital sign.” As more emphasis is placed on the assessment and treatment

of pain, reliable measurement tools will be needed to assess the effectiveness of pain therapies.

To measure anything, it is necessary first to define it. There are numerous definitions of pain, but the one most commonly used is that proposed by the International Association for the Study of Pain: "Pain is an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage."¹ This definition implies that pain is not a simple entity but rather a multidimensional experience. Measuring and quantifying pain can be difficult because the experience and report of pain are influenced by several factors such as cultural conditioning, expectancies, social contingencies, and behavior.

Early research on pain assumed that pain is purely a sensory experience. It is increasingly recognized, however, that pain has a distinctly unpleasant affective quality. To describe pain solely in terms of intensity is like specifying the visual world only in terms of light flux, without regard to pattern, color, texture, and the many other dimensions of visual experience.⁵⁰ The measurement of pain has been studied extensively over the last 30 years, and it is clear that no single tool is suited for every clinical setting. The tools that are appropriate for the measurement of pain differ depending on the patient population to be studied. Researchers have tried for decades to find methods to measure pain "objectively" in a standardized way as we do for most laboratory-type testing. To date, these attempts have not been successful; therefore the only useful tools for the clinical assessment of pain are instruments based on the patient's self-report. The following section of this monograph is limited to tools that are commonly used for the measurement of pain among competent adults in the perioperative setting.

Tools for Pain Measurement

Pain Rating Scales. There is a great variety of pain rating scales. The most commonly used are the numeric rating scale, visual analog scale, and verbal rating scale.

With a numeric rating scale, the patient is presented with a numerically graded scale, which is typically a 10-cm line, with centimeter marks labeled 0 to 10, and with the "0" being "no pain" and "10" being "the worst pain imaginable." The patient is asked to mark a number that corresponds to the intensity of pain experienced.

With a visual analog scale, the patient is presented with an ungraded scale, which is typically a 10-cm line with one end labeled "no pain" and the other end labeled "the worst pain imaginable." The patient is asked to mark the point along the line that corresponds to the intensity of pain experienced.

With a verbal rating scale, the patient is asked to verbally report pain intensity based on a scale, typically ranging from “0” meaning “no pain” to “10” meaning “the worst pain imaginable.”

These scales have some important advantages: they are easy for patients to understand and use⁵¹; they have been shown to be reliable, valid, and sensitive to treatment effect; they have ratio scale properties, and therefore they are amenable to sophisticated statistical analysis; they have been used for many years so that clinical personnel are familiar with them; and they require minimal time commitment and impose little burden on respondents. These are very important attributes if these tools are to be widely accepted and incorporated into routine clinical practices.

The main disadvantage of simple pain rating scales is that they are unidimensional: pain is measured as if it had only one dimension that varies only in intensity. Therefore, they are not appropriate instruments for the assessment of the entire pain experience. Data indicate that all these scales yield similar results⁵¹; therefore, the choice of which scale to use is not as important as the consistent use of one scale.

McGill Pain Questionnaire. The McGill Pain Questionnaire (MPQ)⁵⁰ is designed to assess 3 psychologic dimensions of the pain experience: sensory-discriminative, motivational-affective, and cognitive-evaluative. In addition to a simple pain rating scale, the MPQ includes the pain rating index. The pain rating index consists of several words that might be used to describe pain. These words were chosen to represent the sensory, affective, and evaluative components of pain. The MPQ is scaled on the basis of which words and how many words a patient has identified as descriptive of the pain being experienced. The MPQ has been used widely to evaluate the effectiveness of pain control interventions, because it provides quantitative measurement of multiple pain dimensions. The MPQ is currently the most extensively studied pain assessment questionnaire and its use offers several advantages: it has been validated in many languages; it has been evaluated extensively in many clinical situations; it takes 5 to 10 minutes to administer (with experienced patients), and it is multidimensional and sensitive to the treatment effect.

Short-Form McGill Pain Questionnaire. The short-form MPQ (MPQ-SF)⁵⁰ was created as a shortened version of the original MPQ because the investigators thought that the original was too long to be used for rapid data acquisition. Measurements with the MPQ-SF correlate well with the pain rating index of the MPQ and have been shown to be sensitive to change and to be appropriate for elderly patients.

The Brief Pain Inventory. The Brief Pain Inventory⁵² was developed to be a brief, self-administered, easily understood measurement tool to assess

various aspects of pain. Patients rate their pain at its “worst,” “usual,” and “now.” The Brief Pain Inventory assesses pain intensity, location, and interference that results from pain but does not assess the emotional significance of pain or pain behaviors. The Brief Pain Inventory has satisfactory validity and reliability, has been used extensively in clinical research, and has been translated into many languages.

Selection of an Instrument for Routine Measurement of Pain

The measurement of pain is a complex but extremely important undertaking, for both humanitarian and regulatory reasons.⁴⁹ A wide variety of pain measurement instruments have been assessed in the literature. The presence of numerous tools indicates that this is an area of ongoing research and that there is no single “gold standard” for pain measurement. Simplicity and familiarity are of paramount importance for an instrument to achieve widespread acceptance; therefore, the pain rating scales (ie, numeric, visual, or verbal) are probably the best instruments available for routine assessment. The data are inconclusive about which particular scale is the best for most patient populations, and it may be that these simple scales are more or less equivalent to each other.⁵¹ For complex pain problems that require the measurement of multiple dimensions of pain, it may be preferable to use a more sophisticated tool, such as the MPQ or the MPQ-SF. Although there are many pain measurement tools from which to choose, the more important concern is making the decision to measure pain consistently by some (any!) method as a routine component of postoperative care.

The Problem of Perioperative Pain: Epidemiologic and Contributing Factors

Pain in the postoperative setting, as in most other settings, is a complex phenomenon that includes sensory, emotional, and behavioral factors. The incidence and severity of postoperative pain is dependent on several factors, including (but not limited to) the surgical procedure, and is quite variable between patients. Despite recent advances in the understanding of postoperative pain and the widespread recognition of the problem, clinical surveys indicate that the routine treatment of postoperative pain remains unsatisfactory.⁵³ As with other clinical phenomena, understanding the pattern of development or variation of a condition across time provides a basis for learning about the nature and determinants of the condition. The study of these variations in the postoperative setting provides the opportunity to understand potential risk factors and to develop rational strategies

for prevention. Ideally, epidemiologic studies of postoperative pain should include sufficient preoperative data (including biologic, psychologic, and social factors), operative data, and a characterization of the pain state⁵⁴ over time. Unfortunately, this is rarely achieved.

Patient Characteristics

Demographics. Few clinical studies have been designed to evaluate adequately the risk factors that are associated with pain and adverse outcomes after operation. One such study, from a large consortium of investigators who were studying total hip replacement, evaluated the influence of 8 patient risk factors on postoperative pain and physical function. The risk factors that were evaluated were the age, sex, race, marital status, and education of the patient; whether the patient had polyarticular disease or other comorbid conditions; and the patient's preoperative pain and physical function score. Of the patient risk factors studied, race, education, number of comorbid conditions, and preoperative Health Status Questionnaire score were found to be associated with poor outcome with respect to both pain and physical function at 6 months after operation. This suggests that, aside from obvious comorbidity, demographic and social variables may also be important risk factors for pain and adverse outcomes.⁵⁵

Sex. Sex-related differences in pain, although clearly shown in experimental settings, have not been demonstrated well in clinical studies. In one study of patients who were undergoing oral surgery, Morin and colleagues⁵⁶ asked men and women to complete a pain diary several times each day. Diary data included pain intensity and unpleasantness ratings on visual analog scales and selected verbal descriptors from the MPQ. These investigators found no significant differences between sexes for mean daily ratings of intensity, unpleasantness over time, nor in the total number of words chosen from the MPQ. However, most women experienced a significantly higher intensity of pain during the day, whereas most men had higher pain in the evening. Women used significantly more evaluative words than did men, but it is unclear whether this represents a gender-based difference in the description of a painful experience or a difference in the actual experience. Similarly, Taenzer and colleagues⁵⁷ showed that, after arthroscopic anterior cruciate ligament reconstruction operation, women reported significantly higher pain scores at rest and with activity on the first postoperative day compared with men. Women were also significantly less able to perform the straight leg-raising maneuver on the first and second postoperative days. Notably, there was no difference in the amount of opioid consumed at any time during the study period.

Therefore, although women seem to experience greater intensity of pain after this arthroscopic procedure as expressed through verbal rating scores and measures of function, these differences did not result in a higher use of analgesics. It is unclear whether these variations result from differences in either response to analgesics or neural processing, but this is an area of ongoing research. Although there is some suggestion in animal studies of a potential for genetic predisposition to persistent postprocedural pain,⁵⁸ this has not been evaluated systematically in humans.

Race/Ethnicity. There are many studies that document racial disparities in health care. Cultural background or ethnicity has been investigated as a predictive variable for descriptions of pain, reactions to pain, coping strategies, and expected levels of pain or disability related to pain. Few studies have investigated cultural differences of pain parameters in the perioperative setting. Ng and colleagues,⁵⁹ in a retrospective record review, studied whether ethnicity influenced patient-controlled analgesia (PCA) use for the treatment of postoperative pain. These investigators reported no difference in the amount of self-administered opioid but found significant differences in the amount of opioid prescribed to different ethnic groups. Similar conclusions have been drawn from other studies of ethnicity as a risk factor for inadequate analgesia in other clinical settings.⁶⁰ The cross-cultural literature reveals wide variations in pain-related perceptions, beliefs, and reactions and confirms that pain phenomena have both universal and ethnic-specific aspects.

Behavioral Risk Factors. Behavioral risk factors such as smoking, exercise, and dietary habits have not yet been evaluated critically in terms of their influence on incidence of postoperative pain. However, aside from the pulmonary implications of smoking, there is some speculation in the literature about the potential enzymatic modulatory effects that tobacco and other substances may have (ie, cytochrome enzyme induction). These effects may alter indices of recovery (such as postoperative nausea and vomiting, emergence from anesthetics, and the experience of pain).⁶¹ Physical activity has great potential to influence normal and pathologic structures, functions, and processes favorably. Although patients with severely impaired exercise tolerance are considered at high risk for postoperative morbidity and death, the potential for preoperative physical conditioning to influence postoperative pain symptoms and rehabilitation has not yet been critically evaluated.

Patient Satisfaction. The factors that account for patient satisfaction with postoperative pain treatment are more elusive. Consistently, there has been an inverse, but small, association between pain severity and patient satisfaction. Despite this association, most patients who are in severe pain

still report that they are satisfied with their pain treatment.⁶² Although several studies have compared different techniques for postoperative pain treatment with regard to efficacy (as measured by simple pain scale) and adverse effects, there is less known about patient satisfaction and its sources. Eagan and Ready⁶³ showed that the technique of analgesic delivery (intravenous PCA vs epidural analgesia) did not affect overall patient satisfaction significantly. However, among the different groups, there were clear differences among features that patients found attractive or advantageous for each technique. For example, patients who received intravenous PCA analgesia identified “personal control” and “method worked quickly” as advantages, whereas patients who received epidural analgesia identified “clear mind,” “effective relief resting,” and “effective relief while moving or coughing.” The single disadvantage identified more frequently by patients with PCA was “pain immediately after operation before method became effective”; disadvantages identified more frequently by patients who received epidural analgesia were “side effects” and “poor pain relief.”

Another study that was designed to assess whether perceived control mediates the relationship between pain severity and patient satisfaction found that there was a significant association between perceived control over pain and patient satisfaction; perceived control partially mediated the relationship between pain severity and satisfaction.⁶⁴ Therefore, although individuals who reported severe pain were less satisfied than individuals with less pain, it was the perception of having control over the pain that most related to satisfaction with pain relief. This finding not only further elucidates the importance of context and meaning that are associated with the pain experience but also underscores the risk of the interpretation of patient satisfaction as a surrogate measure for favorable outcome, particularly in the setting of postoperative analgesic studies.

Patient Expectations. Psychologic factors, trait anxiety, coping behaviors, and health locus of control all seem to affect postoperative recovery and postoperative pain.⁶⁵ Moreover, these factors tend to exert their effects largely independent of the extent of surgical trauma. Although it has been demonstrated that previous pain experiences seem to modify expectations of postoperative pain,⁶⁵ it is not clear whether previous experience influences actual postoperative pain experience. It is apparent, regardless of previous pain experience, that many patients and physicians still view poorly controlled postoperative pain as an expected feature of the perioperative experience,^{53,66} and most patients are prepared to experience pain in the postoperative period.⁶⁷ If preoperative expectations affect postoperative pain, efforts to modify expectations may result in more favorable

outcomes. The potential effect of such an intervention could be large, based on the high prevalence of morbid preoperative expectations for postoperative pain, and the low frequency with which patients are currently counseled about postoperative pain.⁵³ Certainly, other forms of counseling about postoperative pain before the operation have been shown to be effective.³⁸

Provider and Setting Characteristics

In addition to patient characteristics, the characteristics of the setting and processes of care are important to the patient's experience of postoperative pain and thus to understanding factors likely to influence the incidence and severity of pain and the outcomes of care. Anesthesiology-based postoperative pain treatment services have been developing over the past decade, and descriptive studies have suggested that this has resulted in improvements in postoperative pain control.⁶⁸ The penetration of this organized structure of care, however, is relatively low. In 1995, only 42% of hospitals that were surveyed in the United States had established acute pain treatment programs, and an additional 13% of hospitals had plans to establish such programs.⁵³

Coincidental to the establishment of anesthesiology-based postoperative pain treatment services has been the transition of surgical care to the outpatient setting. Ironically, superior surgical, anesthetic, and analgesic techniques have facilitated rapid recovery, mobilization, and discharge from the hospital, which leaves a largely unmet challenge for assuring adequate analgesia in the outpatient setting. In an outpatient surgery study, 40% of patients reported moderate to severe pain during the first 24 hours after hospital discharge.⁶⁹ Pain was severe enough to interfere with daily activities in many patients, and 25% of patients had to contact a health care provider because of pain at home.

There is some evidence that the type of surgical operation and differences in technique can influence the incidence of postoperative pain. For example, the type of operation may affect the incidence of pain after breast surgery.⁷⁰ Furthermore, the experience level of the surgeon (ie, senior attending vs fourth-year surgical resident) who performs the procedure may also influence the extent of postoperative pain.⁵⁶

Communication

There must be successful communication between patient and health care provider regarding pain intensity and response to intervention if pain is to be controlled adequately. Recent reviews of the literature suggest that patients may be unclear of their role in pain treatment. For example,

TABLE 1. Barriers to postoperative pain treatment

Patient factors
Fear of drug addiction
Fear of being bothersome to providers
Fear of adverse effects
Expectations for pain after operation
Provider factors
Time constraints
Limited knowledge about pain treatment
Expectations that inadequate pain relief will be obvious
Concern about drug addiction
Limited acceptance of innovative treatment approaches
Health care system factors
Limited access to providers because of outpatient shift
Lack of organized pain treatment services

McDonald and colleagues⁷¹ found that patients avoid or delay communicating their pain symptoms at some point during their hospitalization as a result of “not wanting to complain,” “not wanting to take the provider away from other patients,” “avoiding unpleasant analgesic side effects,” and “not wanting to take ‘drugs.’” There are also many factors that may influence the health care provider’s assessment of pain and therefore influence the treatments used in the treatment of pain.⁷² Aside from these common social barriers to communication, patients who have difficulty communicating their pain pose an exceptional challenge to providers. This group includes those patients at the extremes of age, those patients with cognitive or sensory impairments, or those patients with functional deficits or other limitations. Common barriers to pain assessment and treatment are listed in Table 1.

Unfortunately, the epidemiologic features of persistent pain after operation are difficult to assess because so few well-designed studies have focused on this issue. Previous attempts at the review of mixed studies to determine the incidence of chronic postoperative pain have concluded that the frequency of persistent postsurgical pain is likely to be grossly underestimated.⁷³ Persistent pain is said to occur more frequently after certain operations (such as thoracotomy, nephrectomy, cholecystectomy, herniorrhaphy, vein stripping, and limb amputation). However, prospective randomized studies are needed for all types of operations to ascertain the best approach to postoperative analgesia and determine how different approaches can influence the incidence of chronic postsurgical pain. Such evidence could then be used to establish treatment strategies to minimize both acute postoperative pain and chronic postsurgical pain.

Techniques of Perioperative Pain Treatment

Systemic Analgesics

The optimal use of systemic analgesics is an important component of perioperative patient care. Opioid analgesics are the most widely used pharmacologic agents for the treatment of acute and/or postoperative pain. In general, these drugs are readily available, highly effective, and well tolerated, which results in routine clinical use. Despite considerable advantages that favor the use of opioid analgesics, their use is often associated with side effects that may include sedation, respiratory depression, nausea, vomiting, decreased gastrointestinal motility, biliary spasm, pruritus, urinary retention, and the development of tolerance. Nonopioid analgesics (ie, nonsteroidal anti-inflammatory drugs and acetaminophen) and rarely other miscellaneous analgesics (systemically administered local anesthetics, antiseizure medication, and antidepressant medication) are used alone, in combination, or with opioid analgesics to improve pain control or to avoid or minimize opioid-related adverse effects.

Nonopioid Analgesics. Nonopioid analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are widely used in perioperative pain treatment and have been widely studied in this context. Although the efficacy of these drugs in the control of mild to moderately severe pain is well known, their use is limited by a “ceiling effect” such that, beyond typical clinical doses, further dose increases do not provide further pain relief. Therefore, in the treatment of moderate-to-severe perioperative pain, nonopioid analgesics are indicated primarily to enhance the quality of opioid-based pain therapies or to reduce the requirement for opioid analgesic and thereby to avoid or reduce opioid-related adverse effects.⁷⁴

Nonsteroidal Anti-inflammatory Drugs.—NSAID Mechanism of Action. Although opioids and NSAIDs are both clinically used to relieve pain, the types of pain in which these 2 classes of drugs are effective are somewhat different.⁷⁵ NSAIDs are most effective in relieving pain in settings in which there has been significant facilitation of nociceptive signaling, often through tissue injury and peripheral inflammation. In such settings, NSAIDs serve to reduce the observed hyperalgesia (increased responsiveness to noxious stimuli) back towards the baseline responsiveness observed before the tissue injury or inflammation. To emphasize the limitation of pain-relieving efficacy to settings that involve hyperalgesia from tissue injury or inflammation, NSAIDs may be described as “antihyperalgesics.” By comparison, opioid analgesics not

only provide pain relief in settings of hyperalgesia but will also raise the threshold of detection of noxious stimuli above baseline.⁷⁵

The utility of NSAIDs as antihyperalgesics is in keeping with their known mechanism of action. Almost 100 years after salicylic acid was synthesized initially and after decades of clinical use of salicylates and other NSAIDs, Vane⁷⁶ and others identified the mechanism of action of NSAIDs as blocking the synthesis of prostaglandin by prostaglandin synthase. Prostaglandin synthase, now generally referred to cyclo-oxygenase (COX), is known to be the first enzyme in the formation of prostaglandins and thromboxanes from arachidonic acid. There are 2 isoforms of COX, known as cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2). COX-1 is present constitutively in virtually all tissues and produces prostaglandins that serve local regulatory function. COX-2 is known to be produced constitutively in the CNS and kidney,^{77,78} but its synthesis is induced in many tissues in the presence of inflammation. The inducible COX-2 enzyme is the isoform responsible for the prostaglandin and thromboxane production that is central to inflammatory cascades. Therefore, the important anti-inflammatory and pain-relieving effects of NSAIDs appear to stem predominantly from the inhibition of COX-2, whereas many of the adverse effects that are associated with NSAIDs are linked to COX-1 inhibition (eg, gastrointestinal ulceration, inhibition of platelet function). The development of NSAIDs that selectively inhibit COX-2 has been of significant clinical use in settings in which concern for COX-1 inhibition-related side effects have precluded NSAID use.^{77,78}

Although the peripheral anti-inflammatory effects contribute to pain relief after NSAID administration in some postoperative settings,⁷⁹ other mechanisms also appear to play significant roles. The disassociation of peripheral anti-inflammatory effects from antinociceptive effects of COX inhibition is perhaps most clearly shown in a comparison of aspirin with acetaminophen: although both are effective analgesics, only aspirin has a clinically significant anti-inflammatory effect.⁷⁵ Acetaminophen appears to produce its analgesic effect through COX inhibition but seems to have a greater impact on the production of prostaglandins in the CNS than in peripheral tissues. The inhibition of COX in the CNS may be an important analgesic mechanism of action for NSAIDs and acetaminophen. Systemically administered acetaminophen and NSAIDs (to a variable extent) do penetrate into the cerebrospinal fluid. There is animal evidence that COX-2 is expressed constitutively in the CNS, with increased levels induced by peripheral injury or inflammation.⁷⁵ In experiment animals, spinal injections of NSAIDs and acetaminophen have been shown to have analgesic efficacy at doses far below those needed for systemic effect.

Spinal or systemic administration of ibuprofen to rats that were previously instrumented with spinal microdialysis catheters was shown to inhibit spinal production of prostaglandin in response to experimental peripheral inflammation.⁸⁰ Taken together, these observations strongly suggest that at least a component of the antihyperalgesic effects of NSAIDs is based on a CNS effect.

A new class of NSAID-related drugs, nitric oxide-releasing NSAIDs, has been developed and is undergoing evaluation. These nitric oxide-releasing NSAIDs, in which a nitric oxide-related moiety has been added, appear to have reduced gastrointestinal toxicity significantly⁸¹ and enhanced anti-inflammatory effects. Already nitric oxide-releasing NSAIDs have proved to be useful research tools with which to probe for new knowledge concerning inflammation and its regulation, but they may also prove to be clinically useful analgesics with improved efficacy and reduced adverse effects.⁸²

Efficacy of NSAIDs in Perioperative Pain.— The efficacy of NSAIDs in the treatment of acute and perioperative pain is well known. Systematic reviews of the published data on the use of NSAIDs in the control of postoperative/acute pain clearly indicate that the systemic administration of aspirin, ibuprofen/diclofenac, or piroxicam⁸³ is effective analgesic therapy for mild-to-moderate postoperative pain. In the treatment of more severe pain, NSAIDs still have a significant role in the improvement of the quality of pain relief and reduction of the requirement for opioid analgesics. On the other hand, the routine perioperative use of NSAIDs is not appropriate because of concern for adverse effects but also because of the potential for a lack of benefit if an NSAID is added to an otherwise highly effective analgesic regimen. The opioid-sparing effect of NSAIDs in postoperative pain treatment can be important if used as part of a coordinated, accelerated recovery program in perioperative care.^{74,84}

Adverse Effects of Perioperative NSAIDs.— Given that COX-1 is expressed constitutively in virtually all tissues and COX-2 is inducible in a wide range of tissues by injury or inflammation,⁷⁷ it is little wonder that there are complex clinical decisions to be made regarding the use of NSAIDs in the perioperative period. On the basis of theoretic concern or practical experience, NSAIDs may adversely affect gastrointestinal mucosal protection, renal function and electrolyte balance, wound healing (including bone fusion and fracture healing), hemostasis, hepatic function, and cognitive function (at least in elderly patients). Although clarification of the significance of some of these concerns must await further clinical research, data are currently available to assist with the correct use of NSAID use in the perioperative period.

NSAID-related Gastrointestinal Toxicity.—NSAIDs can induce gastrointestinal ulceration by direct chemical irritation (especially aspirin) or by inhibition of prostaglandin synthesis.⁸¹ This is a particular concern in the perioperative period when physiologic stress may increase the risk of acute stress ulceration of gastroduodenal mucosa and subsequent acute gastrointestinal hemorrhage. In general, the short-term use of NSAIDs in the perioperative period is not felt to be associated with an increased risk of significant gastrointestinal complications (eg, perforation, bleeding). It is apparent that long-term use of NSAIDs may be associated with an increased risk of gastrointestinal complications after operation, especially with ketorolac, which suggests that the duration of ketorolac use should be limited to 5 days. COX-2 selective NSAIDs do appear to be associated with a significantly lower rate of acute ulceration (studied in the general population and not in the postoperative period) than nonselective NSAIDs.⁸¹ It seems reasonable to conclude that COX-2 selective NSAIDs would be associated with a reduced risk of gastroduodenal ulceration or bleeding in the perioperative period, but conclusive clinical documentation of this fact has not yet been published. It is expected that preparations of COX-2 NSAIDs that are suitable for parenteral injection will be available soon in the United States and will likely serve to focus additional attention on the impact of COX-2 selective NSAIDs on the risk of perioperative gastrointestinal complications. Although early in development, nitric oxide-releasing NSAIDs may eventually prove to be the NSAIDs of choice for perioperative use, in part because of their potential for the augmentation of gastroduodenal mucosal defense and ulcer healing.⁸¹

NSAID-related Renal Toxicity.—A systematic review of the impact of postoperative NSAID use on renal function failed to identify significant nephrotoxicity or any incidence of acute renal failure.⁸⁵ Although the risk of significant renal toxicity from NSAIDs appears to be quite low in general, that risk is increased significantly with renal insufficiency, congestive heart failure, hypotension, hypovolemia, or other factors that cause the impairment of renal perfusion.⁷⁷ In these settings, the maintenance of adequate renal cortical perfusion is dependent on prostaglandins that are synthesized by COX-1. Other aspects of renal function (eg, sodium excretion, renin release, and antagonism of antidiuretic hormone) are dependent on constitutive and induced COX-2; therefore, it is necessary to avoid the use of both COX-2 selective and nonselective NSAIDs in settings in which there is significant concern for NSAID-associated nephrotoxicity. In patients with hypovolemia, postoperative NSAID administration can impair the urine output significantly and potentially increase the risk of acute renal failure.

Wound Healing Effects of NSAIDs.—NSAIDs may adversely affect wound healing in some settings. Although most of the available data are from animal research, this is an area of real concern for clinical practice. Part of the pathogenesis of NSAID-associated peptic ulcer disease is now recognized to be impairment of normal ulcer healing.⁸¹ COX-2 inhibition (with COX-2 selective or nonselective NSAIDs) appears to be associated with delayed healing of gastrointestinal ulcers,⁸¹ perhaps related to angiogenesis that requires COX-2–produced prostaglandin. These concerns logically might apply to the postoperative healing of gastrointestinal anastomoses as well.

The control of pain after orthopedic trauma or operation has been one of the common indications for NSAID use, yet there is concern that NSAIDs may adversely affect the healing of bony fractures and intended spine fusions. Animal models of acute femur fracture suggest that NSAIDs impair fracture healing.⁸⁶ In a retrospective study of patients after internal fixation of femoral fractures, NSAID use was associated with a significantly increased risk of nonunion.⁸⁷ In the setting of spine fusion operation, a similar situation exists; there are animal data and retrospective clinical data that raise the concern that postoperative NSAID use may be associated with nonunion. Final resolution of the effects of NSAIDs on healing after fracture and spine fusion⁸⁸ must await further prospective clinical research.

Effects of NSAID on Hemostasis.—Concern about the potential for NSAID-induced inhibition of platelet aggregation to lead to postoperative bleeding has limited NSAID use in a variety of surgical settings. This NSAID effect is mediated through COX-1 inhibition,⁷⁸ so COX-2 selective inhibitors should not be associated with significantly increased bleeding. Recent research data indicate that COX-2 is induced in vascular endothelial cells in response to injury or inflammation and appears to have a protective function, which suppresses cell proliferation, cytokine release, and adhesion receptor expression.⁸⁹ The question of whether the loss of COX-2 function after NSAID administration in the postoperative period could lead to an increased risk of cardiovascular complications is unanswered at this time. The complexity of prostaglandin and thromboxane function in hemostasis and cardiovascular regulation is such that further clinical and applied research will be required to clarify the risks and benefits of postoperative NSAID administration.

NSAID-related Hepatotoxicity.—As a class of medication, NSAIDs are felt to be associated with a potential for liver injury, but the actual incidence of clinically significant hepatotoxicity among patients who were receiving NSAID therapy is very low. Nearly all NSAIDs have been reported to cause at least asymptomatic elevation in aminotransferase lev-

els, although this abnormality typically resolves with discontinuation of the prescribed NSAID.⁹⁰ The mechanisms of observed hepatotoxicity are numerous but not related to COX inhibition. The most common hepatotoxic reactions are based on idiosyncratic immunologic responses to individual NSAIDs and are associated with fever, rash, and eosinophilia. Significant hepatotoxicity has been associated with aspirin, sulindac, and diclofenac; even in these cases, the risk of death is low, but deaths have been reported. Aspirin hepatotoxicity is most common in patients with pre-existing immunologic disease (juvenile rheumatoid arthritis, systemic lupus erythematosus). Routine screening for hepatotoxicity is not recommended for patients who receive NSAID therapy.

NSAID and Cognitive Dysfunction.—Postoperative cognitive impairment, which ranges from mild confusion to acute delirium, is more frequently a problem in elderly patients. Although several factors may contribute to such cognitive impairment, attention is often focused on the possible role of opioid analgesics and/or hypnotics. Acute, high-dose NSAIDs may be associated with cognitive impairment in the elderly patient,⁸⁰ although data are accumulating that indicates chronic use of low-dose NSAIDs may help to preserve cognitive function in the elderly patient.

Acetaminophen.—Acetaminophen is currently one of the most commonly used drugs⁹¹; however, its use in the treatment of perioperative pain has been limited by its modest potency and the concern for hepatotoxicity. With better understanding of the use and adverse effects of acetaminophen, this drug may prove to have significantly increased importance in perioperative pain treatment in the future. Acetaminophen is an effective analgesic for the treatment of mild-to-moderate postoperative pain, without the concern for platelet dysfunction, gastrointestinal ulceration, or renal impairment that may accompany NSAID use. Acetaminophen use may improve the quality of pain relief or decrease the requirement for opioid analgesics after major surgical procedures. Current dosing practices for acetaminophen may result in the under dosing of adults and thereby fail to achieve the maximal potential analgesic effect,⁹² but further studies of perioperative acetaminophen pharmacokinetics are needed, before higher doses can be encouraged.

The mechanism of action of acetaminophen remains somewhat unclear, although there is evidence that its analgesic effect is due to the inhibition of prostaglandin formation in the CNS.⁷⁵ There are also data to suggest that inhibition of nitric oxide production in the CNS may be an important mechanism of action for both NSAIDs and acetaminophen. Nitric oxide, in turn, is an important mediator of inflammation in the periphery and neuronal signaling in the CNS.³

Acetaminophen has high bioavailability after oral administration, but it is only minimally absorbed from the stomach. Effective enteral absorption of oral acetaminophen is dependent on gastric emptying, which, if impaired after the operation, may limit the effectiveness of orally administered acetaminophen.⁹² Rectal acetaminophen suppositories have been used for postoperative pain control, but recent analyses in adults suggest that rectal acetaminophen is not effective for the control of postoperative pain.⁹³

Although acetaminophen is generally very well tolerated in healthy adults at the usually prescribed doses (10-15 mg/kg/per dose) and at regular intervals (approximately 4 hours), single doses of 150 to 250 mg/kg (approximately 10-15 g) are potentially hepatotoxic. Death from acute liver failure is a potential outcome of higher doses (approximately 20-25 g).⁹⁴ Acetaminophen is metabolized in the liver, largely to non-toxic metabolites that are excreted in the urine⁹¹; however, a small amount is converted to a highly reactive intermediary that is rapidly metabolized in a glutathione-dependent reaction. In the setting of acute overdose, it appears that hepatic glutathione stores are depleted, which results in toxicity from the build-up of the toxic reactive metabolite. Pre-existing hepatic illness or alcohol abuse may increase the risk of hepatotoxicity from acetaminophen, but significant toxicity from therapeutic doses is rare, and systematic studies have been difficult. Prolonged fasting may lead to glutathione depletion and thereby increase the risk of acetaminophen toxicity.⁹⁵ As a result, it seems prudent to be cautious in the dosing of acetaminophen in ill, fasted patients in the postoperative period, especially if there is pre-existing liver disease or a history of alcohol abuse.

Systemic Opioid Analgesics. The as-needed intramuscular administration of opioid analgesics had been the standard for postoperative pain treatment for decades before the development of PCA devices in recent years. Opioid analgesics are highly efficacious in a variety of clinical pain settings, readily available for medicinal purposes, and generally inexpensive for short-term use. Common adverse effects are dose dependent and reversible by discontinuation of therapy. With these factors favoring the use of opioid analgesics, it is no wonder that opium extracts and derivatives have been used continuously in Western society for the control of pain for more than 450 years.⁹⁶ Although sometimes referred to as “narcotics,” a better term for these drugs is *opioid analgesic*, because “opioid” is more precise in meaning and less pejorative than “narcotic.” *Opiate* refers to those drugs that have a chemical structure that is related to that of morphine (eg, hydromorphone, codeine, and heroin), but *opioid* is a

TABLE 2. Equianalgesic doses of commonly used opioid analgesics

Analgesic	Equipotent dose (mg)		Plasma half-life (hr)
	Intramuscular/intravenous	By mouth	
Morphine	10	30	2-3
Codeine	120	200	2-4
Fentanyl	0.1	N/A	3-4
Hydrocodone	N/A	30	4
Hydromorphone	2	8	2-3
Levorphanol	2	4	12-16
Meperidine	100	300	3-4
Methadone	10	15	30
Oxycodone	N/A	20	4
Propoxyphene	N/A	300	6-12

N/A, Not applicable.

more inclusive term that is used to indicate those agents that have analgesic mechanism of action similar to morphine (eg, not only opiates, but also meperidine, fentanyl, and endorphin peptides).

Morphine and other opioid analgesics produce predictable, dose-dependent antinociceptive effects. For example, the efficacy of parenteral morphine for the control of moderately severe postoperative pain has been documented in several placebo-controlled trials, which have been reviewed systematically.⁹⁷ Such fixed-dose analgesic trials likely underestimate the true clinical utility of opioid analgesics, because opioids should not be administered in fixed doses but rather titrated to effect. Because most adverse effects of opioids are also dose-dependent, titration of opioid dosing for each patient is essential for optimal use of these drugs.

In general, most opioid analgesics are fairly similar, except for variations in potency and elimination half-life. Approximate equianalgesic doses are listed in Table 2. General concepts for the effective use of systemically administered opioid analgesics have been reviewed elsewhere,^{96,98} but the following points are particularly important (Table 2):

- (1) In general, the analgesic duration of effect is roughly equivalent to the systemic elimination half-life. This is not true for spinal administration of opioid analgesics, for which the analgesic effect may be significantly longer than the systemic elimination half-life. With regular (systemic) dosing, all drugs will accumulate to reach a steady-state level in approximately 5 times that drug's systemic elimination half-life. Although morphine accumulates to reach a steady-state level over several hours, drugs with a longer elimination half-life (eg, methadone, levorphanol, and propoxyphene) do not

reach steady state for a few days. Because of accumulation of long half-life drugs are somewhat more difficult to titrate in the setting of fluctuating pain intensity, such as may be experienced in the postoperative period.

Although methadone and morphine are equally potent for single dose administration, the elimination half-life of methadone is 10 times longer than that of morphine. One consequence of the use of a drug with a long elimination half-life is that the drug's potency will appear to increase with chronic dosing, because of accumulation, as the steady-state level is reached. With single-dose administration (or on the initiation of methadone therapy), intravenous methadone is roughly equipotent to intravenous morphine on a milligram-per-milligram basis. With chronic dosing, methadone accumulates much more than morphine because of its longer elimination half-life, and patients require roughly 10 times less methadone per unit of time (at steady state). For example, at steady state, the amount of intravenous morphine per morphine elimination half-life (3 hours) would be roughly equivalent to an equipotent dose of methadone to be given per methadone elimination half-life (30 hours). In short, 10 mg of intravenous morphine every 3 hours is roughly equivalent to 10 mg of intravenous methadone every 30 hours at steady state.

- (2) Meperidine and propoxyphene have toxic metabolites (eg, normeperidine, norpropoxyphene) that are produced through hepatic metabolism of the parent drugs. These renally excreted toxic metabolites have elimination half-lives of approximately 30 hours and therefore accumulate to higher levels than the more rapidly metabolized parent drugs, with repetitive dosing. To avoid normeperidine toxicity (ie, anxiety, tremulousness, and seizures) and norpropoxyphene toxicity (ie, anxiety, tremulousness, and cardiac arrhythmias), these drugs should only be used at moderate doses for short periods and be avoided in individuals with renal impairment. Because of first-pass hepatic metabolism, all enterally administered opioids must be administered in higher doses to have the equivalent effect of a parenteral dose. Higher enteral doses of meperidine can lead to particularly high levels of normeperidine; therefore, the oral administration of meperidine is not recommended.⁹⁶
- (3) The equipotent doses shown in Table 2 for propoxyphene and hydrocodone are rough estimates because these drugs are not commonly used for severe pain. These drugs are available for enteral use only (in the United States) and are formulated with acetaminophen, which limits the dose (to avoid acetaminophen toxicity).

Mechanism of Action of Systemic Opioid Analgesics.—The antinociceptive effects of opioid analgesics are mediated through opioid receptors in the spinal cord and brain, although opioid receptors on peripheral nerve endings also appear to influence pain signaling in the setting of peripheral inflammation.⁹⁹ In the dorsal horn of the spinal cord, activation of opioid receptors, present on presynaptic nerve terminals of C-fiber nociceptors, inhibit the release of excitatory neurotransmitters. The presynaptic inhibition of neurotransmitter release is felt to be particularly important to the antinociceptive effect of opioid analgesics. Opioid receptors are also present on the postsynaptic membranes of spinal wide dynamic range interneurons and spinal nociceptive neurons that receive input from peripheral nociceptors. Inhibitory effects of postsynaptic opioid receptors decrease the responsiveness of spinal neurons and decrease spinal pain signaling. In addition, the activation of opioid receptors in the mid-brain and medulla (especially the PAG, the nucleus raphae magnus, and the locus ceruleus) cause enhanced activity in the inhibitory bulbospinal pathways, which further dampens spinal nociceptive neural transmission. Adverse effects, such as respiratory depression and nausea, are attributed to the presence of opioid receptors in the brainstem and medulla, respectively.^{27,96}

Although the mu (μ) opioid receptor is the principal receptor for clinical analgesic effects, some opioids may exert analgesic action through kappa (κ) and/or delta (δ) receptors.⁹⁶ Opioid receptors are classic G-protein-coupled metabotropic receptors, which affect cellular regulation through intracellular “second messengers.”¹⁰⁰ Like other members of this important group of cell membrane receptors, opioid receptors are hydrophobic proteins that span the neuronal membrane, linking extracellular portions of the receptor (the opioid binding site) to intracellular portions, which interact with the G-proteins. G-proteins (guanyl nucleotide-binding regulatory proteins) are bound to the inner surface of the cell membrane and, once activated, influence the enzymatic production of intracellular “second messengers,” such as cyclic adenosine monophosphate (cAMP). Different G-proteins have various inhibitory or excitatory effects on cellular enzymes and/or ion channels. Important actions of opioid-receptor coupled G-proteins include (1) the inhibition of adenylyl cyclase formation of cAMP, which results in decreased activity of cAMP-dependent protein kinases; (2) the activation of potassium ion channels, which results in increased potassium outflow, cell membrane hyperpolarization, and decreased responsiveness; and (3) the inhibition of voltage-gated calcium ion channels, thereby restricting calcium entry into the cell and limiting cellular depolarization and responsiveness.

Rat μ , δ , and κ opioid receptors have been cloned, which allows extensive research into the complex and expanding field of opioid receptor function.¹⁰¹ There is marked variability in G-protein subunit structure and function, with some G-protein subunits having opposing actions. The diversity of G-protein subunits may allow for cellular integration of receptor activation and explain some of the observed complexity of opioid action. Other factors that contribute to the variable action of opioids include multiple adenylyl-cyclase subtypes, receptor modification by phosphorylation, and the complexity of receptor gene regulation. What is clear is that the widespread clinical use of opioid analgesics rests on a complex molecular pharmacologic situation. It seems likely that, as the molecular actions of acute and chronic opioid administration are better understood, clinical use of opioid analgesics can be further refined.

Adverse Effects of Systemic Opioid Analgesics.—Most patients tolerate opioid analgesics quite well, but associated adverse effects are common. Sedation, potentially associated with respiratory depression and even respiratory arrest, causes the greatest concern with the clinical use of opioids. In addition, gastrointestinal effects (eg, nausea/vomiting, delayed gastrointestinal motility/constipation, biliary spasm), functional urinary outlet obstruction, pruritus, increased sweating, neuroendocrine effects, and other adverse effects are all well known.⁹⁶ Fortunately, sedation and respiratory depression usually can be treated with dose reduction.

In the setting of postoperative pain treatment, the most problematic adverse effects of opioid analgesic use are those adversely affecting gastrointestinal function. Although gastrointestinal motility and function are affected by a host of factors in the perioperative period, opioid analgesics appear to delay the return of normal bowel function after operation. Minimizing the use of opioid analgesics to facilitate the return of normal bowel function is one of the principal factors that motivates the development of newer analgesic techniques.

One potential adverse effect that is associated with the use of opioid analgesics that is not widely recognized among clinicians is immune suppression. Although the clinical significance of opioid-induced immune suppression in routine postoperative care is unclear, it may contribute to the immune dysfunction that is related to the physiologic stress of surgical procedures. Immune suppression has been demonstrated in experimental animals after acute and chronic opioid administration.¹⁰² The clinical significance of these animal data is unclear because the dose of opioid used to demonstrate immune suppression in animals (25 mg/kg) was much higher than that typically used for acute pain treatment (0.1 mg/kg).¹⁰² In addition, pain itself is known to cause immune suppres-

sion.¹⁰³ Some animal data suggest that opioid administration ameliorates the immune suppression that is associated with surgical procedures.¹⁰⁴ Research data suggest that immune suppression that is related to opioid analgesics may be variable and that different opioid analgesics affect immune function to different degrees.¹⁰⁵ With chronic exposure, tolerance appears to develop to the immune suppression effects of opioid but not to the immune suppression effects of pain.¹⁰³ Clarification of the impact of various analgesic techniques on immune function in the postoperative period must await further clinical research.

Patient-controlled Analgesia.—The intermittent administration of opioid by the health care staff on an as-needed basis results in a significant proportion of patients who experience periods of severe pain.¹⁰⁶ Intravenous PCA has been a major development in postoperative pain treatment and is now considered the therapeutic standard for the treatment of acute postoperative pain.¹⁰⁷ Intravenous PCA results in improved analgesia and higher patient satisfaction,¹⁰⁸ but there is no clear evidence that this improvement translates into improved outcomes.

It is important to note that intravenous PCA is not a “one size fits all” method, even though many hospitals have developed “standard” intravenous PCA orders. The initial orders must be modified in at least 50% of patients,¹⁰⁹ and it may be necessary to switch to a different opioid because of adverse effects. Reliable data about the incidence of respiratory depression after intermittent nurse-administered opioid is not available. It has been reported that intravenous PCA can result in nocturnal hypoxemia because of respiratory depression, and the use of supplemental oxygen has been suggested.¹¹⁰ It might be expected that the addition of a continuous opioid infusion in addition to intravenous PCA bolus doses would result in more stable, better pain control, but the existing data indicate that this is not the case. A basal opioid infusion does not seem to provide any additional benefit but increases the total dose of opioids administered and the risk of adverse effects.¹⁰⁹

Intravenous PCA is generally not cost-effective for patients who stay in the hospital for less than 48 hours.¹⁰⁹ There is clearly a need for further study about the safety and cost-effectiveness of intravenous PCA and for the establishment of protocols for its use. The use of intravenous PCA by inexperienced hospital staff actually may be less cost-effective than conventional intermittent intramuscular administration of opioids.¹¹¹

Adjuvant Analgesics. A variety of adjuvant analgesics have been used for postoperative pain control, with varying degrees of success. The rationale for the use of such drugs in the postoperative period is to reduce opioid requirements, to reduce opioid-related adverse effects, and to improve

pain control, especially neuropathic pain.¹¹² Spinal administration of α_2 -agonists (eg, clonidine) has been shown to be effective in the treatment of acute pain, but α_2 -agonists are usually used in combination with other analgesic techniques to minimize the adverse effects of hypotension and sedation.²⁷ Antidepressant medications and anticonvulsants are used widely in the treatment of chronic neuropathic pain but appear to have a very limited role in the treatment of acute pain. Of course, it is reasonable to begin the use of these medications early in the postoperative period in those patients who report significant neuropathic pain (ie, phantom limb pain, traumatic neuralgias).

The systemic administration of lidocaine does have analgesic efficacy in acute pain and in neuropathic pain. Some of the benefits of epidural local anesthetic may be related to the systemic absorption (and systemic effects) of the local anesthetics, although the analgesic potency and utility of epidural local anesthetic are greater than that of systemically administered local anesthetics. Nonetheless, the systemic administration of lidocaine is a useful technique in a variety of complex, intractable pain problems, including the treatment of severe neuropathic pain in the immediate postoperative period.¹¹²

Neuraxial Analgesic Techniques

There is considerable evidence that epidural or subarachnoid anesthesia, as either the sole anesthetic or a component of balanced anesthesia, contributes to improved outcome.¹¹³ There is also evidence that epidural or subarachnoid analgesia contributes to improved outcomes.¹¹⁴ It is therefore reasonable to hypothesize that the use of neuraxial anesthesia followed by neuraxial analgesia in the postoperative period may result in further improvement in outcomes. Neuraxial analgesia, whether provided through the epidural or the subarachnoid routes, has specific benefits and disadvantages.

Subarachnoid (Spinal) Analgesia. In contrast to epidural analgesic administration of opioid, there are few data regarding the pharmacologic features of subarachnoid opioid administration.¹¹⁵ The pharmacology of subarachnoid opioids is simpler than those of epidural opioids; the issues of dural penetration, epidural fat deposition, and systemic absorption of drug are not clinically significant. The analgesic dose of subarachnoid morphine is only 5% to 10% of the dose that is required when administered into the epidural space and only 1% to 2% of the intravenous dose. Therefore, subarachnoid administration is advantageous because it provides excellent, predictable, and prolonged analgesia, with only a fraction of the morphine dose compared with epidural analgesia.²⁷

Despite the efficacy of subarachnoid administration of opioid, the epidural route of administration is used more widely, probably because of concerns about spinal cord neurotoxicity from subarachnoid medication administration, fear of delayed respiratory depression, and concerns about postlumbar puncture headache.¹¹⁵ Delayed respiratory depression has been reported with subarachnoid morphine doses as low as 0.3 mg. Delayed respiratory depression can also occur after epidural opioid administration, but there are data that show that the risk is higher with subarachnoid administration.¹¹⁶

Epidural Analgesia. Three main types of medications have been used epidurally for pain relief: opioids, local anesthetics, and clonidine.

Epidural Opioids.— Neuraxial opioid analgesia was a major development in the treatment of postoperative pain, labor pain, chronic pain, and cancer pain. Neuraxial administration of opioid can produce profound analgesia with potentially fewer systemic adverse effects compared with systemically administered opioid.¹¹⁵ Opioids can be classified as water-soluble or lipid-soluble. Lipid solubility is a major factor that influences the pharmacokinetics of medications that are administered epidurally. Lipophilic (lipid-soluble) opioids, such as fentanyl, are readily absorbed into the epidural veins, and therefore at least part of their analgesic action is mediated through systemic effects. Water-soluble opioids, such as morphine, are less readily absorbed from the cerebrospinal fluid into the systemic circulation and are therefore cleared from the cerebrospinal fluid more slowly. Water-soluble opioids have fewer systemic effects but may migrate with the cerebrospinal fluid to the brain and cause significant respiratory depression,²⁷ which can occur many hours after opioid administration.

Epidural opioids can provide profound analgesia without sensory, motor, or autonomic blockade; therefore, epidural opioid administration should not interfere with ambulation. Epidural opioids do not necessarily provide better analgesia compared with systemic opioids, but the dose of epidural morphine needed to provide analgesia is only 10% of the intravenous dose. As a result, the desired analgesic response to epidural opioid is achieved with significantly less medication and therefore potentially less systemic opioid-related side effects than with systemic administration. Adverse effects related to the CNS action of epidural opioids may include respiratory depression (early and late), pruritus, nausea, and urinary retention.²⁷

Epidural Local Anesthesia.—Epidural local anesthetics exert their analgesic effect by blocking conduction at the level of the nerve root, which also results in autonomic blockade. This may be beneficial because of a reduction of the neuroendocrine stress response to surgical stimulation and postoperative pain. Systemic absorption of local anesthetics is signif-

icant after epidural administration, and systemic toxicity can occur if epidural administration of local anesthetics is excessive. The combination of local anesthetic and opioid solutions can result in superior analgesia, compared with opioids alone, particularly during movement.¹¹⁷ Pain control during movement is very important because of the need to facilitate perioperative rehabilitation.

Epidural Clonidine.—Clonidine is a selective α_2 -adrenergic agonist that produces analgesia, especially after epidural or subarachnoid injection. Epidural clonidine has some significant advantages, compared with epidural local anesthetics and opioids: it does not cause respiratory depression, urinary retention, or motor blockade. The main side effects of clonidine are hypotension, bradycardia, and sedation. Clonidine can prolong the duration of local anesthetic blockade and therefore can be used as an adjunct to epidural local anesthetic analgesia. It can be used also in conjunction with epidural opioids to prolong and enhance epidural opioid analgesia.^{27,115}

Expected Benefits of Epidural Analgesia.

Superior Analgesia and Improved Cognitive Function.—The administration of epidural opioid, local anesthetic, and/or clonidine can result in superior analgesia, when compared with systemic opioid analgesia.^{118,119} There is some evidence that epidural analgesia can result in decreased opioid requirements in the postoperative period and therefore contribute to less sedation and cognitive dysfunction.¹²⁰ The benefit that epidural analgesia may offer in the preservation of cognitive function deserves further investigation.

Attenuation of Perioperative Neuroendocrine Stress Response.—Pain may contribute to the perioperative neuroendocrine stress response and thereby adversely affect organ function and contribute to perioperative morbidity. Epidural analgesia with local anesthetic can attenuate the perioperative stress response,¹²¹ but the effect of epidural opioid on the stress response is not as clear.¹²² Overall, there is significant evidence that the perioperative neuroendocrine stress response can be attenuated with the use of epidural anesthesia and analgesia, and this attenuation may result in improved perioperative outcomes.¹²¹⁻¹²⁴

Decreased Incidence of Cardiac Complications.—Thoracic epidural administration of local anesthetics can decrease pulmonary capillary wedge pressure,¹²⁵ increase coronary perfusion through coronary vasodilatation, and decrease cardiac work by decreasing systemic vascular resistance. Thoracic epidural analgesia has been shown to reduce the severity of myocardial ischemia through the reduction of myocardial mechanical activity and myocardial metabolism. Because of these beneficial effects,

thoracic epidural local anesthetic infusions have been used for the treatment of cardiac-related pain after myocardial infarction¹²⁶ and with refractory angina.^{127,128} On the basis of these observations, it is plausible to expect that epidural analgesia can contribute to the improvement of cardiac outcomes in the perioperative period. There is evidence that epidural analgesia results in fewer myocardial complications.^{124,129} However, there are also studies that failed to show a reduction of adverse outcomes, such as congestive heart failure, myocardial infarction, or death.¹¹⁷ The role of epidural analgesia in improving myocardial outcomes after operation is still unresolved and needs further investigation.

Improved pulmonary function.—The epidural administration of local anesthetic or opioid analgesics can provide improved pain control during cough, movement, and ambulation compared with systemic analgesics. By enabling patients to undergo the activities necessary for postoperative rehabilitation with less pain, epidural analgesic techniques may improve pulmonary function and reduce postoperative pulmonary complications.^{114,130,131} However, the evidence is not conclusive, because there are also data that show no benefit from epidural analgesia. The combination of epidural opioids and local anesthetics may provide some additional benefit, which is manifested as improved gas exchange, compared with epidural opioid alone.¹³²

Reduced Postoperative Hypercoagulability.—Epidural local anesthetics result in a less pronounced hypercoagulable state in the postoperative period. This may result in a decreased risk of graft thrombosis in vascular surgery and a lower risk of perioperative thromboembolic complications.^{133,134}

Accelerated Recovery of Gastrointestinal Function.—The administration of epidural opioids delays gastric emptying and prolongs intestinal transit time in healthy volunteers and therefore contributes to ileus, which is reversible by naloxone.¹³⁵ In the perioperative period, however, there is some evidence that the use of epidural opioids can result in the faster recovery of gastrointestinal function after operation, compared with the use of systemic opioid analgesics. Epidural local anesthetic administration at the thoracic level results in the conduction blockade of sympathetic innervation to much of the gastrointestinal track. Blockade of sympathetic innervation leaves the parasympathetic innervation to the gastrointestinal track unopposed, which results in increased gastrointestinal motility. Likely reflecting the results of sympathetic blockade, epidural analgesia with local anesthetics has been shown to result in less nausea and faster recovery of gastrointestinal function after gynecologic surgery,¹³⁶ orthopedic surgery,¹³⁷ colorectal surgery,¹³⁸⁻¹⁴⁰ and thoracic surgery.^{117,118,130,131} In addition to effects on the sympathetic nervous system, epidurally

administered local anesthetics may have systemic effects on gastrointestinal function. There is evidence that lidocaine that is administered intravenously can also speed the return of bowel function in the postoperative period.¹¹²

Earlier Mobilization and Ambulation.—Perioperative pain can interfere with patients' ability to move, cough, and ambulate and therefore can contribute to prolonged recovery after operation. Epidural analgesia can provide improved pain control with these activities and facilitate postoperative rehabilitation. Numerous studies show that the use of epidural analgesia can contribute to earlier extubation¹¹⁹ and mobilization, shorter intensive care unit stay, and earlier hospital discharge.^{140,141}

Complications of Epidural Analgesia. In selected patient populations, the benefits of epidural analgesia appear to outweigh the risks, particularly when epidural analgesia is used in the context of a multimodal recovery program. Epidural analgesia, like any other medical intervention, carries some risk of complication and technical failure, which must be considered when making decisions regarding postoperative pain treatment therapies. The exact frequency of technical failures is not known, but in a recent survey, epidural analgesia was discontinued in 23% of patients, usually because of catheter dislodgment.¹⁴²

Respiratory Depression.—Initially, clinicians did not appreciate the potency of neuraxial opioids, which resulted in cases of severe respiratory depression. In one study from Sweden in the early 1980s, the incidence of respiratory depression after epidural morphine was 0.25% to 0.4%.¹¹⁶ The true incidence of respiratory depression after epidural opioid administration in current practice is unknown, but it is probably low. In fact, one of the major indications for the use of epidural opioid analgesia is in compromised patients at high risk for respiratory depression from systemic opioids.¹²⁴

Respiratory depression from epidural opioids can be early or delayed. Early respiratory depression may occur within 1 hour of morphine administration but within minutes after administration of lipid-soluble opioids, such as fentanyl.¹¹⁵ Delayed respiratory depression can occur unexpectedly several hours after opioid administration and therefore can be more dangerous. The risk of delayed respiratory depression is higher with epidural morphine than with epidural fentanyl, which reflects differences in the pharmacokinetics of these agents.²⁷ The respiratory rate does not seem to be an adequate parameter for the detection of delayed respiratory depression; therefore, patients who receive epidural morphine require careful monitoring for the onset of progressive sedation, which can lead to respiratory depression. This requires skilled nursing care but does not generally require observation in an intensive care unit or specialized recovery area.

The combination of epidural opioids with local anesthetics may result in a lower total dose of opioids and a lower risk of respiratory depression. A recent survey on the use of combined epidural local anesthetic and opioid for postoperative pain control epidural found 2 episodes of severe respiratory depression and 1 case in which a patient could not be aroused, during a total of 3858 treatment days.¹⁴³

Hypotension.—Autonomic blockade from epidural local anesthetics can result in decreased blood pressure,^{144,145} heart rate,¹⁴⁴ and systemic norepinephrine release¹⁴⁵ in the perioperative period. Orthostatic hypotension may be a serious concern in patients who are encouraged to ambulate. However, the reduction of blood pressure that is observed with low-dose thoracic epidural bupivacaine infusion is generally limited and typically does not interfere with ambulation after thoracic¹⁴⁶ or abdominal procedures.¹⁴⁷

Urinary Retention.—Postoperative urinary retention is commonly encountered and has been reported to occur in 4.7% of male patients and 2.9% of female patients, based on a large survey of surgical patients. The incidence increases with age and seems to be highest after thoracotomy and hip surgery.¹⁴⁸ Epidural morphine can further increase the risk of urinary retention, but opioid-induced retention can be reversed with intravenous naloxone. Because of concern for postoperative urinary retention, some physicians routinely delay the removal of urinary bladder catheters from patients who receive epidural analgesics, until after the epidural catheter has been removed. Prolonged urinary drainage, however, results in an increased risk of urinary tract infection. Not all patients with epidural analgesics will experience the development of urinary retention without bladder catheterization, and the need for routine urinary drainage during continuous epidural analgesia requires further clarification through clinical research.¹⁴⁹

Lower Extremity Weakness.—The administration of epidural local anesthetics for postoperative pain control can potentially result in lower extremity weakness, prevent ambulation, and thereby delay recovery and increase the risk of complications. The severity of leg weakness is influenced by the position of the epidural catheter tip (weakness is rare with thoracic epidural catheters) and by the dose of local anesthetic. Combining epidural opioids with local anesthetics can provide adequate analgesia while limiting the dose of local anesthetics, so that ambulation is generally possible. In a prospective study of 1014 patients with thoracic or lumbar epidural catheters, epidural bupivacaine 0.1%, administered with fentanyl, resulted in significant unilateral or bilateral motor block in only 3% of patients.¹⁵⁰

Neurologic Complications.—Dural puncture is the most common technical complication of epidural catheter placement; it occurs in 0.16% to

1.3% of cases¹⁵¹ and can result in postlumbar puncture headache. Neurologic injury is rarely a complication of epidural analgesic therapy and occurs in 0.01% of patients or less.¹⁵² Paraplegia is the most feared complication of epidural catheter placement, but paraplegia is rare, occurring in less than 1 in 100,000 cases. Epidural hematoma is one cause of paraplegia after an epidural catheter. The risk of epidural hematoma after epidural catheter placement is greater in patients who have hemostatic abnormalities. In response to the concern about hemorrhagic complications after neuraxial anesthesia and analgesia, there are guidelines regarding the use of neuraxial techniques in patients who are receiving anticoagulants.^{153,154} It is important to note that the removal of an epidural catheter may also be traumatic; there have been case reports of epidural hematoma after epidural catheter removal in patients with coagulopathy.

Epidural analgesia has been reported to mask the symptoms of serious postoperative events. Examples include the masking of systemic tumor embolism after thoracotomy,¹⁵⁵ massive myocardial infarction,¹⁵⁶ or the development of compartment syndromes or other neurologic complications.¹⁵⁷

Pruritus (usually limited to the face, neck, or chest) is the most common adverse effect after neuraxial opioid administration. There is no obvious relationship between the incidence of pruritus and the dose of neuraxial opioid. Patients usually do not bother to report pruritus, yet it can be intense. Pruritus from neuraxial opioids is probably not related to histamine release, but antihistamines can be beneficial. Severe pruritus that is associated with epidural opioid can be treated with systemic administration of an opioid agonist-antagonist, such as nalbuphine or butorphanol or small doses of naloxone.

Infection that is related to epidural catheters for postoperative pain control has been described in the literature, but the risk seems to be low. A recent survey found no epidural infections among 1062 patients who had received epidural analgesia.¹⁴² Infections can be superficial, at the site of skin entry, or deep into the epidural space and can result in meningitis or abscess formation. Epidural abscesses can occur after epidural catheterization when systemic infection is present but can also occur after epidural analgesia in the absence of other systemic infection. An expanding epidural abscess can result in spinal injury; therefore, daily inspection of the epidural catheter insertion site is imperative for all patients with epidural catheters to assure early diagnosis of infection.

Patient-controlled Epidural Analgesia. Patient-controlled epidural analgesia (PCEA) allows patients to self-administer epidural analgesics on an as-needed basis to control pain. PCEA developed from the safe, effec-

TABLE 3. Typical agents, doses and time intervals used for the delivery of patient-controlled epidural analgesia (PCEA) at Washington University School of Medicine Medical Center

Epidural analgesic solutions	Basal infusion rate (mL/hr)	Demand dose (mL/dose)	Lockout (min)
Hydromorphone (20 µg/mL)	4-10	4-10	20
Fentanyl (3-5 µg/mL)	4-10	4-10	20
Bupivacaine (0.1%-0.15%)	4-8	2-3	30
Bupivacaine (0.1%) with fentanyl (3 µg/mL)	4-8	2-3	30

tive, and popular intravenous PCA. Although efficacy and safety data are limited, there is some evidence that PCEA can improve the safety and analgesic efficacy of epidural analgesia¹⁵⁸ and result in higher patient satisfaction. PCEA may also decrease the delivery cost of epidural analgesia by decreasing the demands on physician and nursing time, but there are no data to support this contention.¹¹⁵

The inpatient pain service at the Washington University Medical Center uses PCEA for most patients who receive epidural analgesia. In our experience, the use of PCEA is safe and has resulted in significantly reduced demands on physician time (unpublished data). Medications and doses used for PCEA at the Washington University Medical Center are summarized in Table 3.

Discontinuation of Epidural Analgesia. Epidural analgesia is usually used for 2 to 3 days, depending on the nature of the operation and the condition of the patient. Beyond this time, the benefits of epidural analgesia are not as clear, and prolonged use may increase the risk of epidural infection. In our clinical practice, PCEA is generally continued until specific endpoints have been reached. The choice of analgesic agents and the appropriate endpoints for epidural analgesia vary according to the type of operation, the spinal level of the epidural catheter, and the condition of the patient. Table 4 summarizes the use of epidural analgesia at Washington University Medical Center.

Neuraxial Analgesia: Questions for Further Research. There is a convincing body of evidence that shows that epidural analgesia is superior to systemic opioids, at least for some subsets of patients. However, the following important questions deserve further study:

- (1) Neuraxial versus systemic analgesia. Under what circumstances is neuraxial analgesia preferable to systemic opioid analgesia?
- (2) Thoracic versus lumbar epidural analgesia. There are patient populations in which thoracic epidural analgesia appears to be the preferred modality, but further research is needed to define specific patient populations in whom thoracic epidural analgesia should be used.

TABLE 4. Choice of epidural analgesics and endpoints for discontinuation of epidural analgesia used at Washington University School of Medicine Medical Center

Operative site	Epidural catheter position	Analgesic agent	Clinical endpoints
Abdomen	Lumbar	Hydromorphone 20 µg/mL or morphine 80 µg/mL	Nasogastric tube removed; oral intake
Abdomen	Thoracic	Bupivacaine 0.15% or bupivacaine 0.1% with fentanyl 3 µg/mL	Nasogastric tube removed; oral intake
Thorax	Lumbar	Hydromorphone 20 µg/mL or morphine 80 µg/mL	Tracheal tube removed; chest tubes removed; oral intake
Thorax	Thoracic	Bupivacaine 0.15% or bupivacaine 0.1% with fentanyl 3 µg/mL	Tracheal tube removed; chest tube removed; oral intake
Pelvis	Lumbar	Hydromorphone 20 µg/mL or morphine 80 µg/mL	Nasogastric tube removed; oral intake; chest tube removed
Pelvis	Thoracic	Bupivacaine 0.15% or bupivacaine 0.1% with fentanyl 3 µg/mL	Nasogastric tube removed; oral intake; chest tube removed
Lower extremity	Lumbar	Bupivacaine 0.15% or bupivacaine 0.1% with fentanyl 3 µg/mL	Oral intake; ambulation

- (3) Opioid versus local anesthetic versus combination epidural analgesia. There are cases in which local anesthetics confer a clear advantage, but more work is needed to clarify when the choice of agent is important.
- (4) Pre-emptive versus postoperative neuraxial analgesia. There is some evidence that suggests that initiating epidural analgesia before the operation, rather than limiting it to the postoperative period, may confer additional benefits in some settings, but the cost/benefit implications of this practice are not clear.
- (5) Endpoints for the discontinuation of neuraxial analgesia. There are no well-defined criteria for the optimal duration of neuraxial analgesia. Medicare administrative rules generally limit payment for postoperative epidural analgesia to 3 days, but data from outcome studies are needed to define the optimal duration of epidural analgesia for different procedures.

Regional Analgesic Techniques

Regional analgesic techniques, including peripheral nerve blocks and local infiltration with local anesthetics, are techniques that may be used to provide high-quality relief of postoperative pain. Although neuraxial anal-

gesic techniques (eg, epidural analgesia) are used more widely, regional analgesic techniques have been shown to be effective pain treatment therapies after several surgical procedures¹⁵⁹ in both inpatient and outpatient settings. Modifications of standard regional anesthetic techniques that use percutaneous catheters and external infusion devices allow for the continuation of these therapies after the operation. These techniques can also be adapted for use as PCA therapies.¹⁶⁰ In addition to improving the quality of pain relief, regional analgesic techniques potentially allow for a significant reduction in the requirement for opioid analgesics and facilitation of postoperative recovery and rehabilitation.

The simplest example of a potentially useful regional analgesic technique is the infiltration of local anesthetic into the tissues surrounding a surgical wound. Although not associated with major improvements in perioperative morbidity, infiltration of local anesthetic appears to be safe and effective and is not associated with untoward effects on wound healing.¹⁵⁹ A variation on wound infiltration is the injection of local anesthetic into the joint capsule after orthopedic operation, which has been shown to be an effective analgesic therapy.¹⁶¹

Although regional blockade and local anesthetic infiltration techniques are widely available, they are not used routinely in many centers. Regional analgesic techniques must be used selectively in clinical settings and require varying amounts of skill and time for application. Successful incorporation of regional analgesic techniques into routine perioperative treatment will require cooperative planning on the part of surgeons and anesthesiologists, but such techniques may potentially play a significant role in multimodal accelerated recovery programs.

Nonpharmacologic Techniques in Perioperative Pain Treatment

Psychological and Behavioral Medicine Therapies. Psychologically preparing the patient adequately for operation may have a substantial impact on postoperative pain and recovery. For example, patients who are trained in relaxation experienced less pain; pain interfered less with their daily activities, and they performed at a higher activity level 3 weeks after operation, compared with nontrained patients.¹⁶² Psychosocial support (eg, identifying/alleviating concerns, reassuring, problem-solving with patient, encouraging questions, increasing frequency of support) and educational interventions have been used to alleviate patient distress and pain and to improve patient well-being after operation. It is therefore important that patients have access to these treatments as adjuvants to medication. The overall clinical relevance of psychosocial and educational interventions in the treatment of postoperative pain is clear, but the choice of spe-

cific methods of care is still controversial. Given the potency of environmental influences on pain experience (safety and economic advantages notwithstanding), further efforts to improve such interventions are likely to improve patient recovery, postoperative pain, psychologic distress, and length of hospital stay.

Transcutaneous electrical nerve stimulation (TENS) is a treatment whereby selective stimulation of certain nonnociceptive neurons apparently blocks transmission of pain signals. TENS is used in many parts of the world, with no adverse effects reported; however, it does not appear to have a role for controlling acute postoperative pain. In a systematic review by Carroll and colleagues,¹⁶³ 14 trials that used TENS versus disabled (sham) TENS found no significant difference in postoperative pain.

Acupuncture. There have been several studies that evaluated acupuncture in the perioperative setting. One of the challenges of acupuncture research is designing appropriate control groups. The role of acupuncture analgesia in the treatment of postoperative pain has yet to be clearly evaluated. For example, acupuncture analgesia has no additional effect when administered to patients under anesthesia who are undergoing knee arthroscopy.¹⁶⁴ Investigations to define the optimal acupuncture technique and its relative efficacy compared with conventional methods of analgesia are currently underway.

Multimodal Postoperative Care and Rehabilitation

The practice of medicine continues to evolve with increasing emphasis placed on efficiency, cost reduction, and outcomes assessment. In this context, the perioperative care of surgical patients is constantly re-evaluated in an attempt to accelerate recovery, shorten hospital stay, and decrease costs, while maintaining or improving the quality of care. "Multimodal" or "accelerated surgical recovery" programs have been described, which use clinical care pathways or critical pathways, a concept adopted from industrial quality treatment science. Multimodal recovery programs combine adequate perioperative analgesia, early mobilization, and early oral nutrition in an attempt to accelerate patient rehabilitation and reduce hospital stay.^{117,140} These programs challenge traditional wisdom, and attempts to implement such programs may meet resistance. However, as more health care institutions are trying to re-engineer their care processes and increase efficiency, these programs are gaining acceptance.

Preoperative Patient Education

Patient acceptance and active participation are important for a multimodal recovery program to be successful.¹⁶⁵ Patients who know what to

expect, how to relax, how to take deep breaths, and how to move have less pain and experience a smoother perioperative course. In fact, patients who receive preoperative education have postoperative opioid requirements that are 50% lower and are ready for discharge earlier compared with control patients.^{38,166} Such education may be provided by either a physician or a nurse.¹⁶⁷

Modification of Surgical Practice

Endoscopic or minimally invasive surgical procedures are becoming increasingly common. The stress response can be decreased by minimally invasive techniques, such as laparoscopic abdominal operation¹⁶⁸ or less invasive thoracic operation.¹⁶⁶ The use of such techniques can result in less postoperative pain,¹⁶⁹ early mobilization, and shorter hospital stay.¹⁴⁰

Until recently, perioperative care paths included prolonged fasting, routine use of drains, immobilization, and lengthy hospital stays. The benefit of many routines (such as the use of nasogastric tubes, surgical drains, opioid analgesics, and postoperative immobilization) has not been rigorously tested. For example, some surgeons routinely place drains in the pelvis after colorectal anastomosis.¹⁷⁰ Studies in animals¹⁷¹ and in humans^{172,173} have shown, however, that such prophylactic drainage does not decrease morbidity. There is now evidence that early oral feeding and early mobilization^{74,140,146,174-176} may significantly contribute to accelerated patient recovery and shorter hospital stay.

Multimodal or Balanced Analgesia

Effective pain relief is not just “the right thing to do,” but it is an essential component of postoperative care. Postoperative pain relief can enhance functional restoration by allowing the patient to breathe, cough, and move more easily. “Balanced analgesia” is a strategy of combining different analgesic regimens to optimize pain control and minimize analgesic-related adverse effects. Single analgesic modalities are generally not adequate in the achievement of pain control during activities such as cough or ambulation.¹²² Balanced analgesia, by combining techniques that act at different levels along pain pathways, potentially provides improved pain control with fewer adverse effects. Analgesic therapies commonly used in combination include pre-emptive analgesia, regional techniques, neuraxial techniques, opioids, and nonopioid analgesics. This approach may accelerate recovery and shorten hospital stay,¹⁴⁰ but the impact of balanced analgesia on other patient outcomes is still unclear.¹²²

The Lung Volume Reduction Surgery Program at Washington University School of Medicine

Recent improvements in perioperative care have resulted in the extension of surgical options to patients who were previously considered “inoperable.” The Lung Volume Reduction Surgery (LVRS) Program¹⁴⁶ at Washington University Medical Center is an example of a comprehensive multimodal approach to patient treatment. The LVRS program incorporates preoperative patient optimization, balanced perioperative analgesia (with thoracic epidural local anesthetic administration and minimal use of opioid medications), early extubation, and aggressive postoperative mobilization and pulmonary rehabilitation.¹⁴⁶

Lung volume reduction is a fairly new operation for patients with advanced emphysema. The apex of each lung is resected to reduce the excess total lung volume and improve the respiratory mechanics. Of the first 200 patients who underwent LVRS at Washington University (age, 61.4 ± 8.2 years; 48.5% women; smoking history, 59 ± 29 pack-years tobacco smoking), 39% of the patients required continuous oxygen supplementation, and 93% of the patients required supplementation during exercise before the operation (J. Cooper, MD, written communication, with permission). Preoperative pulmonary function testing results showed a forced expiratory volume in 1 second of 0.71 ± 0.26 L ($25\% \pm 7\%$ of predicted), a forced expiratory volume in 1 second/forced vital capacity of 0.29 ± 0.07 , a residual volume of 5.8 ± 1.3 L, and a total lung capacity of 8.3 ± 1.6 L. All patients underwent extensive preoperative rehabilitation and education (up to 6 months). The operation was performed through a median sternotomy (except in 1 patient), with the goal of extubating all patients immediately after operation. All patients underwent extubation within hours after the operation, but 13 patients (6.5%) required reintubation for respiratory failure, and 10 patients (5%) underwent tracheostomy. After recovery, most patients did achieve improved respiratory mechanics and improved exercise tolerance.

Pain Control after Lung Volume Reduction Surgery. Pain control is achieved with a balanced analgesia approach consisting of thoracic epidural analgesia supplemented with opioids through intravenous PCA and NSAIDs and/or acetaminophen. A radiopaque thoracic epidural catheter (Theracath, Arrow International, Inc, Reading, Pa) is placed before the operation with the use of fluoroscopy. Fluoroscopy is used to ensure that each patient will have a well-functioning epidural catheter. The catheter is advanced until the tip reaches the superior margin of the T4 vertebral body, close to the midline. General anesthesia is supplemented with

epidural bupivacaine 0.25% during the operation. After the operation, bupivacaine 0.15% is continuously infused for pain control at a rate from 0 to 10 mL/hr, depending on the patients' pain intensity and hemodynamic stability. The epidural infusion is combined with a low dose intravenous PCA and supplemented, as needed, by NSAIDs or acetaminophen. The use of epidural local anesthetic infusion with intravenous PCA opioid facilitates titration of each therapy and optimization of pain control.

The choice of NSAID versus acetaminophen depends on the patient condition and clinical course. NSAIDs are preferred in patients with normal renal function, unless there is particular concern about postoperative coagulopathy. Patients with impaired renal function or coagulopathy receive acetaminophen. This balanced analgesia approach provides adequate pain relief, so that patients are able to tolerate chest physical therapy, to cough effectively, and to ambulate. The epidural infusion is usually continued until all chest tubes are removed; therefore, epidural analgesia is generally used 3 to 4 days or longer, depending on patient needs. The median hospital length of stay in this patient population was 9 days. The 90-day mortality rate was 4.5%; the 1-year survival rate was 93%; and the 5-year survival rate was 75%. These excellent results were achieved with a multimodal treatment approach that was based on collaboration among surgeons, pulmonologists, anesthesiologists, nurses, respiratory therapists, and other health care professionals.

Future Research Areas

The development of multimodal recovery programs is a relatively recent development. Table 5 summarizes evidence for innovative analgesic approaches and postoperative rehabilitation that accelerates recovery and decreases morbidity and hospital stay. These results are encouraging; however, there is a need for more data on the effectiveness of these programs. More widespread application of multimodal strategies, with appropriate use of currently available techniques, could result in substantial improvements in perioperative care.

Clinical Treatment Strategies for Specific Postoperative Pain Treatment Problems

Treatment of Pain in Individuals Who Are Opioid Tolerant

Tolerance to opioid analgesics significantly complicates perioperative care for both the health care professional and the patient who is opioid tolerant. By definition, patients who are opioid tolerant will have a diminished response to given doses of opioid and therefore often have inade-

quate pain control when given standard doses of opioid analgesics. Of course, in clinical practice in general, and especially in the perioperative period, the report of unusually severe pain must be evaluated carefully for pathologic significance. Based on extensive experience in the treatment of pain after operation, Ready¹⁷⁷ has suggested that increased pain and decreased sensitivity to opioid-related adverse effects, despite increased doses of opioid, should suggest the diagnosis of opioid tolerance, which is most likely related to chronic opioid use. The range of opioid tolerance seen in clinical practice is wide. For example, individuals who receive the equivalent of a few codeine tablets per day before operation may require only a moderate adjustment in opioid doses to control postoperative pain. Individuals who receive the equivalent of gram doses of morphine daily may become almost completely resistant to opioids for the control of new, acute pain. To add insult to the injury of uncontrolled pain, many health care professionals may misdiagnose the syndrome of opioid tolerance and erroneously conclude that the patient has a "low threshold for pain" or has "drug seeking behaviors" that suggest drug addiction. Especially in the postoperative period when pain from tissue injury is expected, "drug seeking behavior" most likely reflects inadequate pain control rather than drug addiction. The observed decreased responsiveness to opioid analgesics is due, at least in part, to the facilitation of pain signaling in the CNS. The pain experienced by patients who are opioid tolerant really may be "out of proportion to that expected"; however, it may be the clinician's expectations that are in error, rather than the patient's neurophysiologic status.

Even when the problem of opioid tolerance is recognized properly and promptly, adequate control of pain in individuals who are opioid tolerant may be difficult to achieve. In many cases, continuing the sound clinical practice of titration of opioid analgesics to effect is all that will be required. The use of intravenous PCA may be very effective in providing patients who are opioid tolerant access to adequate doses of opioid, although an increase of the PCA bolus dose may be necessary. Mixed agonist-antagonist opioids and/or partial agonists should be avoided in patients with opioid tolerance because the use of such agents may precipitate a marked opioid withdrawal syndrome. The use of nonopioid analgesic therapies, neuraxial or regional analgesic techniques, and behavioral techniques for pain treatment is especially to be encouraged in patients who are opioid tolerant to complement opioid therapies. Epidural infusions of bupivacaine and sufentanil have been reported to be efficacious in patients who are opioid tolerant who failed to receive adequate pain control from epidural infusions of bupivacaine and morphine.¹⁷⁸ However, the use of sufentanil should be directed by physicians who are familiar with

TABLE 5. Publications on “accelerated” or “multimodal” postoperative rehabilitation programs

Study	Intervention	Findings
Moiniche et al ¹⁹⁶ (1992; 13 patients; hip replacement pilot investigation)	Epidural analgesia (bupivacaine-morphine), ibuprofen, intensive mobilization regime	11 Patients ready for discharge on day 6; 2 patients discharged on day 9 (traditional hospitalization, 13 d)
Pedersen et al ¹⁶⁵ (1994; prospective study; breast surgery; questionnaires from 373 patients)	Standardized clinical protocols; support from senior management personnel; expanded educational resources for patients	Decreased of length of stay, 39% increase of patient volume, 22%; low incidence of surgical complications;
Weingarten et al ¹⁹⁷ (1994; retrospective, 230 patients; total hip replacement)	Practice guideline: 5-day postoperative stay in “low-risk” patients	Practice guideline can reduce hospital length of stay from 8.4-5.9 d
Moiniche et al ¹⁷⁴ (1995; uncontrolled pilot investigation, 17 patients; open colonic resection)	No nasogastric tube, oral feeding in 24 hrs; early mobilization; VAS zero at rest, minimal with mobilization	Defecation normal in 12 patients within 48 hrs; median hospital stay, 5 d
Liu et al ¹¹⁸ (1995; 54 patients, 4 groups; partial colectomy)	Multimodal recovery program	Epidural analgesia: superior, but more orthostatic hypotension, earlier gastrointestinal function recovery; epidural bupivacaine combined with morphine (best balance of analgesia and side effects)
Collier ¹⁹⁸ (1995; 186 patients; care pathway for elective carotid endarterectomy)	Preoperative education; same-day admission; regional anesthesia; selective use of intensive care unit; discharge in 1 d	10% Intensive care unit admission; 157 patients discharged on first postoperative day; average stay, 1.27 d; cost savings, \$3000/patient
Cooper et al ¹⁴⁶ (1996; 150 patients with advanced chronic obstructive pulmonary disease; bilateral lung volume reduction surgery)	Preoperative patient education and optimization, balanced general-epidural anesthesia, balanced analgesia, early mobilization, intensive chest physiotherapy	Tube removal at end of operation, 149 patients; 90-day mortality, 4%; hospital stay shorter with experience; median stay (last 50 patients), 7 d

this exceedingly potent μ -opioid agonist. The control of pain in patients with opioid tolerance is an example of the complex problems in postoperative pain treatment that may be best coordinated by a multidisciplinary acute pain service.^{66,177}

Pain Treatment in Patients with Drug Addiction

Criteria for the psychiatric diagnosis of opioid dependence¹⁷⁹ are not entirely applicable to those individuals who are receiving opioid anal-

TABLE 5. Cont'd

Study	Intervention	Findings
Mixter and Hackett ¹⁷⁵ (1997; 100 patients; laparoscopy)	Plan of care: pre-emptive analgesia, rapid ambulation, early feeding, non-opioid pain medications	More rapid discharge of patients from the hospital
Macario et al ¹⁹⁹ (1998; 63 patients; knee replacement; historic control subjects)	Defined clinical pathway, epidural anesthesia	Hospital costs (mean \pm SD): \$21,709 \pm \$5,985 (before) vs \$17,618 \pm \$3,152 (after); hospital stay: 6.7 \pm 1.7 d vs 5.7 \pm 0.9 d
Worwag and Chodak ²⁰⁰ (1998; 100 patients; radical in both prostatectomy, 2 pathways: epidural morphine vs systemic methadone analgesia)	Epidural anesthesia, epidural morphine or systemic methadone, early nutrition regardless of bowel activity, predefined discharge criteria	Median hospital stay, 1 d pathways (traditionally the average hospital stay was 4-8 d)
Tovar et al ¹⁶⁶ (1998; 10 patients; lung lobectomy)	Extensive patient education, minithoracotomy, cryoneurolysis for analgesia, early mobilization, early removal of chest tubes	8 patients discharged on postoperative day 1; 2 patients on day 2
Kehlet and Mogensen ¹⁷⁶ (1999; 16 patients, no control subjects; elective sigmoid resection; median age, 71 y)	Combined spinal-epidural , anesthesia epidural analgesia, immediate oral nutrition and mobilization	Median hospital stay, 2 d; no surgical complications
Bardram et al ¹⁴⁰ (2000; 50 patients; median age, 81 y; intended laparoscopic colonic resection; 22% open resection)	Combination of epidural analgesia, early oral nutrition, mobilization for 8 hrs on day 2, avoidance of morphine, tubes, drains, and prolonged bladder catheterization	Pain relief \rightarrow early mobilization in elderly patients \rightarrow accelerated recovery; median hospital stay, 2.5 d in laparoscopic group
Basse et al ⁷⁴ (2000; 60 patients; median age, 74 y; prospective study, no control subjects; elective colonic resection)	Defined postoperative care program: thoracic epidural , analgesia enforced early mobilization, enteral nutrition, planned 48 hour hospital stay	Normal gastrointestinal function returned within 48 hours in 57 patients; median hospital stay, 2 d (formerly, 6-12 d); 15% readmission rate

VAS, Visual analog scale.

gesics for the control of pain. Some of the established criteria are based on the development of tolerance, which may reflect chronic use, but not necessarily addiction (in the context of appropriate medical prescribing). The principal feature of opioid dependence is the continued, compulsive use of opioid analgesic, despite self-harm.¹⁸⁰ These compulsive behaviors or associated harms may not be identified during the initial encounter; rather, these behaviors and consequences become evident over time, as the physician comes to know the patient. Fortunately, in most patients who are

receiving opioid analgesics for the control of pain, the diagnosis of dependence/addiction can be excluded easily.

The diagnosis of opioid dependence should not be based simply on the presence of drug-seeking behaviors. The term *pseudoaddiction* has been coined¹⁸¹ to describe the syndrome whereby the under treatment of pain leads to pronounced drug-seeking behaviors and a crisis in the doctor-patient relationship. By definition, cases of pseudoaddiction are best treated by the initiation of appropriate analgesic therapies. If the diagnosis of dependence is in doubt, consultation with a psychiatrist and/or addictionologist is indicated.

There is marked variability between individuals with opioid dependence who may need pain treatment therapies, depending on whether or not the person is actively abusing opioids, is enrolled in a methadone maintenance or other drug treatment program, or has a history of opioid dependence. A person with a history of opioid abuse who has abstained from opioid use for some time may be hesitant to take any opioid, even for the control of severe pain, for fear of reinitiating dependency. If the patient is in a methadone maintenance program, verification of the daily methadone dose is useful because this may help gauge the extent of opioid requirement. When providing perioperative pain therapy for patients with opioid dependence, it is appropriate and often necessary to titrate opioid analgesics, in addition to using nonopioid analgesic therapies, to provide relief of acute pain. Concern for recidivism should not preclude the use of analgesic therapies for the control of acute, postoperative pain.

Postoperative Delirium and Pain Treatment

Delirium is an acute and fluctuating disturbance of consciousness that is associated with the impairment of both attention and cognitive function. Affected individuals may appear sedated or agitated and frequently experience disorientation, hallucinations, or other perceptual disturbances.¹⁷⁹ Acute, postoperative delirium is well recognized and frequently reported, but the causes and pathophysiologic mechanisms that produce delirium are poorly understood. What is clear is that acute postoperative delirium is a common and serious problem. Various studies have reported the incidence of postoperative delirium to be as low as 2% or as high as 60%.¹⁸² Postoperative delirium is associated with prolonged hospitalizations and markedly increased morbidity and mortality rates.¹⁸³

Increased age is the most consistently reported risk factor for postoperative delirium,¹⁸⁴ but other factors may include poor physical condition, other medical illness, history of alcohol abuse, and multiple medications (polypharmacy). Unfortunately, these known risk factors do not offer sig-

nificant opportunities for intervention toward the prevention of delirium, other than the accepted clinical practice of optimizing an elderly patient's health status before elective operation. Given that advanced age is a risk factor for postoperative delirium, it may be helpful to discuss this potentially life-threatening complication with elderly patients before the operation.

Factors that lead to an embarrassment of cognitive function can have profound effect on pain and its report; pain is a cognitive experience. Knowing that one has had an operation, has an anticipated course of recovery, is under the care of skilled professionals, and has analgesic therapies available can markedly affect pain and pain behavior. If one cannot recall where one is, what has happened, or the identity of other people, then one will not be able to interpret perceived pain normally, and certainly one's response to pain will not be "normal." It is not surprising that many delirious or otherwise cognitively impaired persons experience pain that is "out of proportion to that expected."

Although opioid analgesics (and virtually all other medications that may cause sedation) have been associated with delirium, there is no evidence that withholding adequate analgesic therapy would decrease the risk of delirium. To the contrary, one clinical trial identified a correlation between poorly controlled pain at rest and delirium, whereas no such correlation existed between the cumulative dose of opioid and delirium.¹⁸² In another study, elderly patients who underwent major abdominal surgery and who received epidural analgesia had better pain control, faster return of bowel function, and more rapid clearing of mental status changes than those patients who received systemic opioids.¹²⁰

In patients with acute postoperative delirium, the fluctuations in attention and mental status may confound appropriate attempts to titrate analgesics. It is recognized that if people can carry out meaningful communication to any significant degree, they will likely be able to report current pain accurately. Therefore, even in acute delirium, it is appropriate to accept a person's self-report of pain as valid. Although the use of nonopioid analgesic therapies should be emphasized in the care of patients with delirium, it is appropriate to use short-acting opioid analgesics as needed, titrated to effect.

Phantom Limb Pain

Phantom limb pain is a well-recognized problem after amputation. It is essential to distinguish between phantom limb sensation, phantom limb pain, and stump pain because they are distinct in character and likely represent different underlying mechanisms. There are many studies that do not make this distinction and blur the available information on this com-

plex problem. Although most commonly recognized and studied after the amputation of a limb, phantom pain also occurs after amputation or removal of other organs, such as breast, tooth, penis, or visceral organs.¹⁸⁵

The pathophysiologic features of phantom pain are not well understood. Both peripheral and central mechanisms have been proposed to explain this phenomenon. The literature suggests that spinal cord mechanisms play an important role in the generation and modulation of phantom pain. Because there is not a single mechanism that could explain the observed variety of phantom pain phenomena, Melzack¹⁸⁵ proposed that these phenomena could be explained better by the concept of a neuromatrix. According to the neuromatrix theory, the altered input (ie, lack of sensory input after amputation or excessive input from damaged nerves) modifies the pattern generated by the neuromatrix, which results in an output that is experienced as phantom pain. Psychologic and social factors can also produce input that alters the matrix, which affects phantom pain.

The onset of phantom pain is variable and may occur immediately after an amputation or have a delayed onset of weeks, months, or years. Epidemiologic data regarding phantom pain exist only for phantom limb pain. In summarizing prevalence estimates drawn from studies that incorporated a period of observation after amputation, it appears that the prevalence of phantom limb pain ranges between 53% and 72% and remains relatively constant over a period of at least 5 years.¹⁸⁶ The data are too limited to make any general statements beyond this time frame, although there are certainly individuals who are plagued by phantom pain for much longer than 5 years.

Based on what limited information we do have regarding potential risk factors, there does not appear to be a relationship with age. Preoperative pain may be a factor, but there is not universal agreement across studies. Jensen and colleagues¹⁸⁷ report the association between preoperative pain with the presence of phantom limb pain at 8 days and at 6 months, but not at 2 years, which indicates that perhaps this association is time-dependent. There may be other risk factors for phantom pain that have not been studied systematically, which may prove to be relevant to attempts at preventing the development of phantom pain.

There are ongoing investigations to determine the role of pre-emptive measures in the anesthetic preparation of patients who undergo amputation to reduce the risk of phantom limb pain. Methodologic concerns have made comparisons across published pre-emptive studies difficult, which result in uncertainty about the role of epidural analgesic techniques in the prevention of the development of phantom limb pain after surgical amputation.¹⁸⁸⁻¹⁹⁰ Surveys of amputees show that few patients with established

phantom pain receive treatment.¹⁹¹ Currently, there are no specific interventions that clearly prevent or treat phantom limb pain. Treatment strategies resemble those strategies that are used for neuropathic pain in general. Stump revision for persistent phantom pain is unlikely to provide significant benefit in most cases; however, carefully selected surgical intervention may assist in the treatment of stump pain because of localized neuroma.

Future Developments in Perioperative Pain Treatment

Clinical Research Directions

There are various broad directions of clinical research in the field of pain treatment. Briefly described are areas that are related to new analgesics and their combinations, new techniques (in both surgical and anesthetic approaches), and the impact of new settings of health care and policies. Broad as these may seem, by no means do they represent a complete list of the vast opportunities for clinical investigation in perioperative pain treatment.

New Agents. COX-2 inhibitors have already demonstrated analgesic efficacy similar to NSAIDs with improved gastrointestinal safety in the settings of osteoarthritis, rheumatoid arthritis, and acute pain. Nevertheless, COX-2 selective inhibitors continue to be developed, with a focus on enhanced receptor specificity and on a broader range of administration routes (ie, intravenous). Clinical trials are already underway to determine the safety and efficacy of these agents and are anticipated to document usefulness in a variety of clinical settings, including the perioperative period. New local anesthetics are currently in clinical trials. Alternative approaches to produce prolonged local anesthesia include sustained release formulations that use existing local anesthetics and the development of new classes of local anesthetics. Future directions may include targeting drugs to specific sodium channel subtypes or other ion channels, including calcium and potassium channels.

New Drug Combinations. Investigation of the therapeutic usefulness of combinations of analgesic agents is another area of ongoing study. Recent advances in understanding pain mechanisms have led to a growing recognition that polypharmacy may play an important role in the treatment of pain. For example, one might hypothesize that a modulator of central sensitization (ie, gabapentin) might potentiate analgesia from NSAIDs in the treatment of inflammatory pain. Not only might such combinations leverage multiple modes of action on a potentially complex (multimodal) problem, but also combined preparations may ease patient compliance. In addi-

tion, the potential for “dose-sparing effect,” such as that seen with opioids when used in combination with nonopioid analgesics, has the potential advantage of reducing the risk of adverse effects that are observed with single agents at higher doses. Although challenging in design complexity, we can anticipate future clinical trials of combination therapies as our understanding of underlying pain mechanisms evolves.

Innovative Techniques and Their Relative Cost/Benefit Ratios. Innovative regional anesthetic techniques continue to evolve to provide satisfactory surgical anesthesia, potentially diminish adverse effects that are attributed to general anesthetics, and analgesia that extends into the postoperative period. On the other hand, with the evolution of less invasive surgical approaches (such as endoscopic procedures), the added benefits of regional techniques may be less apparent. New does not always mean better. The relative cost and benefits of innovation must be considered continually in the entirety of the perioperative setting to determine the best strategy of care.

Monitoring Outcomes. Particularly in the setting of a rapidly changing health care environment, there is much need for health services research to determine the adequacy of pain treatment methods using patient-centered outcomes. For example, preliminary findings show that, despite an increasing trend toward ambulatory surgical procedures, pain control and analgesic side effects continue to be a significant problem.¹⁹² Overcoming barriers to providing patients with information or counseling regarding pain treatment must be widespread to provide optimal treatment of postoperative pain. Although data do not support the assumption that adequate postoperative analgesia alone improves outcome, there are outcome data to support the role of postoperative analgesia when integrated into a multimodal accelerated recovery program.¹⁹³

Economic Analyses. The value of incorporating improved postoperative pain therapies into routine perioperative care paths should be realized in improved outcomes and improved relief of pain to all surgical patients. To date, this value has not been adequately demonstrated, except in specific subgroups of patients. Further research is needed in a variety of patient groups to assess thoroughly the value and cost-effectiveness of enhancing postoperative pain treatment programs. Such research efforts will require a focus on defining the limiting factors that keep patients in the hospital after surgical procedures. Only when good data about outcomes are available is it feasible to design care paths that will address the limiting factors that are specific to each procedure. Redesigning these care paths may involve modifications of the surgical procedure (ie, laparoscopic instead of open procedure when feasible), balanced analgesia with decreased opioid

use, changes in postoperative nursing care, early oral feeding, and early intensive physiotherapy and mobilization. Preliminary data suggest that such approaches can result in accelerated recovery, improved patient well-being, and shortened hospital stays. Converting these outcomes to economic terms will be the next challenge.

Training a New Breed of Clinician

Successful treatment of any patient with pain—acute, chronic, or cancer-induced—demands an understanding of and attention to the biopsychosocial model of pain and of pain management and rehabilitation. Education and training of clinicians in this relatively new area must bridge all aspects of medicine. Although formal fellowship training in pain management has been available through many anesthesiology training programs, interest in this field is growing among physicians with other training backgrounds (ie, rehabilitation medicine, neurology, psychiatry, surgery). Based on an awareness of the complexity of pain, all pain treatment fellowship training programs are required to provide instruction to trainees in multidisciplinary pain treatment. Hopefully, the scientific, educational, training, financial, and patient-outcome considerations will drive a change toward integration of acute, chronic, and cancer pain programs and lessen the tendency toward isolated acute pain service delivery.¹⁹⁴ However, physical location, specialty “turf,” and individual attitudes and practice patterns may limit the enthusiasm for change in many institutions and health care services. Therefore, despite the potential major gains in humanitarian, patient outcome, and economic terms, there will be major hurdles in changing attitudes, practices, and systems.

Administrative Planning

One of the ongoing challenges for administrative planning is to find mechanisms to support the broad availability of improved pain treatment therapies. Current reimbursement structures do not motivate wider incorporation of improved pain therapies into routine perioperative practice. Consequently, perioperative pain treatment services are often limited to selected patient populations. There is little room for doubt that accelerated postoperative recovery cannot be accomplished without the optimization of pain control and analgesic techniques. Despite the resource implications of pain treatment interventions, few studies to date have explicitly considered financial ramifications in terms of net savings per patient. Although some studies use medication intake or length of hospital stay as outcome measures, they fail to convert these into direct estimates of economic impact. Ongoing quality improvement of care is an essential feature

of administrative planning for the optimization of pain treatment therapies.¹⁷⁷ One strategy to make improved pain treatment therapies less expensive and more universally available to patients who undergo surgical procedures is to integrate more widely nursing services with pain control services.¹⁹⁵ The new pain treatment standards introduced by the Joint Commission on Accreditation of Healthcare Organizations⁴⁹ may facilitate the integration of pain therapies into broad areas of clinical practice. Careful collaboration with surgeons and other health care professionals to develop pain treatment strategies into accelerated rehabilitation programs will require concerted physician effort and ongoing leadership by pain treatment specialists.

Conclusion

The gate control theory and all that we have learned regarding nociception and nervous system processing points to a multimodal approach for effective pain treatment. The development of optimal postoperative recovery services will require close collaboration between anesthesiologists, surgeons, nurses, physical therapists, administrators, and others involved in the treatment of patients after operation. Optimization of perioperative care will, of course, be an ongoing process that will be enhanced by clinical investigation. However, making significant improvements to clinical practice need not wait for additional research data but should proceed now, with broader application of techniques known to enhance rehabilitation and recovery. The challenges of the delivery of ideal perioperative recovery services seem likely to be rewarded with improved patient outcomes and reduced cost. Hopefully, a dedicated focus on the needs of patients and the opportunity for financial savings will help to continue the trend that has already begun.

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