Editor
Marion E. Doctor, LCSW
Denver, Colorado

Pain management in burn patients consistently occupies a position of prominence at national and regional burn conferences and in related publications. Burn care professionals have come to acknowledge the importance of optimal pain management and have been challenged to increase their knowledge base surrounding this critical aspect of burn care. The understanding and management of pediatric pain management has presented an even greater challenge.

This article is the last in a series of articles devoted to pediatric pain management. The series is presented in the spirit of acknowledging contributions of dedicated researchers and clinicians and of providing a consolidation of materials spanning theoretical understanding and practical application.

My thanks to the authors and to those who have served as guest editors. Their knowledge of the topic matter and sensitivity to the comfort level of young burn patients is inspirational and gratifying.

A special thanks to Thurber, Martin-Herz, and Patterson for their excellent two-part article, The Psychological Principles of Burn Wound Pain in Children I. Theoretical Framework, and II. Treatment Applications, which provided a framework upon which to build and understand subsequent material. And to Stoddard, Sheridan, Saxe, King, Chedekel, Schnitzer, and Martyn for one of the most comprehensive and thorough articles written on the treatment of burn pain. Your collective efforts have provided a major contribution to the treatment of pediatric burn patients.

Treatment of Pain in Acutely Burned Children

F. J. Stoddard, MD, R. L. Sheridan, MD, G. N. Saxe, MD, B. S. King, MD, B. H. King, MD, D. S. Chedekel, EdD, J. J. Schnitzer, MD, PhD, J. A. J. Martyn, MD
Boston, Massachusetts

The child with burns suffers severe pain at the time of the burn and during subsequent treatment and rehabilitation. Pain has adverse physiological and emotional effects, and research suggests that pain management is an important factor in better outcomes. There is increasing understanding of the private experience of pain, and how children benefit from honest preparation for procedures. Developmentally appropriate and culturally sensitive pain assessment, pain relief, and reevaluation have improved, becoming essential in treatment. Pharmacological treatment is primary, strengthened by new concepts from neurobiology, clinical science, and the introduction of more effective drugs with fewer adverse side effects and less toxicity. Empirical evaluation of various hypnotic, cognitive, behavioral, and sensory treatment methods is advancing. Multidisciplinary assessment helps to integrate psychological and pharmacological pain-relieving interventions to reduce emotional and mental stress, and family stress as well. Optimal care encourages burn teams to integrate pain guidelines into protocols and critical pathways for improved care. (J Burn Care Rehabil 2002;23:135–156)

How should pain in the burned infant, child, or adolescent be managed? What does the control or elimination of burn pain imply for the development of a child? Are analgesic requirements still underestimated, and are psychological methods neglected in burn care?[1] Do new drugs and research on genes hold promise for better pain management? Pain has become a major focus of burn care, new research, and medical training in the last 10 years. It is essential to differentiate, with the patient's help, the source of

pain, whether from the burn injury, surgery, amputation, debridement, physical therapy, or other causes. Because contemporary burn care is collaborative, this multidisciplinary team of authors who work together join in this article to review pain treatment from basic science to clinical levels.

PAIN FROM INFANCY THROUGH ADOLESCENCE

There has been a dramatic shift from efforts to enable children to cope with pain[2] to targeted efforts for the prevention,[3,4] continuous assessment and treatment of pain and anxiety. Recent publications address posttraumatic,[5] psychiatric[6] and neurobiologic aspects of burn pain at different postburn and developmental stages as well as its management,[7] but both the science and clinical practice are rapidly changing. No longer does pain hold a secondary place in providing life-saving care to the burned child. Pain is an essential focus in critical pathways, practice guidelines, and treatment monitors, and the relief or prevention of the excruciating suffering of burned children is increasingly achievable.

A primary medical task on the burn unit is the relief of pain and anxiety, each of which can exacerbate the other. Pain can be the most common reason for psychiatric consultation requests to a burn unit.[8] Diagnosis of mental disorders is essential to providing efficient and safe pain relief. Preexisting vulnerabilities, including mental disorders, may render a child at increased risk of trauma due to unrelieved burn pain. Diagnosis of preexisting abuse, attention deficit hyperactivity disorder, depression, psychosis, mental retardation, or conduct disorder will influence the choice of diagnostic procedures, precautions, and pain-relieving methods. Also influencing overall care are new diagnoses such as delirium, brain injury, acute stress disorder, or substance abuse. Failure to recognize and address absence of pain response in the abused child or in the chemically paralyzed patient or suicide risk in the delirious or depressed patient or high blood alcohol levels, may lead to preventable suffering or even death.

This review addresses major aspects of pediatric pain relevant to burn pain, based on the current scientific literature. The biochemistry of pain is being elucidated at the genetic, cellular, systemic, and neurobiological levels, with an increasing array of pharmacological agents acting at these levels available to reduce pain. Pharmacological and imaging research promise to further elucidate the mechanisms of action of both pharmacological and psychological methods of pain reduction. The anatomy of burn pain is clarified below and plays a major role in choice of treatment. Advances in pain assessment from infancy on up are one source of reliable and valid methods to evaluate pain and pain treatment. We describe, generally, the methods of pain assessment as well as the adverse consequences of untreated pain. The principles and methods of pain management are described in detail, including tested protocols currently in use. The review ends by addressing ethical aspects of pain management, conclusions from this review, and future directions.

One major consequence of recent progress in pain management in critical care is the goal to prevent, identify, and treat stress disorders caused by pain to infants, children, and adolescents—recently termed a new frontier in critical care.[9] Opiates have been associated with reducing subsequent stress, but other pharmacological agents and psychological methods also reduce stress.[4,10] Further, there is evidence associating anxiety and stress with other factors such as preexisting psychopathology, surgery, parental presence, social stigmatization, and lack of protocols for pain management.

Together with other references provided here, and in recent articles on this topic in this journal, this review is a guide to current understanding of pain management in burned children. It points the way to future developments in burn pain management.

Anatomy of Burn Pain

Several important concepts, not generally known, about pain mechanisms are explained here: pain receptors in the skin (nociceptors), the opioid system, increased pain sensitivity (hyperalgesia), and the emerging role of the enzyme cyclooxygenase 2 (COX 2) and new drugs which inhibit it. Pain associated with an acute burn or other tissue injury is transmitted by peripheral nociceptors, the peripheral endings of primary sensory neurons whose cell bodies are in the dorsal root of the spinal cord and trigeminal ganglia. Unlike other sensory receptors in the skin, nociceptors are without specialized transducing structures, and essentially exist as free nerve endings. Different classes of nociceptive fibers can be involved in the experience of burn pain (Table 1).

Thermal or mechanical nociceptors convey stimuli rapidly (up to 30 meters per second) via thinly myelinated, small diameter fibers classified as "A" or "A delta." Polymodal nociceptors are also activated by hot stimuli, but transmit impulses more slowly (up to 2 meters per second) along small-diameter unmyelinated "C" fibers. Both A delta and C fibers are widely distributed in skin and in deep tissues.[11] Nociceptive fibers, both A and C,

Table 1. Characteristics of Nociceptors

Type	Diameter	Myelination	Conduction Rate	Distribution
A-delta	1–4 μ	Yes	Upto30m/sec	Skinanddeeptissues
Polymodal (C)	0.2–1 μ	No	Upto 2m/sec	Skinanddeeptissues

enter the dorsal horn of the spinal cord and split into ascending and descending branches. The fibers terminate primarily in laminae I and II, although some A fiber afferents may terminate more deeply in lamina V. Within lamina I, different projection neurons process incoming stimuli. "Nociceptive specific" neurons are only excited by nociceptors, but "wide dynamic range" neurons receive their input from both nociceptors and other mechanoreceptors.

Several ascending pathways convey afferent stimuli to the brain. The spinothalamic tract is the major ascending pathway for nociceptive input and originates in laminae I and V-VII. The nociceptive-specific and wide dynamic range projection neurons in this tract terminate in the contralateral thalamus, particularly ventrobasal and posterior thalamic nuclei. The spinoreticular tract originates in laminae VII and VIII and sends both ipsilateral and contralateral projections to the reticular formation and thalamus. The spinomesencephalic tract originates in laminae I and V where it projects to the contralateral mesencephalic reticular formation, the periaqueductal gray, and other sites within the midbrain. The spinocervical tract, and even the dorsal column of the spinal cord also can convey nociceptive stimuli. Also, in the dorsal horn, A-B fibers conveying sensations such as vibration and light touch are involved in the modification of pain transmission via inhibitory interneurons.

There are multiple projections from thalamic nuclei to the cortex, primarily somatic sensory and association cortex. And while at least two classes of somatosensory cortical neurons can be identified with respect to their receptive fields and source of thalamic input, nociceptive inputs do not map to the cortex as do tactile inputs. Further, lesions to somatosensory cortex do not result in loss of pain, suggesting that parallel or distributed processing of nociception in the cortex is likely.[11] Recent studies examining cortical activation after painful stimuli highlight the multiplicity of regions involved including the contralateral prefrontal cortex including the middle and inferior frontal gyrus (Brodmann areas 6, 8, 9, 44, and 45).[12]

The intense barrage of incoming pain stimuli associated with a burn results in a decrease in thresholds for subsequent excitation of spinal neurons, as well as a greater response to subsequent stimuli and an expansion of receptive fields.[13] All of these adaptive changes likely underlie the increased pain sensitivity, or "hyperalgesia" that typically follows a significant burn injury. Hyperalgesia has long been characterized as "primary" if limited to the area of injury, or "secondary" if it extends to areas adjacent to the site of damage.[14] Primary hyperalgesia appears to require sensitization of both peripheral nociceptors and spinal neurons, whereas secondary hyperalgesia seems to depend on sensitization of spinal neurons alone.[15,16] Both types of increased pain sensitivity can occur immediately after injury, but secondary hyperalgesia may take hours before reaching its peak and is likely to resolve before primary hyperalgesia.[17] Interestingly, recent data suggests that chemosensitive nociceptors can be recruited to become mechanosensitive receptors after injury.[18] This ability to recruit otherwise "silent" nociceptors may play a role in primary hyperalgesia after burn injury (Table 2).

Any large (>20% TBSA) burn injury results in a local and systemic response which includes fever, anorexia, and pain in the injured (primary hyperalgesia) and uninjured areas. Until recently, as indicated in the previous paragraph, this sensation was thought to occur by transmission of impulses via nerve impulses from the injured region to the spinal cord to the brain.[19] Recent evidence[20] suggests that other mechanisms in addition to nerves may play a role. Drugs that silence sensory nerves work well to relieve acute pain. When inflammation occurs drugs effective for acute pain are less effective. Local inflammation at the site of injury (eg, burn) causes rapid and long-lasting increase in the proinflammatory signal-

Table 2. Hyperalgesia

Type	Location	Mediators	Timing from Injury
Primary	Limited to injury	Peripheral nociceptors spinal neurons	Immediate
Secondary	Injury and areas adjacent	Spinal neurons	Immediate and delayed

ing molecule in the brain, especially interleukin-1B in the CSF. Blockers of interleukin 1B (eg, COX-2 inhibitors) strongly inhibited the hypersensitivity to pain.[19,20] Increased levels of interleukin-1B causes increased expression of cyclooxygenase-2 (COX-2), and prostaglandin E synthase with resultant increase in prostaglandin E_2. Thus the use of COX-2 inhibitors currently available will not only have anti-inflammatory and antipyretic effects but also have antihyperalgesic effects, by acting at local and central sites. Among those available are celecoxib (Celebrex™, Pfizer, Inc., New York, NY), rofecoxib (Vioxx®, Merck & Co., Inc., West Point, PA), nimesulide, and meloxicam (Mobic®; Boehringer, Ingelheim Pharmaceuticals, Inc., Ridgefield, CT).

Genetics

This section briefly outlines new discoveries in the genetics of pain, especially the genes which affect how opiates work, and important genetic determinants of racial differences to drug response. Laboratory research is clarifying the synthetic and degradative pathways by which the levels of endogenous opioids are maintained in the body.[21,22] In addition to the clarification of the dynorphin gene, the neural systems involved in pain and anxiety have been located, and the neurobiological development, and genetic control of those systems is being worked out also. Osgood and Szyfelbein[23] state that " a major impetus to this work is the discovery of stereo-specific opioid binding sites (receptors) in the central nervous system (CNS) and the endogenous opioid substances (endorphins) that bind to with these receptors." The three classes of peptides, which are known, include the endorphin, met-leu-enkephalin, and dynorphin. These systems are affected by the monoamine (dopamine, norepinephrine, and serotonin) systems, substance P, and the GABA (gamma-aminobutyric acid) system—each with their own specific brain receptor sites. Selection of analgesics such as anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, narcotics, benzodiazepines, anticonvulsants, and adjuvants (eg, stimulants, tricyclic or serotonergic antidepressants, neuroleptics) may be made to target those systems.

Many studies in burn injury and pain in humans have not described ethnic or racial background of their subjects. In spite of this limitation, findings from one study are applied to other ethnic and social groups. The importance of genetic factors controlling drug disposition and response has received increased attention.[24] The so-called standard doses of a drug may have toxic effects in some but fail to produce expected effect in others. These differences can be due to pharmacokinetic, pharmacodynamic, or pharmacogenetic factors. Racial and ethnic differences have been described for a range of drugs and reflect genetic, environmental (cultural and dietary), and pathogenetic causes. Polymorphism of drug metabolizing enzymes (eg, CYP 2D6 of the cytochrome P450 system) is well recognized and can affect drug therapy, such that lower or higher drug doses should be used. The identification of such genetic differences will result in better therapeutics. The role of pharmacogenetics can be confounded also by burn-induced alterations in drug metabolism.[25]

Biochemistry of Pain During Development

Although the neurotransmitters and other signaling molecules involved in pain pathways are generally expressed early on in human development, their ontogeny is characterized by transient overexpression in amounts and in locations not seen in adulthood.[26,27] For example, Åkesson and colleagues[28] have shown that glutamate receptor subtypes are present at least as early as 4 weeks gestational age in the human fetal spinal cord. Further, the distribution of these receptor subtypes is homogeneous, and does not become restricted to the dorsal cord until 11 weeks of gestation. Substance P terminals also appear in the substantia gelatinosa at about this time.[29] Taken together with data suggesting that NMDA-mediated excitation is greater in the immature CNS, Fitzgerald[26] posits that wind-up and central excitability evoked by C-fiber stimulation may be more apparent in the neonatal spinal cord than that found in adulthood. With respect to opioidergic systems, the full complement of receptor subtypes and opioid peptides appears to be present at birth, but dramatic increases characterize opioid receptor binding sites and/or coupling with their respective G-proteins during the first weeks of life. In the rodent, this increase translates to a significant amplification of opioid-mediated analgesic properties.[30]

It is widely recognized that systemically administered opioids provide analgesia through their actions on the central nervous system. The receptors which modulate pain sensations include the u, o, and k opiate receptors.[31] The opioid receptors are part of a super family of G protein-coupled receptors possessing seven membrane-spanning regions.[31] The principal result of activation of the opioid receptor is reduced neurotransmission, occurring mainly by presynaptic inhibition of neurotransmitter release, although postsynaptic inhibition may also occur. Analgesia caused by microinjection of opioids at various sites in the CNS results from activation of descending antinociceptive pathways originating in the midbrain-periaqueductal gray matter, and this analgesia inhibits transmission of nociceptive messages

(eg, pain messages relayed from free nerve endings) from the spinal cord.[32] Injection of opiates at the spinal cord level also produces profound analgesia which can be effective in relief of burn pain.

Recent research clarifies that nociception can occur or be modulated at the peripheral nerve terminals as well.[33] Opioid receptor-mediated analgesia manifests considerable plasticity, and is not a simple on-off phenomenon. Opiate receptors are synthesized in the cell bodies of nociceptors in the dorsal root ganglion, and are transported within the ganglions both centrally and peripherally.[17] Peripheral activation of opioid receptors may occur as a result of release of endogenous ligands by immune cells infiltrating inflamed tissue.[16,33] The opioid receptors in the peripheral nerves can be activated or upregulated due to injury, and can either directly decrease neurotransmitters or inhibit the release of excitatory neurotransmission such as substance P and thereby modulate the perception of pain.[17,33] Sensitization of primary afferent nociceptors by pharmacological agents occurs via activation of stimulatory G proteins, with activation of adenyl cyclase and an increase in levels of cyclic adenosine monophosphate (cAMP), the second messenger of nociceptor sensitization. In blocking this change in altered or increased sensitivity, opiates activate *inhibitory* G proteins, which inhibit adenylate cyclase and decrease production of cAMP. Several other substances in addition to prostaglandins cause sensitization through increased levels of cAMP. Therefore, this is another justification for the use of NSAIDs or COX-2 inhibitors in treating pain induced by inflammation.[19] Some reports describe the use of peripheral opioids to treat inflammation-induced pain through instilling small quantities of opiates locally directly into the region of injury.[33,34] This has been found useful in treatment of localized burn pain, but has not been tested for extensive burns.[34] The finding that large doses of topical lidocaine significantly relieved burn pain confirms the importance of peripheral opiate receptors.[35]

Classically opioids produce analgesia and side effects after acute administration. However, after chronic administration, tolerance and dependence can develop. Recently it has been recognized that tolerance can develop acutely also.[36] Acute tolerance can also lead to hyperalgesia. Activation of N-methyl-D-aspartate (NMDA) receptors in the CNS after noxious stimuli underlies the development of the hyperalgesic state and transmission of signals interpreted as pain.[37] The hypothesized underlying mechanism is that opioid receptor activation leads to increased protein kinase C activity (PKC) which phosphorylates target proteins including NMDA receptors. This phosphorylation of NMDA, by further demonstrating signaling effects, leads to opioid receptor downregulation (underlying tolerance) and hyper-responsiveness (underlying hyperalgesia). Thus the administration of NMDA antagonist, ketamine, prevents opioid-induced hyperalgesia and also overcomes the tolerance to analgesics.[38] Thus ketamine, used for four decades to treat burn-induced pain, now makes pharmacological and clinical sense.

METHODS OF PAIN ASSESSMENT

Pain is, by definition, a private experience. This poses unique challenges for its objective assessment. These challenges are particularly relevant for infants and young children who are not able to report on their own experiences. Accordingly the measurement of pain in children has developed to assess both the self-report of pain experience and the observations of behaviors that suggest pain. This latter type of measurement is inherently problematic as it requires an inference on the part of the clinician that the behaviors correspond to the actual subjective experience of pain. Behavioral observations have largely been developed to assess pain in infants and young children. Self-report measures are usually used for children above the age of four but they do require sufficient cognitive and language abilities to be accurate. Older children with limited cognitive and language skills may not be able to accurately complete self-report measures of pain.

Assessing Pain in Infants and Young Children

The methods to assess pain in infants and young children[39] usually relate to either the infant's behavioral or physiological reactions to painful signals. This assessment requires an inference that these reactions truly correspond to the internal experience of pain. Studies of neonatal intensive care nurses have reported that the most common indices used to assess pain in infants was crying and increased locomotor activity.[40] Such indices may be quite inaccurate in intensive care settings as tracheal intubation may limit crying and pharmacological treatment may limit activity. Surveys of pediatric anesthesiologists have reported that infants respiratory rate is more commonly used by that group of clinicians as an indicator of pain.[41] A variety of behavioral indices have been used with infants and young children. Facial expression has been studied and a variety of coding systems have been developed to link specific changes in facial muscle movement with a variety of emotional states including pain.[42–45] Body movement, particularly limb withdrawal to painful signals[41,46] and vocalizations,

particularly crying[47] have also been successfully employed as a behavioral measure of pain in very young children. Psychophysiological indices have included blood pressure, pulse, respiratory rate, and neurochemical activity.[48] Recent research on very young children has used measures with combined behavioral and psychophysiological indices, for example, the COMFORT scale[49] has been used to assess postoperative pain. Psychometric studies of this instrument have found that the variables that most accurately measured pain were behavioral activity, mean arterial pressure, and heart rate.[50] The Premature Infant Pain Profile uses such indices as behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow to accurately assess pain.[51,52] Given the complexities of assessing pain in infants and very young children, this research which uses empirically validated combinations of behavioral and psychophysiological indices is an extremely promising line of research and can be integrated into clinical practice.

Assessing Pain in Older Children

A variety of methods have been used to assess pain in children older than four. These measures take advantage of children's increasing abilities to describe their own symptoms and experience as they get older. Accordingly, many scales have been developed which are both clinically useful and which have acceptable psychometric properties.[53] The Poker Chip Tool[54] has been developed for children ages 4 to 8 years old to describe their pain as "pieces of hurt" using one to four poker chips. This measure is highly clinically useful as it allows younger children to describe their symptoms using a method that is developmentally appropriate for this age group. The Faces Scale[55] is a measure of pain which asks children to choose a picture of a face with expressions of various gradations of pain. The Faces Scale has good psychometric properties and is easily used by school aged children. It has a high degree of clinical utility. Numerous visual analogue instruments have been developed which ask children to describe their pain on a continuum of intensity along a line using numerical anchors. Visual Analogue scales are widely used, have good psychometric properties and are easily administered to children. More recently McGrath[56] has enhanced the psychometric properties of ordinary visual analogue instruments by adding color to the intensity rating. Pain diaries have emerged as being useful for older children and adolescents. Pain diaries require the repeated numerical rating of pain over the course of time along with other relevant information such as activities, stressors, or medications. Pain diaries can be very useful to both plan and assess treatment of pain in older children (Table 3).

Clinical Approaches

The objective of pain assessment is to 1) detect the presence of pain, 2) estimate the impact of this pain, and 3) determine the impact of interventions designed to relieve pain.[39] Research and clinical care of children have developed so that clinicians have many tools at their disposal to accurately assess pain at the bedside and in the community. There are thus great opportunities to help children with burns through accurate assessment and the corresponding construction of interventions for pain. Although the most challenging area of pain assessment is in infants and very young children, measures such as the COMFORT scale have developed as empirically grounded measures of pain using behavioral and psychophysiological indices. For preschoolers, the Poker Chip Tool is an excellent measure of pain. Clinicians can easily use the Faces and Visual Analogue Scales for

Table 3. Descriptions of Pain Ratings According to Utility by Age

Measure	Description
Infants and Very Young Children	
Premature Infant Pain Profile	Behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow to assess pain
COMFORT Scale	Combined behavioral and psychophysiological indices
Preschoolers	
Poker Chip Tool	Description of pain as "pieces of hurt" using one to four poker chips
School Age	
Faces Pain scale	Description of pain as a picture of a face with expressions of various gradations of pain
Visual Analogue Scales	Description of pain on a continuum of intensity along a line using numerical anchors
Adolescent	
Pain Diary	Repeated numerical rating of pain over the course of time along with other relevant information such as activities, stressors, or medications

school age and older children. Pain diaries are useful measures for preadolescents and adolescents.

OVERVIEW: METHODS OF PAIN MANAGEMENT

Variability and a lack of predictability characterize the relationship between burn pain and virtually any other factor including severity of injury, age, sex, ethnicity, education, occupation, and socioeconomic status.[57] Further, pain after burn injury will have different temporal courses and causes, for example, that associated with the injury, with grafting procedures, with therapeutic procedures—particularly debridements, and even after wound healing.[58] Consequently, opportunities for pain management vary both by type and by time. Henry and Foster[59] have generated a time line for problems, treatments, and supportive care in the burn patient that highlights the complexity of care and the potentially overwhelming number of opportunities for the experience of pain.

Pharmacological approaches are the mainstay of treatment and will incorporate different strategies depending upon whether the target symptom is pain at rest, or due to procedures. Emotional distress, including traumatic memories, anticipatory fears about treatment and recovery, and confinement in a new and potentially frightening hospital environment all may contribute to pain and form the focus of psychotherapeutic intervention. Among the many specific intervention strategies are cognitive behavioral therapy, relaxation training, hypnosis and guided imagery, biofeedback, distraction, and art, music, and play therapies.[58–62] Massage, acupressure, application of ice and heat and therapeutic touch are also used in a complimentary way with pharmacological analgesia.[58,63] Psychoeducation for children and families is particularly critical, and rehabilitation is best introduced and emphasized from the start of hospitalization.[58,59]

It is particularly valuable to stop pain before it starts, because once it has begun, relief of pain is much more difficult, and the associated conditioned anxiety response complicates pain management. Clear "up-front" protocols have been developed for use by all members of the burn team, to reduce the risk of a child developing a conditioned anxiety response to pain. Defining the types of pain or anxiety which occur during burn care is part of such a protocol. "Background" is defined as steady state pain from wounds or steady state anxiety related to illness and immobility. "Procedural" is defined as increased pain or anxiety related to dressing changes, line insertions, physical therapy, or other procedures. "Breakthrough" pain or anxiety is defined as that which increases above baseline level for reasons not related to procedures. "Postoperative" is pain or anxiety occurring on emergence from anesthesia related to operative site stimulation (eg, donor sites, incisions, etc) (Table 4).

This example of a protocol,[64] addressing different categories of patients is described in more detail below under "Shriners Burns Hospital, Boston, Guideline for Pain Management." The rest of the article describes adverse effects of pain, its pharmacological and psychological management, practical guidance for the burn team, ethical issues, and future directions.

ADVERSE EFFECTS OF PAIN

The large burn (greater than 20%) is an altered physiologic condition characterized by a massive sympathetic outflow mediated by the hypothalamus.[65] Surgical treatment leads to a similar sympathetic response.[66] The neurohumoral response to burns and surgery is an extreme elevation in catecholamines, insulin, growth hormone, antidiuretic hormone, beta-endorphin, aldosterone, glucagons, thyroxine, and interleukins.[67] The quantity of the stress response is related to the magnitude of the injury.[68] Higher plasma levels of the stress response markers further correlates with increased morbidity and mortality.[67]

The counter-regulatory hormones lead to a catabolic state of increased oxygen consumption, glycogenolysis, lipolysis, and gluconeogenesis.[69] The effects seen include perioperative lactic acidemia, hypoglycemia, and negative nitrogen balance.[70] Comparable insults between infants and adults demonstrate a greater catabolic state induced in infants than in adults.[71,72] The catabolic effect of the stress response may be partly due to dysfunction of the hypothalamic-pituitary axis.[73] The resulting redistribution of proteins from skeletal muscle to provide substrate for vital organs diminishes immune function and impairs wound healing.[74,75]

Attempts to minimize the stress response have been most successful with epidural blockade in surgical patients.[76–78] However, this is not a safe option in septic children with massive burns where concerns of infection of the CNS precludes transcutaneous administration of agents. Narcotics and anxiolytics are therefore used liberally to attenuate the physiologic impact of pain. Sufficient doses of opioids can blunt the stress responses to trauma and surgery by reducing neuroendocrine activation of regulating hormones.[79]

Significant stress-related neuroendocrine changes may affect the actual growth and architecture of the brain, which could have a lifelong impact on arousal and the processing of emotional stimuli.[80,81] Accord-

Table 4. Guidelines for Pain and Anxiety Management

Patient Category	Background Pain	Background Anxiety	Procedural Pain	Procedural Anxiety	Transition to Next Clinical State
Category 1: Mechanically Ventilated Acute	Morphine sulfate intravenous infusion	Midazolam intravenous infusion	Morphine sulfate intravenous bolus	Midazolam intravenous bolus	Wean infusions 10–20% per day and substitute nonmechanically ventilated guideline
Category 2: Nonmechanically Ventilated Acute	Scheduled enteral morphine sulfate	Scheduled enteral lorazepam	Morphine sulfate enteral or intravenous bolus	Lorazepam intravenous or enteral bolus	Wean scheduled drugs 10–20% per day and substitute chronic guideline
Category 3: Chronic Acute Patient	Scheduled enteral morphine sulfate	Scheduled enteral lorazepam	Morphine sulfate enteral bolus	Lorazepam enteral bolus	Wean scheduled and bolus drugs 10–20% per day to outpatient requirements and pruritus medications
Category 4: Reconstructive Surgical Patient	Scheduled enteral morphine sulfate	Scheduled enteral lorazepam	Morphine sulfate enteral bolus	Lorazepam enteral bolus	Wean scheduled and bolus drugs to outpatient requirement

The guidelines were developed by a subcommittee of the hospital ethics committee. For each of the four clinical states, five subguidelines were developed: 1) background pain, 2) background anxiety, 3) procedural pain, 4) procedural anxiety, and 5) methods of transition from one clinical state to the next. Highlights of each of the twenty subguidelines are illustrated. Children experiencing agitation not controlled by the guideline were given haloperidol (2 patient-days). Chloryl hydrate (13 patient-days) was used to facilitate radiographic studies or sleep in occasional children. No other sedatives or analgesics were used during the interval of study.

ingly, we have been particularly interested in developing preventative interventions for children after an acute burn. In a naturalistic study we have found, for example, that the dose of morphine received by a child in the hospital after a burn injury was significantly related to a reduction in posttraumatic stress disorder (PTSD) symptoms over 6 months.[5] This study has important implications both for the possibility of preventing PTSD and for how neurobiological systems mediating pain and PTSD may be closely related.

Between 25 and 33% of burn-injured children eventually develop PTSD,[82,83] and over 50% display some posttraumatic symptoms. PTSD is a disorder that represents some of the core features of a child's reactions to diverse traumatic events. Symptoms of this disorder include intrusive recollections, numbing and avoidance, and hyperarousal.[84] The expression of many of these symptoms is fueled by environmental triggers, reminiscent of the trauma. Children with burns also develop mood, anxiety, sleep, conduct, elimination, learning, and attentional problems.[82,83,85] PTSD symptoms cause tremendous morbidity and in some children may persist for many years. Recent evidence indicates that once posttraumatic symptoms become persistent, they are refractory to treatment.

Children hospitalized with an acute burn frequently develop severe psychological reactions such as nightmares, flashbacks, behavioral regressions, and posttraumatic play.[82,83,85] The psychological intensity of burn trauma, and particularly the relentless stress of hospital treatment for a burn, has been compared to "inescapable shock" or "learned helplessness,"[86] both of which have been described as models of PTSD.[87,88] The effective management of pain and anxiety as described here reduces this stress.

PHARMACOLOGICAL MANAGEMENT OF ACUTE BURN PAIN

General Principles

The absence of a clear and explicit approach to the management of burn pain and anxiety can be associated with undesirable degrees of patient discomfort, nonuniform drug selection with inconsistent dosing of unfamiliar drugs, varying tolerance of patient discomfort by different staff members and bedside disagreements over management of patient distress.

Boston Shriners Burns Hospital Guideline for Pain Management

To facilitate effective management of pain and anxiety, and to permit more objective assessment of changes in this management, a pain and anxiety guideline was developed and has been followed and

updated over several years.[64] The objective of our effort was to develop a guideline for pain and anxiety management that: 1) was safe and effective over the broad range of ages and injury severities seen in the unit, 2) was explicit in its recommendations, 3) had a limited formulary to optimize staff familiarity with agents used, and 4) took advantage of the presence of a bedside nurse to continuously evaluate efficacy and intervene when needed through dose ranging. Guideline development was assigned to a subgroup of the hospital ethics committee.

Four patient categories were created: 1) mechanically ventilated acute burns, 2) acute burns not requiring mechanical ventilation, 3) chronic acute patients (defined as those who still had ongoing surgical needs more than a month after initial injury) and 4) reconstructive surgery patients. A specific guideline for background, procedural and transition pain and anxiety management was developed for each patient category (Table 4). Thus, a total of 20 "sub-guidelines" were written. A small and consistent formulary was emphasized. The guideline has been distributed to all incoming house staff and is part of a resource on the patient care units. Pain and anxiety control is addressed during daily rounds, much as hemodynamic, pulmonary, nutritional and wound issues.

After implementing and using the guideline for two years, we prospectively recorded all pain and anxiety medications given to all acutely burned children (categories 1, 2, and 3) admitted for 12 consecutive months. Averaged daily background pain, procedural pain, background anxiety and procedural anxiety discomfort scores were noted using a 5 level action-based bedside nursing scoring system, with "1" representing an over medicated and "5" an under medicated state. We felt that the potential problems associated with a subjective scoring system were outweighed by the utility of a scoring system that focused on the practical judgments of the bedside nurse.

We examined pain and anxiety management in 125 consecutive children with acute burns admitted during a 12-month interval. There were 2025 patient-days of care rendered to these children, 72 in category 1 (ventilated acute), 1696 in category 2 (nonventilated acute) and 257 in category 3 (chronic acute). Doses of individual pain and anxiety medications were calculated as mg per kg per patient day in each category. We found that the guideline was being closely followed, with doses within guideline specifications. Category 1 patients, the ventilated acutely burned, were managed predominantly with infusions of morphine sulfate and midazolam. Category 2 patients, the nonventilated acutes, were managed predominantly with enteral morphine sulfate immediate release and oral lorazepam. Category 3 patients were managed predominantly with enteral morphine sulfate immediate release, enteral long acting morphine preparation and oral lorazepam. Children experiencing agitation not controlled by the guideline were given haloperidol (2 patient-days). Chloryl hydrate (13 patient-days) was used to facilitate radiographic studies or sleep in occasional patients. No other sedatives or analgesics were used during this study.

Although any subjective scoring system has liabilities, we felt that the potential problems associated with such a scoring system were outweighed by the utility of a scoring system that focused on the judgment of the experienced bedside nurse for the need of additional medication. Therefore, the efficacy of the guideline was judged by a daily average of four discomfort scores: 1) background pain, 2) procedural pain, 3) background anxiety, and 4) procedural anxiety. Perfect control of these states was a "2" and adequate was a "3."

Overall, the averaged discomfort scores were within the acceptable range of between 2 and 3. Background and procedural pain and anxiety were well controlled. Somewhat to our surprise, when comparing averaged daily discomfort scores of patients in the three clinical states, it was found that the state most often associated with a suboptimal discomfort score was the ventilated acute state. This may be an artifact of our decreased use of neuromuscular blockade and the consequent greater need to achieve ventilator synchrony with analgesics and anxiolytics only, while still facilitating weaning and extubation. This has become a topic of focused effort to improve comfort management. Thirty-five percent of patient days in this group were associated with discomfort scores greater than 3. We wanted to verify that the guideline was effective across the broad range of patient ages and sizes. We looked at this by dividing the 125 children into three weight categories, 0–12.5 kg (n = 42), 12.6 (n = 41) to 22 kg, and greater than 22 kg (n = 42). Our conclusion based on these evaluations was that the guideline was effective in all size groups, with no statistically significant difference between them. There were no complications related to overmedication experienced during the interval.

Classes of Drugs

Several classes of drugs are useful for ameliorating the pain and anxiety experienced by burn patients. Most common among these are nonsteroidal NSAIDs, COX-2 inhibitors, opiates, benzodiazepines, sedative-hypnotics, neuroleptics, dissociative drugs, antidepressants, and miscellaneous other agents. Each

has its utility, and a working knowledge of all is useful for the burn clinician.

Nonsteroidal Anti-Inflammatory Agents. Nonsteroidal anti-inflammatory agents inhibit cyclooxygenase and thereby prostaglandin production.[89] The prototypical agent, acetyl salicylic acid, should not be used in acutely ill children because it may result in the development of Reye's syndrome.[90] Other NSAIDs, such as ibuprofen, are safe within established dose range and frequencies. They will reduce pain and modify the systemic inflammatory response through cyclooxygenase inhibition, classically manifest by reduction of fever. It has been proposed that regular administration of NSAIDs to critically ill patients may have benefits in terms of reduced systemic inflammation,[91] but these data are as yet insufficient to support general use for this indication. Although there has been some use of the new COX-2 inhibitors in burn care, they have not yet been systematically evaluated. Gastric ulceration and decreased renal tubular function are known side effects that can have detrimental consequences.

Opiates. Perhaps no other agents have proven as durably useful in the alleviation of burn pain as opiates. The trend of increasing use of opioid analgesics to relieve pain does not appear to have contributed to increases in opioid abuse.[92] Clinically useful opiates are both natural derivatives of the poppy plant, and completely synthetic.[93] These agents work through their binding of central opiate receptors, which are sensitive to endogenous opiods.[94] Opiate utility is limited by the side effects, principal among which are respiratory depression and physiologic addiction. Decreased bowel activity can also be problematic, and has been addressed with enteral Narcan® (Dupont Pharmaceuticals, Wilmington, DE) or promotility agents with mixed results.[95] Rapid development of tolerance occurs and requires that doses are escalated, titrated to effect, during the protracted hospitalizations typical of patients with large burns.[7]

Benzodiazepines. Benzodiazepines have been increasingly used in burn care because the central role of anxiety in the distress of burn patients has been appreciated, as distinct from pain.[96] These agents work through enhancement of gamma aminobutyric acid (GABA) receptor activation. Side effects are similar to those of opiate drugs, including respiratory depression, physiologic addiction and the rapid development of tolerance.[97] However, their synergy with opiates to relieve the distress associated with large burns, makes careful benzodiazepine use very appropriate in these patients.[98]

Nonbenzodiazepine Sedative-Hypnotics. Nonbenzodiazepine sedative-hypnotic agents include barbiturates and chloral hydrate, among others.[99,100] All are generalized central nervous system depressants, most having their effect through the GABA receptor. They are of occasional utility as adjuncts to opiates and benzodiazepines, which form the backbone of most pain and anxiety management programs. Their side effects relate principally to respiratory depression, which must be even more vigilantly watched for when opiates and benzodiazepines are used simultaneously. More recently, propofol infusions are increasingly used to sedate intubated mechanically ventilated patients (see below under "Other Agents).

Neuroleptics. Neuroleptics, such as haloperidol[101] rarely play an adjunctive role in those patients whose agitation is not adequately controlled with opiates and benzodiazepines.[102] Haloperidol has a proven record for efficacy and safety[103] in adults, although dyskinetic syndromes and cardiac complications must be watched for.[104–106] Although it was reported to be useful in seriously burned children,[107] today it is rarely used. Other neuroleptics which may have a role for agitated patients in pain are droperidol, which is given IV, and oral neuroleptics, risperidone, ziprasidone, and olanzapine.

Dissociative Drugs. Ketamine is a dissociative anesthetic that has been widely used to provide comfort during burn related procedures, such as dressing changes, particularly in children.[108–110] This has included preemptive use, or "ketamine loading."[108,111] Its strength is the lack of respiratory depression at standard doses and the fact that hypotension rarely occurs with its administration.[112] Its principal drawback is the unpredictable occurrence of agitated delirium after administration, most commonly seen in adult patients.[113] Studies with S+ ketamine isomer suggest that its use may be associated with fewer side effects than its racemic mixture.[114] Simultaneous administration of benzodiazepines may reduce the occurrence of this complication.[115] However, we do not favor ketamine use given its potential complications,[116–119]and prefer debridement in the operating room rather than at the bedside.

Stimulants and Antidepressants. Stimulants (eg, methylphenidate, amphetamine) and tricyclic antidepressants have been demonstrated to act as adjuvants to enhance the effectiveness of analgesics. Both also may relieve depressive affect associated with pain, and tricyclic antidepressants have the additional benefits for some children of sedation and relief for posttraumatic stress symptoms.[120] While selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline, paroxetine etc) have not been evaluated specifically for pain, their antidepressant and anxiolytic properties make them useful adjunctive therapies for some

burned children, and are now much more widely prescribed than tricyclic antidepressants. Nefazodone® (Bristol Myers Squibb, New York, NY) and trazodone are also likely candidates for such adjunctive psychopharmacology.

Other Agents. Other agents occasionally useful include anesthetic agents, such as propofol, the antineuropathic or medications, such as gabapentin (Neurontin®; Parke-Davis, Morris Plains, NJ),[121] and rarely nitrous oxide.[122,123] Propofol is a lipid soluble intravenous anesthetic with the useful anesthetic properties of a rapid onset and a short half-life.[124] It has proven safe when used as a continuous infusion in the intensive care of adult patients[125,126] but it has a mixed reputation in young children due to the newly recognized propofol infusion syndrome characterized by fulminant metabolic acidosis.[127–129] Propofol use is now restricted to operative anesthesia, short duration procedures, or in the period immediately prior to extubation.[130–133]

A newer class of antineuropathic agents, such as gabapentin, have occasional utility in burn patients.[121] These drugs will stabilize cell membranes and were originally introduced for seizure control.[134] They are most often useful in those few patients who develop pain syndromes months after the acute injury has been successfully managed.[135]

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) is a technique in which a constant infusion of an opiate pain medication is administered with boluses administered by the patient to a set maximum to ensure safety.[136] This technique has been demonstrated to enhance even patients' as young as 10 receiving timely pain relief, and to provide adequate relief of moderate postoperative pain.[137] Further, studies have demonstrated that the immediate provision of boluses at patient need usually results in an overall decreased consumption of medication, probably because pain does not become as severe with frequent immediate provision of small doses. There is also the added benefit of decreased demands on busy nursing staff to provide pain medication.[138] These devices have an excellent safety record.[139] A baseline infusion can be set and a set bolus dose with a "lockout interval" is also set, so that repeated attempts at dosing by patients only results in a predetermined maximum dosing rate. PCA devices have been used in children,[140] administration done by parents or nurses with success. PCA has also been used in burn patients,[141] although the reported experience is limited, and some patients prefer not to have IVs.

SPECIAL PROBLEMS: VENTILATED PATIENT, MASSIVE BURNS, INTRACTABLE CHRONIC PAIN, AMPUTATION, TISSUE EXPANDERS, WEANING

The Mechanically Ventilated Patient

The burn patient requiring mechanical ventilation presents several unique challenges to comfort management.[142] Not only do the patients have burn pain, but they are confined to the supine position and cannot speak. The discomfort of an endotracheal tube itself can be very significant. The goal is to have a patient who is lightly asleep but arouseable and in synchrony with the ventilator. Oftentimes, during resuscitation or episodes of sepsis, such patients are hemodynamically unstable to the degree that blood pressure is compromised by the administration of adequate analgesic medication, further complicating comfort management. However, in most ventilated patients, infusions of opiates and benzodiazepines to provide for background pain and anxiety should be supplemented with boluses of similar medications to deal with procedural discomfort.

In some critically ill patients with severe respiratory failure, absolute ventilator synchrony is required. Such patients may need neuromuscular blocking drugs to meet this objective. Such agents should generally only be used in this situation and it is essential that patient comfort be ensured. This goal can be difficult to monitor, but can be met by stopping the neuromuscular blocking drugs periodically and evaluating comfort, while running infusions at doses estimated to provide for good control of both pain and anxiety. Bispectral Index (BIS) monitoring can also be used to access the level of consciousness in paralyzed patients but the experience with this modality in the intensive care unit is minimal.[143,144]

Weaning from Mechanical Ventilation

When it is time to extubate, medications are weaned as tolerated to the point where the patient's sensorium is alert enough to be consistent with airway protective reflexes.[145,146] Some patients may benefit from the addition of very short acting sedatives in the hours before planned extubation, as longer acting agents are weaned, to maintain comfort.[147] It is not necessary always to wean infusions of opiates and benzodiazepines off completely prior to extubation. Doing so may provoke withdrawal symptoms in some patients. It is only necessary to reduce medications enough to have a sensorium consistent with airway protection and adequate ventilation.[148]

The Massively Burned Patient

The massively burned patient has pain and anxiety issues that exceed the ability to describe them. These issues begin with the pain and psychologic trauma of the injury itself, and continue with the need for intensive care and frequent operations and donor sites. Regular intensive physical therapy, required to create quality long term outcomes, is also associated with substantial pain at times.[149] Inadequate medication for these issues can be associated with treatment related stress that may complicate recovery. Optimal management is rendered more difficult at times by the astounding degree of tolerance that develops to the opiates and benzodiazepines that are so essential.[150] It is important to prescribe doses based on response, understanding the development of tolerance, and to wean medication very slowly to avoid withdrawal symptoms.

Chronic Pain Syndromes

Some patients will develop chronic pain syndromes. These can be extremely difficult management problems, but fortunately only rarely occur. Most often, these syndromes involve very deeply burned extremities, particularly hands, and may be related to reflex sympathetic dystrophy.[149,151] The symptoms often abate with the passage of months and are commonly alleviated by the administration of gabapentin (Neurontin®) or other antineuropathic medications, ideally in consultation with a pain clinic. In some patients, sympathetic blocks can provide dramatic relief.[152] Care should be taken to recognize the development of pain out of proportion to the expected clinical course to facilitate early referral and to minimize over prescription of narcotic pain medications. In dealing with the difficult practical problems of chronic pain syndromes, it is ideal if one prescriber of pain medication is identified to facilitate control of the amount of drugs dispensed. When a mental disorder is also suspected, which is often the case, this should be diagnosed and treated as well as the chronic pain.

Neuropathic pain states, one type of chronic pain, are those connected with injury, dysfunction, or changes in excitability of parts of the peripheral or central nervous system. This definition indicates that the pain is not nociceptive, that is, it persists independent of continuing tissue injury or inflammation, and may worsen over time. This pain is caused by abnormal messages sent by the nerves, even after the injury has healed, which in some cases represent peripheral seizure focuses. It often includes increased pain sensitivity or hyperalgesia, described earlier. It may occur after burns—especially severe burns, in children, and is common after amputations. It may be due to peripheral nerve damage, amputation,[153] causalgia and reflex sympathetic dystrophy, brachial plexus injury, and spinal cord injury.[154] Treatments include psychological, behavioral, physical therapy, and pharmacological interventions. Pharmacological treatments mainly based on adult studies, include tricyclic antidepressants, anticonvulsants, especially carbamazepine or gabapentin or lamotrigine, Baclofen, local anesthetics, neuroleptics, muscle relaxants, antihistamines, and others.[155]

Amputation Pain

Amputation of digits and extremities is not infrequently required in patients who have been badly burned, and are sometimes followed by phantom pain syndromes that can be extremely distressing. Thomas et al[156] studying 228 children with amputations for burns, of which 35 involved limbs and the remainder digits, underscored the importance of differentiating stump site pain from phantom limb pain, because phantom limb pain is responsive to pharmacological treatment. According to Krane and Heller,[157] phantom limb phenomena occur in nearly all cases if asked about, although Smith and Thompson only found phantom limb pain in one of eight children with traumatic amputations.[158] It is characterized by "cramping, squeezing, lancinating," "electrical," or burning sensations, by aberrant proprioception, or by "a sensation of postural displacement in a nonexistent extremity," and may greatly impair activities of daily living. Again, fortunately, these symptoms often regress with the passage of time, but may persist throughout life.[159,160] Peer support is the most important determinant of self-esteem, and intervention may decrease risk of subsequent depression which occurs in about 19% of pediatric amputees.[161] Occasionally, such symptoms can be linked to a neuroma that can be managed surgically. In most patients, antidepressants, anticonvulsants, possibly "preemptive" regional analgesia, and judicious use of opiates and benzodiazepines can alleviate the symptoms to tolerable degree.[162,163]

Pain Associated with Tissue Expansion

Tissue expanders are being used with increasing frequency in burn reconstruction.[164] They have proven particularly useful in correction of burn alopecia.[165] However, after insertion of the expander, it must be inflated over a period of weeks. These progressive inflations can be quite uncomfortable, especially to young children. Gentle technique and anticipatory medication can make this discomfort bearable for most patients.

Toward Optimal Guidelines

Inadequate control of pain and anxiety will have adverse psychologic and physiologic effects. PTSD will develop in many of those with serious burns, and poor control of pain and anxiety may very well contribute to this,[166] exacerbating postburn psychiatric disorders[167,168] Further, excessive pain and anxiety, by increasing the elaboration of stress hormones, may contribute to the hypermetabolic response.

Pain and anxiety management is not only a psychologic and physiologic issue for patients, but it is also a common area of disagreement among intensive care unit staff. There continues to be wide variations in use of analgesics and anxiolytics for pediatric pain management on burn units. No one wants to cause unnecessary discomfort to another, but some remain concerned about excessive medications. The establishment of a clear and specific guideline to facilitate management of this critically important issue not only helps to eliminate much of this staff discomfort, but provides a consistent platform which facilitates discussion of patient problems and evaluation of new therapeutic approaches. We feel that such guidelines should 1) be safe and effective over the a broad range of ages and injury acuities, 2) be explicit in its recommendations, 3) have a limited formulary to optimize staff familiarity with agents used, and 4) take advantage of the presence of a bedside nurse to continuously evaluate efficacy and intervene when needed through dose ranging. Although many drugs are appropriate, our choices were based on institutional familiarity and simplicity. This process of developing a clear and consistent guideline can be duplicated on any unit.

PSYCHOLOGICAL MANAGEMENT OF ACUTE BURN PAIN FOR MILD TO MODERATE PAIN

Coping with burn injuries depends on a wide variety of factors, including developmental stage,[2,72,169,170] personality style, skill level, culture, and temperament.[171] These psychological factors influence how effectively a child copes with pain. Differences are evident in comparing infants, preschool, school age and adolescent children.[2] Infants generally react to pain through crying, withdrawal, irritability, and sleep or eating disturbances. Regressive behaviors can escalate as anxiety, nightmares, or loss of newly acquired speech or toilet training occur in preschool children. Patterns of hyperactivity, nightmares and regression, or depression or anxiety are seen in latency age children. Similarly, adolescents may exhibit depression or anxiety together with verbal or even physical expressions of anger. It is also important that cultural factors may play an important role in how children express and cope with pain. It is noted by Shaughnessy (Shaughnessy M. Pediatric pain management: script for a videotape intervention, Massachusetts School of Professional Psychology. May 2001. Unpublished doctoral dissertation), that there is little literature addressing cultural factors in the assessment of pain in children. However, Zeltzer[172] noted that as children grow, others in their environment including siblings have an effect in the modification of children's response to pain.

A very important question from a psychological perspective is "what actually is pain?" And also, how is acute pain different from chronic pain? In treating patients with burns, the question is raised—when does acute pain reach a point where it is considered chronic? What seems clear is that pain is a subjective experience. It arises within the brain in response to damage to body tissues or may be dependent on more subtle psychological changes, secondarily experienced as the perception of pain. To put it simply, pain is a personal feeling of hurt which varies in intensity and degree from person to person. It is a complex combination of physically influenced sensations and psychologically influenced perceptions and reactions.

Numerous physical factors influence pain: the location and type of burn injury, the integrity of the nervous system, individual differences in pain threshold and tolerance, response to medication especially analgesics, and responses to physical stimulation including heat, cold, pressure, vibration, and electrical stimulation. Psychological factors such as the meaning of what is causing the pain, previous experience in reinforcement, the sex and age of the patient, the reactions of others to the child's pain, anxiety, depression and also cultural and familial strategies for dealing with pain. It is difficult to determine how much each of these factors contributes to pain being experienced. Psychological factors are no less real than the physical ones. Making such judgments can be very unfair.

Given these concerns, provision of adequate preparation for painful procedures, in the child's own language, is essential for surgical procedures, postoperative care, dressing changes, tubbing, and burn rehabilitation including physical and occupational therapy. Honest communication allows children the opportunity to express their feelings verbally, as well as nonverbally, and to have them validated. Atchison et al,[173] in studying pain during dressing changes, found that high levels of pain were experienced by children whose burns were superficial as well as by those with full thickness burns. A

natural response to pain is for children to engage in behaviors in order to avoid this experience. One thing which is clear is that pain is a very personal matter and only the individual in pain can really understand what it feels like. Anxiety is a major factor in escalating levels of pain in burned children. This "anticipatory anxiety" may be seen prior to uncomfortable procedures, particularly dressing changes and physical therapy, and should be addressed both psychologically, and, if necessary, with anxiolytics.

In thinking about children in pain, it is important to keep in mind that chronic may not evoke the same types of behavioral distress as acute pain. The typical reaction to chronic pain is reduced play activity or other pleasurable behaviors, and depressive affect. Because the child in chronic pain may not appear to be in constant pain, the lack of obvious pain behaviors may create the false impression that the child is not actually experiencing real pain. In general, unless one can clearly determine that a child is manipulating, if she or he says they are in pain, this self-report of pain should be accepted by caretakers at face value. Pain is such a complex issue that it calls for multiple methods of assessment and treatment. The interaction of psychological and physiological responses means that the judicious use of medication may prevent and reduce the child's pain, and block psychological factors (eg, conditioned phobic responses) from exacerbating it.

Psychological interventions either in concert with pharmacological, or alone, are essential in burn treatment. Traditional psychological interventions include hypnosis (including self-hypnosis), muscle relaxation, deep breathing, and guided imagery, all of which are more readily used with children than with adults. In addition, the use of forms of distraction[174] such as reading a story, listening to music,[175] and watching TV are common in alleviating pain in children. Other techniques including biofeedback,[176] massage,[177] and even virtual reality[178] have been introduced. Other forms of distraction such as puppet play, and humor, also are effective for some children (Table 5).

Case Illustration of Distraction for Pain and Anxiety: Steven, Age 5

Steven provides an example of how preschoolers may anxiously regress, become needy and have nightmares.[2,179] He had a 25% TBSA partial thickness burn while running after a ball in the kitchen, when he tripped over a wire connected to a fryolator causing hot oil to spill on him. After initial dressing changes, his anticipatory apprehension quickly escalated whenever a nurse initiated the three times daily dressing changes. Consultation was requested because his phobic anxiety did not vary even in the presence of a reassuring parent seeking to soothe him. His mother explained that he was normally a very playful and imaginative boy, and it seemed that a modified distraction technique might reduce both his pain and anxiety. He stopped focussing on pain when playing with puppets with his psychologist, and in addition a method suggested by Kuttner was tried.[180] His mother shared how he had enjoyed blowing bubbles and competed with his siblings to see who could blow the biggest one. This was adapted, so that during dressing changes the idea of "blowing away the pain" was suggested. This also involved deep breathing which helped him to blow bigger bubbles. As a result of these techniques, and the parental and psychotherapeutic support which was a part of them, his anxiety diminished and his mother joined in the process with him, increasing its effectiveness.

In treating pain it is important to assess the level of pain that the child is experiencing with instruments such as the FACES pain scale[55] or the analog 1 to 10 scale[181] where the child is asked to rate pain with 1 being the least and 10 being the greatest. In determining the most effective interventions, it is important to consider issues of control, although the effectiveness of treatment oriented to enhancing control

Table 5. Psychological Interventions by Age of Child for Relief of Pain

	Psychological Method				
Age (yr)	Deep Breathing	Progressive Muscle Relaxation	Exercise	Distraction	Guided Imagery and Hypnosis
0–2				x	
2–4	x			x	
4–6	x			x	x
6–11	x	x	x	x	x
11–adolescence	x	x	x	x	x

has been usefully challenged[182] recently. However, other research[84] supports the benefits of children participating in painful procedures, and many children seek to have a role. For instance in dressing changes, a child may have a sense of control in helping to remove the dressing and will believe this will cause less suffering. The acuity of the burn and extent of injury can limit a child's ability or willingness to participate in such a process.

Case Illustration of Guided Imagery and Music Therapy: Kathy, Age 12

An interesting example of the use of imagery is illustrated by Kathy. At age 12 she sustained 40% TBSA flame burns in a house fire, affecting her arms and torso. Her dressings occurred three times daily, and each time her distress escalated, resulting in stress exacerbating the pain she experienced. Although analgesics prior to procedures had some effect, anticipatory anxiety was evident. When one of us (DSC) talked with Kathy about things that she liked to do which provided her with a sense of pleasure, she spoke of her singing and how she was part of a school chorus as well as her church choir. We reached a conclusion that for her to sing might be therapeutic during procedures. She was able to use singing before a procedure was initiated and incorporate in this the imagery of being part of the musical groups that were a normal part of her life. Once she engaged in this process, encouraged by her psychotherapist who remained at her bedside the first few times she used the techniques, she began to self-initiate this process and there was a major positive change in her response to dressing changes.

These cases illustrate the fact that there is no one approach that is always the answer. Much depends on the child's age, developmental stage, and receptiveness to one or a combination of interventions. The importance of honesty cannot be exaggerated with regard to what is being done to them and what they can expect, while introducing methods that give them a sense of control over the experience. It is essential to their well being.

The role of essential caregivers, particularly nurses, is of great importance. Thurber et al[182] noted that when nurses give the child control, they may feel that they are giving up some of their own control. However, they note that this need not be the case if they are teaching the child effective ways to exert some control over their own care. As a result, this can lead to greater compliance and pain reduction. Giving children clear explanations as to what is going to happen and acceptable choices about how a procedure can be conducted enhances a child's sense of control, and can decrease their sense of being a victim. It is counterproductive for us as health professionals to behave as if we are the best judges as to how much pain the child is actually experiencing. Never argue with a patient about whether they feel pain or how bad their pain is. For us to deny the existence of the feeling of pain may only cause the child to complain more vehemently in order to prove they actually feel pain. When children feel they are not believed, nor feel that their pain is relieved, they tend to withdraw.

Finally, it is important to address the role of family members, specifically parents, in helping with the management of pain. As described by Chedekel et al,[171] the acute burn phase can be as stressful or perhaps even more so for the family. Thus when parents witness the pain their child is experiencing, their sense of guilt and helplessness can easily escalate. Martin-Herz et al[183] addressed the question of whether or not it can be helpful to have parents present during dressing changes. There have been a number of studies which demonstrated children becoming more stressed when parents are present during dressing changes.[184–189]

However, it has also been evident that parents, if emotionally stable, can provide reassurance and physical comfort to the child during both dressing changes and other stressful interventions, such as physical therapy. As Martin-Herz et al noted, parents can also serve as models of adaptive coping and their presence can also give parents an opportunity to learn wound care. The importance of parents developing care skills before a child is discharged is a key to successful postdischarge recovery, prevention of relapse, and long-term rehabilitation. It is important for parents to be provided necessary supports and training to help them better understand procedures, which can, in turn reduce their own feelings of anxiety when confronted with their child's pain experiences.[188] There is little question that parental anxiety will increase that which is being experienced by the child. It is also true that excessive and unrealistic reassurance by parents that something will not hurt only escalates the child's regression. Parents can, therefore, have a very important role in helping their children cope with painful experiences. What must be kept in mind, as noted by Martin-Herz et al, is that parents prefer to participate in their child's care, and that the child prefers this as well.

The major focus in the psychological management of pain in burned children should be on helping them to develop skills for coping with this experience. Thus, anything which enhances a child's sense of control over what they are experiencing can be beneficial. Predictability is integral to this process as noted by

Kavanaugh[189] addressing dressing changes in burned children. Providing children with both primary and secondary control mechanisms has been shown to reduce pain behaviors and to reduce self-ratings of pain during wound care. A two process model of control provides an effective way of studying the methods that children utilize to cope with wound care.[190] This model provides children with both primary control which involves modifying the objective conditions to fit oneself, and secondary control to adjust oneself to fit objective conditions. These have been found to reduce pain behaviors as well as self-ratings of pain during wound care.[171] The more caretakers teach children how to cope, the better they can adapt to burn care which, in turn, can lead them to improved healing and emotional adaptation to the burn experience.

PRACTICAL STEPS FOR THE BURN TEAM

Several excellent references are available to burn teams in designing pain treatment guidelines and protocols.[191,192] Based on the basic research, clinical studies, and emerging therapeutics of pediatric pain described here, we suggest the following practical steps for the burn team in treating pain:

- Obtain a history of the injury, the child's development, response to pain, prior psychopathology, and family supports before the burn.
- Observe the child's response to psychological preparation for painful experiences and to pain.
- Rate the pain, longitudinally, according to one of the developmentally appropriate scales.
- Evaluate the anatomy and pathophysiology of the wound(s) and the pain response to psychological interventions, analgesics, anxiolytics, and to surgical interventions.
- If the pain treatment is not successful, reevaluate all aspects of care and consider modifying existing treatments or seeking additional consultation.
- Design a hospital-approved pain guideline to provide consistent care.
- Evaluate and monitor the effectiveness and quality of pain treatment, updating guidelines with new treatments.

ETHICAL AND TREATMENT ISSUES

The ethical issues regarding pain management in burned children can best be framed in terms of what practitioners should do or ought to do.[193] Perhaps the most troublesome issues relate to pain assessment. Fortunately, gone are the days when caregivers believed incorrectly that newborns and infants lack pain responses.[194] It is now widely understood and accepted that ethically all children, regardless of age, *should* receive adequate pain relief, and that children in pain do indeed suffer.[195]

Burn wounds are extraordinarily painful. The central question is, how much analgesic is enough, and how do we know? This question may be particularly challenging in infants and small children who are nonverbal or poorly communicative. Assessment is also difficult in acute severely burned children who are in the intensive care setting, intubated, sedated, muscle-relaxed, and perhaps hemodynamically unstable. Strategies for pain assessment in these circumstances were reviewed earlier in this article.[91] Utilization of these strategies helps to prevent under- or over-treatment of pain.

Further assessment necessitates balancing risks and benefits. Beyond determining how much is enough, we need to balance the effects of too much versus too little pain control, and the added risks from side effects, such as respiratory depression, excessive sedation, and physiological dependence. Additional risks are attributable to the method of administration. Intravenous catheters, particularly central venous catheters, carry risk of infection, thrombosis, and bleeding, not to mention risks from the procedure itself in the operating room or intensive care unit, and anesthesia. Other routes of administration (subcutaneous, intramuscular, rectal) are painful in and of themselves; in some instances the absorption via these routes in unpredictable. Caregivers and others frequently worry about issues related to addiction and dependence, particularly with respect to narcotics. Fears of addiction have, in the past, been a barrier to management of pain; there is no evidence that pain management in the intensive care setting is a cause of drug addiction.[196] Temporary physiological dependence occurs during opiate weaning after long-term administration, but weaning strategies, a transition from morphine to other agents such as methadone and anxiolytics, and the clonidine patch, facilitate this process. The use of clonidine by extradural or intrathecal route has not been tested in burned patients although extensively used for treatment of acute postoperative and neuropathic pain.[197]

Additional ethical and clinical issues include involvement of the family in decision making and pain control, the imperative for respect for the child and allowing the patient to exert some appropriate level of control, the necessity for honest communication with the patient, and adequate analgesia for the dying patient.[198,199] In our experience, all of these questions

can be answered and managed by a careful, multidisciplinary, prospective approach to the patient, always keeping in mind what *ought* to be done and including relief of pain as a therapeutic goal.

TOWARD AN INTEGRATION OF PHARMACOLOGICAL AND PSYCHOLOGICAL PAIN MANAGEMENT

This concludes a series of articles devoted to pain management in children. The topic is large and rapidly expanding. The desire to relieve suffering, the gathering of epidemiological data on pain management and its effects, and empirical testing of hypotheses through research are the engines which are driving change in the field. While theories assist in understanding what is observed, it is common for theory to follow, not precede, practice. Neurobiological and neuropsychological research are revolutionizing our understanding of how mind and brain work together: psychological stimuli alter brain and peripheral neurochemistry, and chemical (including pharmacological) stimuli alter a child's psychological experience, eg, perception of pain and stress.

The development of new pharmacological treatment methods and agents, such as oral opiates, midazolam, COX-2 inhibitors, and propofol appear to be making it possible to provide better care, even though all have not been rigorously evaluated with burned children. Greater attention to the benefits and risks of specific medications has led to greater use of opiates and benzodiazepines, but also a shift to shorter-acting agents for the many procedures which are essential to good burn care, and which burned children must endure.

Psychological treatments have been the main focus of this series of articles. They included, in order of publication, articles on psychological principles, psychological treatment applications, music therapy, massage therapy, a developmental perspective on psychological principles. The present article addresses both areas, with a substantial focus on the biology and pharmacology of pediatric pain. It is clear that pain management increasingly has its "subspecialty areas" which are generating new empirical data for reducing the suffering of burned children. Despite this, pain management on the burn unit is a multidisciplinary task from acute care through rehabilitation.

Is it possible, or desirable, to integrate pharmacological and psychological treatments? Certainly where it is clear how to do so, that is a laudable objective. It is not necessarily desirable to integrate the two: empirical testing of specific treatments of each type, or others can indicate that one treatment is best. Generally, it seems that the major areas of integration are two: psychological preparation for procedures—including pharmacological or psychological treatments, and evaluation of the effectiveness of pain relief, during and after either or combined types of treatment. One treatment does integrate the two—PCA, in which the patient has direct control of medication administration. Some other methods seek to integrate the two to varying degrees.

However, because science and practice are improving, a formal integration in treatment may be on the horizon. Guidelines, protocols, care plans, and clinical pathways increasingly will classify children at different treatment phases, based on clinical assessment, as requiring primarily pharmacological, combination pharmacological and psychological, or psychological treatment. These will remain subject to evaluation and modification if a given treatment proves ineffective. As was done in this article, guidelines already do prescribe specific pharmacological and/or psychological treatments, and some of the prior articles have prescribed specific psychological treatments.

CONCLUSIONS AND FUTURE DIRECTIONS

Pain management is a critical part of treating infants, children, and adolescents with acute burn injuries. The basic science of the genetics, biochemistry and anatomy of pain are being revolutionized, bringing in new concepts and more effective drugs with fewer adverse side effects and risks of toxicity. It is subject to an expanding stream of research studies which are continuously improving treatment.[200] Methods of pain assessment are now available which are appropriate for all ages, and there is increasing psychological understanding of how children experience pain, and benefit from honest preparation for painful procedures. Contemporary pain management seeks to respond to developmental, cultural, linguistic, and familial characteristics. Psychiatric assessment is indicated for many children in order to integrate pain-relieving interventions into ongoing care of emotional and mental distress and to provide support for families, and reduce their stress as well. Pharmacologic treatment methods have expanded to previously little used agents or to novel agents recently discovered, and to methods such as patient-controlled analgesia which bridge pharmacological and psychological treatment methods. Psychological methods are increasingly conceptualized according to specific theoretical frameworks, and skills in application of various hypnotic, cognitive, and behavioral methods allow individualization of a specific psychological treatments according to the

needs of the child. Optimal care encourages burn teams to integrate pain guidelines and monitors into the ongoing care plans of each patient. Outcomes research suggests that such care is an important factor in the improving outcomes with severe burn injured children. Just as pain management of burned children has changed and improved dramatically during the past 20 years, it is our hope and expectation that new advances during the next 20 years will continue to revolutionize our management of burned children, so that when we look back in the year 2021, we again be impressed and pleased with the continued progress.

REFERENCES

1. Perry SW. Undermedication for pain on a burn unit. Gen Hosp Psychiatry 1984;6:308–16.
2. Stoddard FJ. Coping with pain: treatment of burned children from infancy to adolescence. Am J Psychiatry 1982;9: 736–40.
3. Pitman RK. Post-traumatic stress disorder, hormones, and memory. Biol Psychiatry 1989;26:221–3.
4. Carr DB. Preemting the memory of pain. JAMA 1998;279: 1114–5.
5. Saxe G, Stoddard F, Courtney D, et al. Relationship between acute morphine and course of PTSD in children with burns: a pilot study. J Am Acad Child Adolesc Psychiatry 2001;40:915–21.
6. Stoddard FJ, Martyn JJ, Sheridan RL. Psychiatric issues in pain of burn injury: controlling pain and improving outcomes. Curr Rev Pain 1997;1:130–6.
7. Sheridan R, Stoddard F, Querzoli E. Management of background pain and anxiety in critically burned children requiring protracted mechanical ventilation. J Burn Care Rehabil 2001;22:150–3.
8. Bastani JB, Baskins MA, Wiebelhaus P. Psychiatric referral pattern in a burn center. J Burn Care Rehabil 1992;13: 709–12.
9. Stoddard FJ, Todres ID. Editorial: a new frontier. Posttraumatic stress and its prevention, diagnosis and treatment. Crit Care Med 2001;29:687–8.
10. Friedman MJ. What might the psychobiology of posttraumatic stress disorder teach us about future approaches to pharmacotherapy. J Clin Psychiatry 2000;61(suppl 7): 44–51.
11. Jessell TM, Kelly DD. Pain and analgesia. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. Norwalk, CT: Appleton and Lange; 1991. p. 385–99.
12. Baron R, Baron Y, Disbrow E, Roberts TP. Brain processing of capsaicin-induced secondary hyperalgesia: a functional MRI study. Neurology 1999;:53:548–57.
13. Lundell JC, Silverman DG, Brull SJ, et al. Reduction of postburn hyperalgesia after local injection of ketorolac in healthy volunteers. Anesthesiology 1996;84:502–9.
14. Hardy JD, Wolff HG, Goodell H. Experimental evidence on the nature of cutaneous hyperalgesia. J Clin Invest 1950; 29:115–40.
15. Warncke T, Stubhaug A, Jorum E. Preinjury treatment with morphine or ketamine inhibits the development of experimentally induced secondary hyperalgesia in man. Pain 2000;86:293–303.
16. Treede RD, Magerl W. Multiple mechanisms of secondary hyperalgesia. Prog Brain Res 2000;129:331–41.
17. Holthusen H, Irsfeld S, Lipfert P. Effect of pre- or posttraumatically applied i.v. lidocaine on primary and secondary hyperalgesia after experimental heat trauma in humans. Pain 2000;88:295–302.
18. Pedersen JL, Kehlet H. Hyperalgesia in a human model of acute inflammatory pain: a methodological study. Pain 1998;74:139–51.
19. Bartfai T. Telling the brain about pain. Nature 2001;410: 425–6.
20. Samad TA, Moore KA, Sapirstein A, et al. Interleukin-1B-mediated induction of Cox-2 in the CNS contributes to pain hypersensitivity. Nature 2001;410:471–5.
21. Borsook D, Falkowski O, Rosen H, et al. Opioids modulate stress-induced proenkephalin in the hypothalamus of transgenic mice: a model of endogenous opioid gene regulation by exogenous opioids. J Neurosci 1994;14:7261–71.
22. Hyman NE, Nestler EI. Initiation and adaptation: a paradigm for understanding psychotropic drug action. Am J Psychiatry 1996;153:151–62.
23. Osgood PF, Szyfelbein SK. Management of pain. In: Martyn JAJ, editor. Acute management of the burned patient. Philadelphia: WB Saunders; 1990. p. 201–7.
24. Wood AJJ. Racial differences in the response to drugs—pointers to genetic differences. N Engl J Med 2001;344: 1393–5.
25. Martyn JAJ. Clinical pharmacology and drug therapy in the burned patient. Anesthesiology 1986;65:67–75.
26. Fitzgerald M. Neurobiology of fetal and neonatal pain. In: Wall PD, Melzack R, editors. Textbook of pain. New York: Churchill Livingston; 1994. p. 153–63.
27. Kinney HC, Ottoson CK, White WF. Three-dimensional distribution of 3H-naloxone binding to opiate receptors in the human fetal and infant brainstem. J Comp Neurol 1990; 291:55–78.
28. Akesson E, Kjaeldgaard A, Samuelsson EB, Seiger A, Sundstrom E. Ionotropic glutamate receptor expression in human spinal cord during first trimester development. Brain Res Dev Brain Res 2000;119:55–63.
29. Marti E, Gibson SJ, Polak JM, et al. Ontogeny of peptide- and amine-containing neurones in motor, sensory, and autonomic regions of rat and human spinal cord, dorsal root ganglia, and rat skin. J Comp Neurol 1987;266:332–59.
30. Thornton SR, Compton DR, Smith FL. Ontogeny of mu opioid agonist anti-nociception in postnatal rats. Brain Res Dev Brain Res 1998;105:269–76.
31. Atcheson R, Lambert DG. Update on opioid receptors. Br J Anaesth 1994;73:132–4.
32. Basbaum AL, Levine JD. Opiate analgesia: how central is a peripheral target? N Engl J Med 1991;332:1168–9.
33. Stein C. Control of pain in peripheral tissue opioids. N Engl J Med 1995;332:1685–90.
34. Dahl JB, Brennum I, Arendt-Nielsen L, et al. The effect of pre versus post injury infiltration with lidocaine on thermal and mechanical hyperalgesia after heat injury to skin. Pain 1993;53:43–51.
35. Brofeldt BT, Cornwell P, Doherty D, et al. Topical lidocaine in the treatment of partial thickness burns. J Burn Care Rehabil 1989;10:63–6.
36. Vinik HR, Kissin I. Rapid development of tolerance to analgesia during remifentanyl infusion in humans. Anesth Analg 1998;86:1307–11.
37. Eissenbach JC. Preemptive hyperalgesia, not analgesia. Anesthesiology 2000;92:308–9.
38. Shimoyama N, Shimoyama M, Inturrisi CE, Elliot KJ. Ketamine attenuates and reverses morphine tolerance in rodents. Anesthesiology 1996;85:1357–66.
39. Porter F. Pain assessment in children: infants. In: Schechter NL, Berde CB, Yaster M, editors. Pain in infants, children, and adolescents. Baltimore: Williams & Wilkins; 1993. p. 87–96.
40. Franck LS. A new method to quantitatively describe pain behavior in infants. Nurs Res 1986;35:28–31.
41. Purcell-Jones G. Pediatric anaesthetists' perceptions of neonatal and infant pain. Pain 1988;33:181–7.

42. Ekman, Oster H. Facial expression in emotion. Ann Rev Physiol 1979;30:527–54.
43. Ekman P, Rosenberg EL, editors. What the face reveals: basic and applied studies of spontaneous expression using the Facial Action Coding System (FACS). New York: Oxford University Press; 1997.
44. Grunau RVE, Craig KD. Pain expression in neonates: facial action and cry. Pain 1987;28:395–410.
45. Grunau RVE, Oberlander T, Holsti L, Whitfield MF. Bedside application of the Neonatal Facial Coding System in pain assessment of premature neonates. Pain 1998;76: ,277–86.
46. Fitzgerald M, Millard C, MacIntosh N. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anesthesia. Pain 1989; 39:31.
47. Lind J, Wasz-Hockert O, Vuorenkoski V, et al. Vocal response to painful stimuli in newborn and young infants. Ann Paediatr Fenn 1966;12:55–63.
48. Porter F. Developmental regulation of physiological and behavioral responses to pain. Infant Behav Dev 1992;15: 637.
49. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive-care environments: the COMFORT Scale. J Pediatr Psychol 1992;17:95–109.
50. Van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability of COMFORT scale as a postoperative pain instrument in 0–3 year old infants. Pain 2000;84:367–77.
51. Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. Clin J Pain 1996;12:13–22.
52. Ballantyne M, Stevens B, McAllister M, Dionne K, Jack A. Validation of the premature infant pain profile in the clinical setting. Clin J Pain 1999;15:297–303.
53. McGrath PA. Pain in children: nature, assessment, treatment. New York: Guilford; 1990.
54. Hester NO, Foster R, Kristensen K. Measurement of pain in children: generalizability and validity of the pain ladder and the poker-chip tool. In: Tyler DC, Krane EJ, editors. Advances in pain research and therapy. Pediatric Pain. New York: Raven Press; 1990. p. 79–84.
55. Bieri D, Reeve RA, Champion GD, Addicoat L, Ziegler JB. The faces pain scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. Pain 1990;41:139–50.
56. McGrath PA, Brigham MC. The assessment of pain in children and adolescents. In: Turk DC, Melzack R, editors. Handbook of pain assessment. New York: Guilford Press; 1992. p. 295–314.
57. Choiniere M, Melzack R, Rondeau J, Girard N, Paquin MJ. The pain of burns: characteristics and correlates. J Trauma 1989;29:1531–9.
58. Latarjet J, Choinere M. Pain in burn patients. Burns 1995; 21:344–8.
59. Henry DB, Foster RL. Burn pain management in children. Pediatr Clin North Am 2000;47:681–98.
60. Miller AC, Hickman LC, Lemasters GK. A distraction technique for control of burn pain. J Burn Care Rehabil 1992; 13:576–80.
61. Patterson DR. Practical applications of psychological techniques in controlling burn pain. J Burn Care Rehabil 1992; 13:13–8.
62. Pal SK, Cortiella J, Herndon D. Adjunctive methods of pain control in burns. Burns 1997;23:404–12.
63. Turner JG, Clark AJ, Gauthier DK, Williams M. The effect of therapeutic touch on pain and anxiety in burn patients. J Adv Nurs 1998;28:10–20.
64. Sheridan RL, Hinson M, Nackel A, et al. Development of a pediatric burn pain and anxiety management program. J Burn Care Rehabil 1997;18:455–9.
65. Sedowofia K, Barclay C. The systemic stress response to thermal injury in children. Clin Endocrinol (Oxf) 1998;49: 335–41.
66. Anand KJ. The stress response to surgical trauma: from physiological basis to therapeutic implications. Prog Food Nutr Sci 1986;10:67–132.
67. Hill AG, Hill GL. Metabolic response to severe injury. Brit J Surg 1998;85:884–90.
68. Smith A, Barclay C. The bigger the burn, the greater the stress. Burns 1997 Jun;23:291–4.
69. Greisen J, Juhl CB, Grofte T. Acute pain induces insulin resistance in humans. Anesthesiology 2001;95:578–84.
70. Bouwmeester NJ, Anand KJ. Hormonal and metabolic stress responses after major surgery in children aged 0–3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001;87:390–9.
71. Anand KJ, Sippell WG. Does halothane anaesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation? BMJ 1988;296:668–72.
72. Swedberg K, Eneroth P. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990 Nov;82:1730–6.
73. Wilmore DW. Metabolic response to severe surgical illness: overview. World J Surg 2000 Jun;24:705–11.
74. Ogawa K, Hirai M, Katsube T. Suppression of cellular immunity by surgical stress. Surgery 2000 Mar;127:329–36.
75. Clark MA, Plank LD, Hill GL. Wound healing associated with severe surgical illness. World J Surg 2000 ;24:648–54.
76. Rao MV, Chari P, Malhotra SK, Dash RJ. Role of epidural analgesia on endocrine and metabolic responses to surgery. Indian J Med Res 1990 ;92:13–6.
77. Brandt MR, Fernades A. Epidural analgesia improves postoperative nitrogen balance. Br Med J 1978;1:1106–8.
78. Mizutani A, Hattori S, Yoshitake S. Effect of additional general anesthesia with propofol, midazolam or sevoflurane on stress hormone levels in hysterectomy patients, receiving epidural anesthesia. Acta Anaesthesiol Belg 1998;49: 133–9.
79. Giesecke K, Hamberger B. High- and low-dose fentanyl anaesthesia: hormonal and metabolic responses during cholecystectomy. Br J Anaesth 1988;61:575–82.
80. Perry BD, Pollard R. Homeostais, stress, trauma, and adaptation: a neurodevelopmental view of childhood trauma. Child Adolesc Psychiatr Clin N Am 1998;7:33–51.
81. Perry BD, Pollard RA, Blakeley TL, et al. Childhood trauma, the neurobiology of adaptation and use-dependent development of the brain: how states become traits. Infant Ment Health J 1995;16:271–291.
82. Stoddard FJ, Norman DK, Murphy JM. A diagnostic outcome study of children and adolescents with severe burns. J Trauma 1989;29:471–7.
83. Stoddard FJ: Care of infants. children and adolescents with burn injuries. In: Lewis M, editor. Child and adolescent psychiatry: a comprehensive textbook. Baltimore: Williams & Wilkins; 1996. p.1016–37.
84. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition. Text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 1994.
85. Tarnowski KJ, Rasnake LK. Long term psychosocial sequelae. In: Tarnowski KJ, editor. Behavioral aspects of pediatric burns. New York: Plenum Press; 1994. p. 81–118.
86. Kavanaugh CK, Lasoff E, Eide Y, et al. Learned helplessness and the pediatric burn patient: dressing change behavior and serum cortisol and beta endorphin. J Pain Symptom Manage 1991:106–77.
87. Charney DC, Deutch AY, Krystal JH, et al. Psychobiolog-

ical mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry 1993;50:294–305.
88. van der Kolk BA. The body keeps the score: Memory and the evolving psychobiology of PTSD. Harvard Rev Psychiatry 1994;1:253–65.
89. Vasoo S, Ng SC. New cyclooxygenase inhibitors. Ann Acad Med Singapore 2001;30:164–9.
90. Sullivan KM, Belay ED, Durbin RE, Foster DA, Nordenberg DF. Epidemiology of Reye's syndrome, United States, 1991–1994: comparison of CDC surveillance and hospital admission data. Neuroepidemiology 2000;19:338–44.
91. Dong YL, Fleming RY, Yan TZ, Herndon DN, Waymack JP. Effect of Ibuprofen on the inflammatory response to surgical wounds. J Trauma 1993;35:340–3.
92. Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. JAMA 2000; 283:1710–4.
93. MacPherson RD. The pharmacological basis of contemporary pain management. Pharmacol Ther 2000;88:163–85.
94. Vaccarino AL, Kastin AJ. Endogenous opiates: 1999. Peptides 2000;21:1975–2034.
95. Friedman JD, Dello Buono FA. Opioid antagonists in the treatment of opioid-induced constipation and pruritus. Ann Pharmacother 2001;35:85–91.
96. Patterson DR, Ptacek JT, Carrougher GJ, Sharar SR. Lorazepam as an adjunct to opioid analgesics in the treatment of burn pain. Pain 1997;72:367–74.
97. Mitler MM. Nonselective and selective benzodiazepine receptor agonists—where are we today? Sleep 2000;23(Suppl 1):S39–47.
98. Young C, Knudsen N, Hilton A, Reves JG. Sedation in the intensive care unit. Crit Care Med 2000;28:854–66.
99. Baum CR. A century of Mickey Finn—but who was he? J Toxicol Clin Toxicol 2000;38:683.
100. Cote CJ, Karl HW, Notterman DA, Weinberg JA, McCloskey C. Adverse sedation events in pediatrics: analysis of medications used for sedation. Pediatrics 2000;106: 633–44.
101. Harvey MA. Managing agitation in critically ill patients. Am J Crit Care 1996;5:7–16; .
102. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. Crit Care Med 1995;23: 1596–600.
103. Cassem NH, Murray GB. Delirious patients. In: Cassem EH, Jellinek M, Rosenbaum J, Stern T, Jellinek MS, editors. Massachusetts General Hospital handbook of general hospital psychiatry. 4th ed. St. Louis: Mosby Year Book; 1997. p. 112–6.
104. Hurford WE. Sedation in the intensive care unit. Int Anesthesiol Clin 1999;37:113–22.
105. O'Brien JM, Rockwood RP, Suh KI. Haloperidol-induced torsade de pointes. Ann Pharmacother 1999;33:1046–50.
106. Riker RR, Fraser GL, Richen P. Movement disorders associated with withdrawal from high-dose intravenous haloperidol therapy in delirious ICU patients. Chest 1997;111: 1778–81.
107. Brown RL, Henke A, Greenhalgh DG, Warden GD. The use of haloperidol in the agitated, critically ill pediatric patient with burns. J Burn Care Rehabil 1996;17:34–8.
108. Warncke T, Stubhaug A, Jorum E. Ketamine, an NMDA. receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. Pain 1997;72:99–106.
109. Parker J. Burn care protocols: administration of ketamine. Review of feature protocol Shriners Hospital for Crippled Children Burns Institute, Galveston, Texas. J Burn Care Rehabil 1987;8:149.
110. Martyn JA. Burn care protocols: administration of ketamine. Ketamine pharmacology and therapeutics. J Burn Care Rehabil 1987;8:146–8.
111. Warncke T, Stubhaug A, Jorum E. Preinjury treatment with morphine or ketamine inhibits the development of experimentally induced secondary hyperalgesia in man. Pain 2000;86:293–303.
112. Maldini B. Ketamine anesthesia in children with acute burns and scalds. Acta Anaesthesiol Scand 1996;40:1108–11.
113. Parker J. Burn care protocols: administration of ketamine. Review of feature protocol Shriners Hospital for Crippled Children Burns Institute, Galveston, Texas. J Burn Care Rehabil 1987;8:149.
114. Kohp R, Durieux M. Ketamine: teaching an old dog new tricks. Anesth Analg 1998;87:1186–93.
115. Humphries Y, Melson M, Gore D. Superiority of oral ketamine as an analgesic and sedative for wound care procedures in the pediatric patient with burns. J Burn Care Rehabil 1997;18:34–6.
116. Pandey CK, Mathur N, Singh N, Chandola HC. Fulminant pulmonary edema after intramuscular ketamine. Can J Anaesth 2000;47:894–6.
117. Gill JR, Stajic M. Ketamine in non-hospital and hospital deaths in New York City. J Forensic Sci 2000;45:655–8.
118. Martinez S, Achauer B, Dobkin de Rios M. Ketamine use in a burn center: hallucinogen or debridement facilitator? J Psychoactive Drugs 1985;17:45–9.
119. Laird SM, Sage M. Psychosis and ketamine. BMJ 1972;1: 246.
120. Robert R, Blakeney PE, Villarreal C, Rosenberg L, Meyer WJ. Imipramine treatment in pediatric burn patients with symptoms of acute stress disorder: a pilot study. J Am Acad Child Adolesc Psychiatry 1999;38:873–82.
121. Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. Anesth Analg 2000;91: 185–91.
122. Baskett PJ. Analgesia for the dressing of burns in children: a method using neuroleptanalgesia and Entonox. Postgrad Med J 1972;48:138–42.
123. Baskett PJ, Hyland J, Deane M, Wray G. Analgesia for burns dressing in children. A dose-finding study for phenoperidine and droperidol with and without 50 per cent nitrous oxide and oxygen. Br J Anaesth 1969;41:684–8.
124. Fulton B, Sorkin EM. Propofol. An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. Drugs 1995;50:636–57.
125. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Crit Care Med 1997;25:33–40.
126. Martin PH, Murthy BV, Petros AJ. Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care. Br J Anaesth 1997;79:276–9.
127. Bray RJ. Propofol infusion syndrome in children. Paediatr Anaesth 1998;8:491–9.
128. Mills DC, Lord WD. Propofol for repeated burns dressings in a child: a case report. Burns 1992;18:58–9.
129. Wolf A, Weir P, Segar P. Impaired fatty acid oxidation in propofol infusion syndrome. Lancet 2001;357:606–7.
130. Hatch DJ. Propofol in paediatric intensive care [editorial]. Br J Anaesth 1997;79:274–5.
131. Hertzog JH, Dalton HJ, Anderson BD, Shad AT, Gootenberg JE, Hauser GJ. Prospective evaluation of propofol anesthesia in the pediatric intensive care unit for elective oncology procedures in ambulatory and hospitalized children. Pediatrics 2000;106:742.
132. Markovitz BP, Feuer P, Cox P. Rare events often happen infrequently: propofol complications revisited [letter]. Crit Care Med 2000;28:2178–9.

133. Reed MD, Blumer JL. Propofol bashing: the time to stop is now! [letter]. Crit Care Med 1996;24:175–6.
134. Magnus L. Nonepileptic uses of gabapentin. Epilepsia 1999;40(Suppl 6):S66–72; discussion S73–4.
135. Hansen HC. Treatment of chronic pain with antiepileptic drugs: a new era. South Med J 1999;92:642–9.
136. Rawal N. Patient-controlled regional analgesia (PCRA). Acta Anaesthesiol Belg 1999;50:221–5.
137. Gaukroger PB. Patient-controlled analgesia in children. In: Schechter NL, Berde CB, Yaster M, editors. Pain in infants, children, and adolescents. Baltimore: Williams & Wilkins; 1993. p. 203–11.
138. Blouin R, Lockett J. Patient-controlled analgesia: optimizing the experience. Clin Nurs Res 1999;8:283–94.
139. Etches RC. Patient-controlled analgesia. Surg Clin North Am 1999;79:297–312.
140. Berde CB, Lehn BM, Yee JD, Sethna NF, Russo D. Patient-controlled analgesia in children and adolescents: a randomized prospective comparison with intramuscular administration of morphine for postoperative analgesia. J Pediatrics 1991;118:460–6.
141. Rovers J, Knighton J, Neligan P, Peters W. Patient-controlled analgesia in burn patients: a critical review of the literature and case report. Hosp Pharm 1994;29: 106,108–11.
142. Sheridan RL. Airway management and respiratory care of the burn patient. Int Anesthesiol Clin 2000;38:129–45.
143. Tobias JD, Berkenbosch JW. Tolerance during sedation in a pediatric ICU patient: effects on the BIS monitor. J Clin Anesth 2001;13:122–4.
144. Sennholz G. Bispectral analysis technology and equipment. Minerva Anestesiol 2000;66:386–8.
145. Razek T, Gracias V, Sullivan D. Assessing the need for reintubation: a prospective evaluation of unplanned endotracheal extubation. J Trauma 2000;48:466–9.
146. Zeggwagh AA, Abouqal R, Madani N, Zekraoui A, Kerkeb O. Weaning from mechanical ventilation: a model for extubation. Intensive Care Med 1999;25:1077–83.
147. Leino K, Nunes S, Valta P, Pikanen O, Vanakoski J, Takala J. The effect of sedation on weaning following coronary artery bypass grafting: propofol versus oxycodone-thiopental. Acta Anaesthesiol Scand 2000;44:369–77.
148. Edmunds S, Weiss I, Harrison R. Extubation failure in a large pediatric ICU population. Chest 2000;119:897–900.
149. Tilley W, McMahon S, Shukalak B. Rehabilitation of the burned upper extremity. Hand Clin 2000;16:303–18.
150. Nelson DL, Klinger JR, Buczko GB, Levy MM. Prediction of post-extubation work of breathing. Crit Care Med 2000; 28:1341–6.
151. van der Laan L, Goris RJ. Reflex sympathetic dystrophy after a burn injury. Burns 1996;22:303–6.
152. Aprile AE. Complex regional pain syndrome. AANA J 1997;65:557–60.
153. Stoddard FJ, Saxe G. A ten-year research review of physical injuries. J Am Acad Child Adolesc Psychiatry 2001;40: 1128–1145.
154. Olsson G, Berde C. Neuropathic pain in children and adolescents. In: Schechter NL, Berde CB, Yaster M, editors. Pain in infants, children, and adolescents. Baltimore: Williams & Wilkins; 1993. p. 473–93.
155. Portenoy RK, Cheveille AL. Chronic pain management. In: Stoudemire A, Fogel BS, Greenberg DB, editors. Psychiatric care of the medical patient. 2nd ed. New York: Oxford University Press; 2000. p. 207–13.
156. Thomas C, Brazeal B, Behrends L, Rosenberg L, Robert R, Blakeney P. Phantom limb sensation and pain in youth burn survivors [abstract]. Book of Abstracts of the 5th International Symposium on Pediatric Pain, London 2000. Glasgow: Meeting Makers; p. 141.
157. Krane EJ, Heller LB. The prevalence of phantom sensations and pain in pediatric amputees. J Pain Symptom Manage 1995;10:21–9.
158. Smith J, Thompson JM. Phantom limb pain and chemotherapy in pediatric amputees. Mayo Clin Proc 1995;70: 357–64.
159. Schwenkreis P, Witscher K, Janssen F, et al. Assessment of reorganization in the sensorimotor cortex after upper limb amputation. Clin Neurophysiol 2001;112:627–35.
160. Fainsinger RL, de Gara C, Perez GA. Amputation and the prevention of phantom pain. J Pain Symptom Manage 2001;20:308–12.
161. Varni JW, Setoguchi Y, Rappaport LR, Talbot D. Effects of stress, social support, and self esteem on depression in children with limb deficiencies. Arch Phys Med Rehabil 1991; 72:1053–8.
162. Gallagher RM, Verma S. Treatment and rehabilitation of chronic orthopedic pain syndrome. In: Stoudemire A, Fogel BS, Greenberg DB, editors. Psychiatric care of the medical patient. 2nd ed. New York: Oxford University Press; 2000. p. 242.
163. Nikolajsen L, Jensen TS. Phantom limb pain. Curr Rev Pain 2000;4:166–70.
164. MacLennan SE, Wells MD, Neale HW. Reconstruction of the burned breast. Clin Plast Surg 2000;27:113–9.
165. Pisarski GP, Mertens D, Warden GD, Neale HW. Tissue expander complications in the pediatric burn patient. Plast Reconstr Surg 1998;102:1008–12.
166. Gilboa D, Friedman M, Tsur H. The burn as a continuous traumatic stress: implications for emotional treatment during hospitalization. J Burn Care Rehabil 1994;15:86–91.
167. Lawrence JW, Fauerbach J, Munster A. Early avoidance of traumatic stimuli predicts chronicity of intrusive thoughts following burn injury. Behav Res Ther 1996;34:643–6.
168. Fauerbach JA, Lawrence J, Haythornthwaite J, McGuire M, Munster A. Preinjury psychiatric illness and postinjury adjustment in adult burn survivors. Psychosomatics 1996;37: 547–55.
169. Stoddard FJ. Body image development in the burned child. J Am Acad Child Psychiatry 1982;5:502–7.
170. Dise-Lewis JE. A developmental perspective in psychological principles of burn care. J Burn Care Rehabil 2001: 255–60.
171. Chedekel DS, Rizzone LP, Antoon AY. Burns. In: Ammerman RT, Campo JV, editors. Handbook of pediatric psychology and psychiatry, Vol. II. Disease, injury and illness. Boston: Allyn and Bacon; 1998. p. 191–205.
172. Zeltzer L. Pain and symptom management. In: Bearson DJ, Mulhern RK, editors. Pediatric psychooncology: psychological perspectives on children with cancer. New York: Oxford University Press; 1994. p. 61–83.
173. Atchison NE, Osgood PF, Carr DB, Szyfelbein SK. Pain during burn dressing change in children: relationship to burn area, depth, and analgesic regimen. Pain 1991;47: 41–5.
174. Stoddard FJ. Psychiatric management of the burned patient. In: JAJ Martyn, editor. Acute management of the burned patient.. Philadelphia: WB Saunders; 1990; p. 256–72.
175. Prensner JD, Yowler CJ, Smith LF, Steele AL, Fratianne RB. Music therapy for assistance with pain and anxiety management in burn treatment. J Burn Care Rehabil 2001;22: 83–8.
176. Attanasio V, Andrasik F, Burke EJ, Blake DD, Kabela E, McCarran MS. Clinical issues in utilizing biofeedback with children. Clin Biofeedback Health 1985;8:134–41.
177. Hernandez-Rief M, Field T, Largie S, et al. Childrens' distress during burn treatment is reduced by massage therapy. J Burn Care Rehabil 2001;22:191–5.
178. Hoffman HG, Doctor JN, Patterson DR, Carrougher GJ, Furness TA III. Virtual reality as an adjunctive burn pain

control during wound care in adolescent patients: a case report. Pain 2000;85:305–9.
179. Stoddard FJ, Chedekel DS, Shakun L. Dreams in burned children. In: Barrett D, editor. Trauma and dreams,. Cambridge: Harvard University Press; 1996. p. 26–45.
180. Kuttner L. Mind-body methods of pain management. Child Adolesc Psychiatr Clin N Am 1997;6:783–96.
181. Whaley L, Wong DL. Nursing care of infants and children. St. Louis: Mosby; 1987.
182. Thurber CA, Martin-Herz SP, Patterson DR. Psychological principles of burn wound pain in children. I. Theoretical framework. J Burn Care Rehabil 2000;21:376–87.
183. Martin-Herz SP, Thurber CA, Patterson DR. Psychological principles of burn wound pain in children. II: treatment applications. J Burn Care Rehabil 2000;21:458–72.
184. George A, Hancock J. Reducing pediatric burn pain with parent participation. J Burn Care Rehabil 1993;14:104–7.
185. Foertsch CE, O'Hara MW, Stodard FJ, Kealey GP. Parent participation during burn debridement in relation to behavioral distress. J Burn Care Rehabil 1996;17:372–7.
186. Shaw EG, Routh DK. Effect of mother's presence on children's reaction to aversive procedures. J Pediatr Psychol 1982;7:33–42.
187. Gonzalez JC, Routh DK, Saab PG, et al. Effects of parent presence on children's reactions to injections: behavioral, physiological and subjective aspects. J Pediatr Psychol 1989;14:449–62.
188. Zeltzer L. Pain and symptom management. In: Bearson DJ, Mulhern RK, editors. Pediatric psychooncology: psychological perspectives on children with cancer. New York: Oxford University Press; 1994. p. 61–83.
189. Kavanaugh C. A new approach to dressing change in the severely burned child and its effect on burn-related psychopathology. Heart Lung 1983;12:612–19.
190. Rothbaum F, Wiesz JR, Snyder S. Changing the world and changing the self: a two-process model of perceived control. J Pers Soc Psychol 1982;42:5–37.
191. American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. JAMA 1995;274:1874–80.
192. U.S. Department of Health and Human Services, Public Health Service. Acute pain management in infants, children, and adolescents: operative and medical procedures practice guideline (AHCPR 92-0020). Rockville, MD: Agency for Health Care Policy and Research; 1992.
193. Nolan K. Ethical issues in pediatric pain management. In: Schechter NL, Berde CB, Yaster M, editors. Pain in infants, children, and adolescents. Baltimore: Williams & Wilkins; 1993. p. 123–32.
194. Anand KJS, Hickey PR. Pain in the fetus and neonate. N Engl J Med 1987;317:1321–9.
195. Cassell EJ. Recognizing suffering. Hastings Cent Rep 1991;21:24–31.
196. Melzack R. The tragedy of needless pain. Sci Am 1990;262: 27–33.
197. MacPherson RD. The pharmacologic basis of contemporary pain management. Pharmacol Ther 2000;88:163–85.
198. Stoddard FJ, Sheridan R, Selter L, Greenberg DB. General surgery: basic principles. In: Stoudemire A, Fogel BS, Greenberg DB, editors. Psychiatric care of the medical patient. 2nd ed. New York: Oxford University Press; 2000. p. 969–87.
199. Schnitzer J, Nankin M, Stoddard FJ. Death and grief counseling in children and adolescents. In: Stoudemire A, Fogel BS, Greenberg DB, editors. Psychiatric care of the medical patient. 2nd ed. New York: Oxford University Press; 2000. p.1127–31.
200. Schechter NL. The status of pediatric pain control. Child Adoles Psychiatr Clin North Am 1997;6:687–90.