Anesthesiology 2002; 96:523–6

Measurement of Pain in Children

State-of-the-art Considerations

THE subject of pain in children and infants has received considerable attention during the past decade. Pain in neonates and children has historically been underreported, undertreated, and frequently misunderstood. Research comparing analgesic usage between adults and children began to emerge in the 1970s and consistently revealed that children received fewer, less frequent, and smaller doses of potent analgesics.[1–3] Recent investigations show limited improvement in prevailing practices in pain management in children[4] despite efforts to change the purview and practice of clinicians. Wide variations still exist in practice philosophies in different pediatric centers.[5] Although multiple methods have been described to measure and assess pain in children, most are not well-validated and not applicable to all age groups, and none have been universally accepted. Young children and children with cognitive disabilities are especially difficult to evaluate for pain because of their limited understanding and communication skills. Despite these difficulties, measurement of pain in children is of major importance for substantiating a therapeutic decision and evaluating the effectiveness of a particular intervention.

In this issue, Breau *et al.*[6] report about the development and validation of the Non-communicating Children's Pain Checklist–Postoperative Version (NCCPC-PV). This publication is of particular importance because anesthesiologists have had significant difficulties in assessing postoperative pain in children with major cognitive disabilities. The perception of pain includes a sensory component, involving neural pathway activation in response to noxious stimuli, and an affective response, which involves behavioral and cognitive aspects. The International Association for the Study of Pain states that, "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[7] Pain is what the subject says hurts.[8] But how is pain described and measured in the preverbal or noncommunicating disabled child?

Pain is clearly subjective and no longer considered an experience in which pain intensity is *only* proportional to the objective degree of injury. It is certain that the pain experience cannot be separated into its physical and emotional components. The complex response to a noxious stimulus results in behavior that is unique and dependent on multiple factors, including one's experiences and perceptions. Pain experience in children is further complicated by the dynamic evolution of conscious awareness and psychologic and physiologic development. Therefore, pain assessment in children is dependent in large part on their level of understanding as well as their ability to convey to others the magnitude of their experience. Obviously, this ability to convey the existence of pain may be significantly limited in the disabled child.

In general, pain assessment instruments in children can be categorized as observational, self-report, and physiologic instruments. Because of the subjective nature of pain, *self-report methods* are considered the best measure of pain in children who are at least 5 or 6 yr old. These methods are less reliable in younger children and children with cognitive disabilities because they rely heavily on visual analogs, sensory associations, and verbal responses. For example, Hester's Poker Chip Tool was validated for children as young as 4 yr of age. However, both sensory and motor responses are required in selecting the "pieces of hurt."[9] Therefore, the application of self-report scales is limited to children who can understand the objectives and descriptors of these techniques. Several *physiologic parameters* have been used to assess pain in children. These include changes in heart rate or in beat-to-beat heart rate variability, blood pressure, serum cortisol concentrations, transcutaneous oxygen tension, and palmar sweating.[10,11] However, physiologic parameters can be influenced by a variety of processes, such as hypoxemia, hypovolemia, and fever, that are unrelated to pain *per se*. Because of the properties of self-report and physiologic measures, preverbal and cognitively disabled children benefit the most from observational measures. The most valuable *observational descriptors* are behaviors such as crying, facial expression, touch behavior, leg position, and general body movements. However, it should be noted that observational measures may be subject to limitations, such as difficulty to separate behavior associated with pain from that caused by fear and anxiety and underestimation of acute postoperative pain.[12]

◆ This Editorial View accompanies the following article: Breau LM, Finley GA, McGrath PJ, Camfield CS: Validation of the Non-communicating Children's Pain Checklist–Postoperative Version. ANESTHESIOLOGY 2002; 96:528–35.

Accepted for publication December 26, 2001. Supported in part by grant No. R01HD37007-01 from the National Institutes of Health, Bethesda, Maryland, and the Patrick and Catherine Weldon Donaghue Medical Research Foundation, Hartford, Connecticut (to Dr. Kain). The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

The observational pain assessment instrument described in the article by Breau *et al.*[6] has to be evaluated in the more general context of a behavioral instrument used in clinical medicine. The development of such instruments in general, as well as those used particularly to assess pain in children, begins with the identification of all descriptors relating to the phenomenon measured. The original publication that described the development of the NCCPC-PV provides extensive content coverage and descriptors of areas related to pain in nonverbal, cognitively impaired children.[13]

The next step involves selecting an appropriate scale of measurement. S. S. Stevens[14–16] made in the 1950s a lasting contribution to the classification of scales of measurement. Stevens[14–16] was the first to conceive the idea of a measurement system that he designated as the familiar nominal, ordinal, equal interval, and equal ratio scales of measurement. The impact of Stevens' work has been great enough that the very words that he suggested, nominal, ordinal, equal interval, and equal ratio, find themselves expressed in every major work on research design.

Stevens[14–16] also suggested an association between the scale type used and the level of reliability and validity of the phenomenon being measured. He indicated that each successive scale (nominal, ordinal, equal interval, and equal ratio) progresses in complexity, by incorporating the defining feature of each preceding scale and adding its own unique feature. The sequence is as follows: The simplest type of scale, a *nominal* scale, contains two or more unordered categories of the entity measured (*i.e.*, presence or absence of pain). At the next level of scale complexity, there are two or more categories of classification, as in nominal scales, but the defining feature that is added is that the categories are now ordered to form an *ordinal* scale (*i.e.*, slight pain, mild pain, moderate pain, severe pain). The third level of scale complexity would be the *equal interval* scale. This scale has three or more categories of classification (the nominal feature), and they are ordered (the ordinal feature), but the defining feature is that one can also identify points on the scale that are equal in interval size. For example, on a 10-point pain scale, a pain experienced as a 7 is to be interpreted as being exactly 3 points less than one of 10. However, the scale does not allow one to conclude that a pain score of 6 refers to twice as much pain as one of 3. The most complex scale, in Stevens' conceptualization, is the *equal ratio* scale of measurement. Such a scale has nominal, ordinal and equal interval features but now incorporates the additional feature of equal ratio categories of classification. For example, on a 10-point pain scale, a score of 2 represents twice as much pain as a score of 1, and a pain score of 9 indicates three times as much pain as a score of 3. The NCCPC-PV developed by Breau *et al.*[6] classifies pain intensity as one of the following: "not at all," "just a little," "fairly often," and "very often." Therefore, at first look, the NCCPC-PV can be classified as a dichotomous ordinal scale with an absence category followed by two or more categories of degree of presence of pain.[17] However, it should be noted that the absence category is used so infrequently that the NCCPC-PV can for all purposes be treated as a continuous ordinal scale with no category of absence.

Interestingly, despite the existence of multiple interval and ratio scales in clinical medicine, most medical decisions are categorical in nature. For example, total cholesterol is measured on an equal ratio scale (*e.g.*, 300 mg/dl is twice as high as 150 mg/dl). However, this has little meaning medically. That is, a level of 300 mg/dl requires treatment, whereas a level of 150 mg/dl does not require treatment. It is also important to indicate that the same clinical phenomenon can be measured on different types of scales of measurement, depending on the research question. For example, if one needs to correlate cholesterol level with age at first myocardial infarction, one would measure cholesterol on an equal ratio scale. In this case, one would lose information and artificially lower the correlation by measuring cholesterol on an ordinal scale, such as 1 = ideal, 2 = borderline, and 3 = high.

S. S. Stevens also believed that in terms of the scientific quality of the information produced, equal ratio scales were superior to all others, equal interval scales were superior to both ordinal and nominal scales of measurement, and ordinal scales were superior only to nominal scales. The direct implication here is that the degree of reliability and validity of a phenomenon increases as a function of the complexity of the scale type. The issue of reliability and validity as a function the complexity of the scale type is currently a source of some debate. Although some scientists agree with the theory developed by Stevens,[18] others strongly disagree. There is considerable research evidence that supports the contrary view to Stevens. For example, a study undertaken by one of the authors and his British colleagues showed that whether psychiatric diagnoses were made on nominal ordinal or equal ratio scales, the levels of interexaminer reliability were essentially interchangeable.[19] Similarly, computer simulation research indicates that equal ratio scales are no more reliable than seven-category ordinal scales.[20] Therefore, we submit that the decision regarding the type of scale used has to be based solely on the nature of the clinical phenomena assessed.

Deciding on an optimal number of categories for a continuous ordinal scale, such as the NCCPC-PV, is a

Table 1. Clinical Significance of Sensitivity and Specificity Indices of Scales of Measurement

Size of Reliability Coefficient	Level of Observed Agreement	Level of Clinical or Practical Significance
< 0.40	< 70%	Poor
0.40–0.59	70–79%	Fair
0.60–0.74	80–89%	Good
0.75–1.00	90–100%	Excellent

complex issue that can be dated back to the early work of Symonds,[21] almost eight decades ago. Most recently, an extensive computer simulation investigation, and an experimental investigation by Preston and Colman,[20,22] indicate that scale reliability tends to increase as the number of categories increases. However, when the number of categories goes beyond seven, there tends to be no material increase in reliability.[20,22] The NCCPC-PV can be classified as a four-category ordinal scale. Given the authors' statement that the absence category is virtually never applicable (at least in their pediatric sample), the NCCPC-PV can be reclassified as a three-category ordinal clinical rating scale. Therefore, a question of whether reliability would increase if the number of the NCCPC-PV categories were to be increased to seven can be raised. This is an intriguing question for Breau *et al.*[6] as well as for the area of pain assessment in children.

Thus far, the discussion has been focused on issues related to the development of a clinical instrument. The last important issue relates to the reliability and validity of the clinical instrument that one develops. Because the appropriate model of the intraclass correlation coefficient (Ri) of chance-corrected agreement can be used with both ordinal and interval data,[23] the choice of Breau *et al.*[6] of this statistic, as recommended in Shrout and Fleiss,[24] is appropriate. Also, the authors' calculation of sensitivity and specificity indices for the NCCPC-PV is entirely appropriate. Cicchetti[25] has recently published a set of criteria that can be applied to assess the clinical significance of sensitivity and specificity indices of scales of measurement (table 1). These guidelines apply whether the scale consists of nominal, ordinal, or mixed scales, such as the NCCPC-PV. Applying these criteria to the current article, a score of 11 on the NCCPC-PV showed very good sensitivity (88%) and good specificity (81%). Finally, one of the last steps in assuring that the reported sensitivity and specificity of a newly developed clinical instrument have more general validity is to apply the receiver operating characteristic methodology, which provides evidence of the optimal levels and ranges of sensitivity and specificity.[26,27] The authors are to be commended for their application of receiver operating characteristic methodology in the development of the NCCPC-PV.

In closing, it should be noted that there are several lessons to be learned from the article of Breau *et al.*[6] First, it is always incumbent on investigators who develop new clinical behavioral instruments to specify the characteristics of the scales of measurement they use, as well as the rationale for the statistics that are used in the assessment of the psychometric properties of their instrument. Second, despite this age of increasing technology and specialization, there is a simultaneous and oppositely motivated increased need for cross-disciplinary collaboration to develop state-of-the-art contributions in pain assessment. Sophistication in assessment design is inherent, but this fact is brought to the forefront when one attempts to develop a valid and reliable pain tool for young and disabled children. Finally, a recent study by Warfield and Kahn[28] estimates that more than half of all adult surgical patients experience moderate to severe postoperative pain. It has been stated that accuracy in self-report can improve pain management practices. In disabled children, this option for self-lobbying is almost nonexistent. The American Pain Society in conjunction with the American Academy of Pediatrics states, "Observation of behavior should be used to complement self-report and can be an acceptable alternative when valid self-report is not available."[29] Therefore, it is imperative that accurate interpretations of behavior are achieved and assumptions are minimized when validating pain in children. There must be a closing of the gap between clinical assessment and scientific measurement, especially if pain and suffering are to be decimated in the disabled child.

The authors thank Charles Berde, M.D., Ph.D. (Children's Hospital, Boston, Massachusetts), for his helpful comments.

Zeev N. Kain, M.D.,* **Domenic V. Cicchetti, Ph.D., Brenda C. McClain, M.D.** *Vice-Chair and Professor of Anesthesiology and Pediatrics and Child Psychiatry, Yale University School of Medicine, New Haven, Connecticut. kain@biomed.med.yale.edu

References

1. Mather L, Mackie J: The incidence of postoperative pain in children. Pain 1983; 15:271–82
2. Eland JM, Anderson JE: The experience of pain in children, Pain: A Sourcebook for Nurses and Other Health Professionals. Edited by Jacox AK. Boston, Little Brown, 1977, pp 453–73
3. Beyer JE, DeGood DE, Ashley LC, Russell GA: Patterns of postoperative analgesic use with adults and children following cardiac surgery. Pain 1983; 17:71–81
4. Gauthier JC, Finley GA, McGrath PJ: Children's self-report of postoperative pain intensity and treatment threshold: Determining the adequacy of medication. Clin J Pain 1998; 14:116–20
5. McGrath PJ, Unruh AM: Perioperative and postoperative pain, Pain in Children and Adolescents. Amsterdam, Elsevier Science Publishers, 1987, pp 103–31
6. Breau LM, Finley GA, McGrath PJ, Camfield CS: Validation of the Noncommunicating Children's Pain Checklist–Postoperative Version. ANESTHESIOLOGY 2002; 96:528–35
7. International Association for the Study of Pain, Subcommittee on Taxonomy: Pain terms: A list with definitions and notes on usage. Pain 1979; 6:249–52
8. Parkhouse J, Pleurvy BJ, Rees JM: Analgesic Drugs. Oxford, Blackwell Scientific Publications, 1979, p 15
9. Hester NK: The pre-operational child's reaction to immunization. Nurs Res 1979; 28:250–4
10. Anand KJS, Carr DB: The neuroanatomy, neurophysiology, and neurochemistry of pain, stress, and analgesia in Newborns and children. Pediatr Clin North Am 1989; 36:795–822
11. Harpin VA, Rutter N: Development of emotional sweating in the newborn infant. Arch Dis Child 1982; 57:691–5
12. Lamontagne LL, Hepworth JT, Salisbury MH: Anxiety and postoperative pain in children who undergo major orthopedic surgery. Appl Nurs Res 2001; 14:119–24
13. McGrath PJ, Rosmus C, Canfield C, Campbell MA, Hennigar A: Behaviours caregivers use to determine pain in non-verbal, cognitively impaired individuals. Dev Med Child Neurol 1998; 40:340–3
14. Stevens SS: On the theory of scales of measurement. Science 1946; 103: 677–80
15. Stevens SS: Scales of measurement, Handbook of Experimental Psychology. Edited by Stevens SS. New York, Wiley, 1951, pp 23–30
16. Stevens SS: Measurement, statistics, and the schemapiric view. Science 1968; 168:849–56
17. Cicchetti DV: Assessing inter-rater reliability for rating scales: Resolving some basic issues. Br J Psychol 1976; 129:452–6
18. Gesheider GA, Bolanowski, SJ: Introduction to conference on ratio scaling of psychological magnitudes, Ratio Scaling of Psychological Magnitude. Edited by Bolanowski SJ, Gesheider GA. Hillsdale, New Jersey, Lawrence Erlbaum, 1991, pp 1–7

19. Remington M, Tyrer PJ, Newson-Smith J, Cicchetti DV: Comparative reliability of categorical and analogue rating scales in the assessment of psychiatric symptomatology. Psychol Med 1979; 9:765–70
20. Cicchetti DV, Showalter D, Tyrer P: The effect of number of rating scale categories upon levels of interrater reliability: A monte carlo investigation. Appl Psychol Meas 1985; 9:31–6
21. Symonds PM: On the loss of reliability in ratings due to coarseness of the scale. J Exp Psychol 1924; 7:456–61
22. Preston CC, Colman AM: Optimal number of response categories in rating scales: Reliability, validity, discriminating power, and respondent preferences. Acta Psychologica 2000; 104:1–15
23. Fleiss JL: Statistical methods for rates and proportions, 2nd edition. New York, Wiley, 1981, pp 212–36
24. Shrout PE, Fleiss JL: Intraclass correlations: Uses in assessing rater reliability. Psychol Bull 1979; 86:420–8
25. Cicchetti DV: The precision of reliability and validity estimates re-visited: Distinguishing between clinical and statistical significance of sample size requirements. J Clin Exp Neuropsychol 2001; 23:695–700
26. Hsiao JK, Bartko JJ, Potter WZ: Diagnosing diagnoses: Receiver operating characteristic methods and psychiatry. Arch Gen Psychiat 1989; 46:664–7
27. Kraemer HC: Assessment of 2 × 2 associations: Generalizations of signal detection methodology. Am Stat 1988; 42:47–9
28. Warfield CA, Kahn CH: Acute pain management: Progress in U.S. hospitals and experiences and attitudes among U.S. adults. ANESTHESIOLOGY 1995; 83:1090–4
29. The Assessment and Management of Acute Pain in Infants, Children and Adolescents: A Position Statement from the American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and American Pain Society Task Force on Pain in Infants, Children, and Adolescents. Glenview, Illinois, American Pain Society, 2001

Anesthesiology 2002; 96:526–7

No Preemptive Analgesia

Is That So Bad?

THE practice of operative anesthesia is an application of Hippocrates' dictum "*primum non nocere*"—first of all, do no harm. A successful anesthetic is one that minimally interferes with the patient's homeostasis and does not add to the unavoidable quotient of surgical trauma. In this context, it is understandable that the notion of preemptive analgesia, by which early application of therapies may diminish later misery, is an enticing grail to pursue. The anesthesiologist's ministrations might then actually improve the patients state, rather than being at best a necessary evil. It is therefore a potential disappointment to conclude, as do Møiniche *et al.*[1] in a detailed meta-analysis published in this issue of ANESTHESIOLOGY, that there is little experimental support for a preemptive analgesic effect in clinical settings. They reviewed 80 randomized and blinded studies that compared various analgesic techniques applied before incision and later in the perioperative period. Only modest differences were noted, and these were present only with epidural injections.

The quest to identify a benefit from preinjury analgesic administration for surgical patients has been fueled by repeated and convincing demonstrations of this phenomenon in animals. The reason that a robust experimental finding cannot be confirmed in patients is not forthcoming, but several explanations can be considered. First, sensory blockade may not be adequate during surgery. The basis of preemptive analgesia is the prevention of increased responsiveness of central nociceptive pathways triggered by intense afferent neural activity. Even very brief sensory events can result in central sensitization,[2,3] so effective prevention may require continuous sensory ablation throughout the surgical event. The intensity of afferent blockade is also important. Addition of systemic morphine to volatile anesthesia has no preemptive effect,[4] whereas the more thorough action of intrathecal morphine does prevent central sensitization in rats.[5] Small doses of intrathecal opioid show no preemptive effect, whereas larger doses have an amplified action given before injury,[6] presumably through greater efficacy in blocking input from small nonmyelinated C fibers.[7] The persistence of neuronal traffic, even during successful neuraxial anesthesia,[8] may limit the preemptive effect of this modality, indicating the importance of thorough regional blockade.[9] Increased strength of sensory stimulation may overcome the preemptive action of analgesics, even spinal local anesthetic, particularly if inflammation is a component of the injury.[10]

Demonstrations of preemptive effects in experimentation on animals have used various types of injuries, including formalin injection and nerve trauma. However, in models that more closely emulate typical clinical surgery, the results are mixed. Spinal hyperexcitability[11] and preemptive analgesia[12] are evident in some studies of abdominal surgical injury, but there is no influence of analgesic timing on pain behaviors after peripheral surgery[13] because of the minimal contribution of central facilitation.[14]

The most obvious reason for diverging experimental and clinical findings is that animals may differ substantially from humans in pain pathophysiology and neuropharmacology. In rats, the species with which most studies of preemptive analgesia have been performed, sensitization is readily induced in spinal sensory pathways after conditioning stimuli. A large effect can then be seen when

This Editorial View accompanies the following article: Møiniche S, Kehlet H, Dahl JB: A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: The role of timing of analgesia. ANESTHESIOLOGY 2002; 96:725–41.

Accepted for publication January 1, 2001. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

intense afferent activity is prevented from reaching the dorsal horn, which may not be the case in other species less prone to sensitization. Because genetic differences, even between various strains of rats, strongly affect the development of neuronal hyperexcitability[15] and hyperalgesia[16] after injury, comparison across species to human injury responses must be suspect.

It is not clear to me that the failure of preemptive analgesia is a great loss in the pragmatic clinical setting. Consider the outcomes used in studies of the topic. The analysis by Møiniche *et al.*[1] tabulates pain scores, supplemental analgesic demand, and time to first postoperative analgesic. Pain scores, while important, should not differ if appropriate care is provided because postoperative pain in the absence of preemptive treatment is nonetheless responsive to adequate doses of analgesia, consistent with electrophysiologic observations in animals.[6] A difference in supplemental analgesic demand should also not be an important medical issue. The need for 12 mg morphine in the recovery room instead of 4 mg before induction of anesthesia is itself not necessarily problematic. Although increased side effects from larger doses can be expected, there are no data to confirm this suspicion. Finally, a decreased time to first analgesic request in the absence of preemptive analgesia should not be a treatment problem, provided timely medication is available when the need arises.

The challenge, of course, is not to use the least amount of drug, but to minimize complications and optimize postoperative recovery. So far, there is minimal support for the belief that preemptive techniques aid recovery. One promising report confirms a favorable effect of early medication on the incidence and severity of chronic postoperative pain.[17] In future studies of the timing of analgesic agents, it will be helpful to focus on aspects of recuperation, not only on initial postoperative pain levels or analgesic consumption.

Rather than being disappointed, I find the conclusions of Møiniche *et al.*[1] to be encouraging. Trauma patients may be adequately treated with analgesics even though their injury has occurred without pretreatment because an early window of opportunity has not been missed. In scheduled surgery, the various side effects and complications that accompany intraoperative analgesic use may be avoided. For instance, intraoperative administration of opiates may lead to histamine release, dysfunction of the bowel, and disfunction of the biliary and urinary tracts, as well as acute opiate tolerance[18,19] and hyperalgesia,[20] which make postoperative pain treatment more difficult. Epidural local anesthetic block may complicate general anesthesia with hypotension and create diagnostic ambiguity afterward if paresis masks neurologic injury. For these reasons, initiating analgesic care at the time of emergence from general anesthesia may be more desirable; this is also a time when analgesic needs can be directly assessed. Because pain is "an unpleasant sensory and emotional experience,"[21] it cannot exist during general anesthesia. If preoperative and intraoperative analgesic treatment has little effect on the long-term course of sensory processes, their use before emergence lacks a clear motive.

There can be little doubt that great benefit will emerge from the burgeoning knowledge of processes underlying pain. Although experimentation may lead to drugs and techniques that can preemptively prevent pain in the clinical setting, our clinical attention must remain on treating pain when it presents, with adequate doses of proven agents.

Quinn H. Hogan, M.D., Professor, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin. qhogan@mcw.edu

References

1. Møiniche S, Kehlet H, Dahl JB: A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: The role of timing of analgesia. ANESTHESIOLOGY 2002; 96:725–41
2. Seltzer Z, Beilin BZ, Ginzburg R, Paran Y, Shimko T: The role of injury discharge in the induction of neuropathic pain behavior in rats. Pain 1991; 46:327–36
3. Yamamoto T, Shimoyama N, Mizuguchi T: Role of the injury discharge in the development of thermal hyperesthesia after sciatic nerve constriction injury in the rat. ANESTHESIOLOGY 1993; 79:993–1002
4. Abram SE, Olson EE: Systemic opioids do not suppress spinal sensitization after subcutaneous formalin in rats. ANESTHESIOLOGY 1994; 80:1114–9
5. Abram SE, Yaksh TL: Morphine, but not inhalation anesthesia, blocks post-injury facilitation. ANESTHESIOLOGY 1993; 78:713–21
6. Chapman V, Haley JE, Dickenson AH: Electrophysiologic analysis of preemptive effects of spinal opioids on N-methyl-D-aspartate receptor-mediated events. ANESTHESIOLOGY 1994; 81:1429–35
7. Woolf CJ, Wall PD: Morphine-sensitive and morphine-insensitive actions of C-fiber input on the rat spinal cord. Neurosci Lett 1986; 64:221–5
8. Lund C, Selmar P, Hansen OB, Hjortso NC, Kehlet H: Effect of epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. Anesth Analg 1987; 66:34–8
9. Shir Y, Raja SN, Frank SM: The effect of epidural versus general anesthesia on postoperative pain and analgesic requirements in patients undergoing radical prostatectomy. ANESTHESIOLOGY 1994; 80:49–56
10. Yashpal K, Katz J, Coderre TJ: Effects of preemptive or postinjury intrathecal local anesthesia on persistent nociceptive responses in rats: Confounding influences of peripheral inflammation and the general anesthetic regimen. ANESTHESIOLOGY 1996; 84:1119–28
11. Lascelles BDX, Waterman AE, Cripps PJ, Livingston A, Henderson G: Central sensitization as a result of surgical pain: Investigation of the pre-emptive value of pethidine for ovariohysterectomy. Pain 1995; 62:201–12
12. Welsh EM, Nolan AM: The effect of abdominal surgery on thresholds to thermal and mechanical stimulation in sheep. Pain 1995; 60:159–66
13. Zahn PK, Brennan TJ: Incision-induced changes in receptive field properties of rat dorsal horn neurons. ANESTHESIOLOGY 1999; 91:772–85
14. Brennan TJ, Umali EF, Zahn PK: Comparison of Pre- *versus* post-incision administration of intrathecal bupivacaine and intrathecal morphine in a rat model of postoperative pain. ANESTHESIOLOGY 1997; 87:1517–28
15. Hao J-X, Wiesenfeld-Hallin Z: Variability in the occurrence of ongoing discharges in primary afferents originating in the neuroma after peripheral nerve section in different strains of rats. Neurosci Lett 1994; 169:119–21
16. Shir Y, Zeltser R, Vatine JJ, Carmi G, Belfer I, Zangen A, Overstreet D, Raber P, Zeltzer Z: Correlation of intact sensibility and neuropathic pain-related behaviors in eight inbred and outbred rat strains and selection lines. Pain 2001; 90:75–82
17. Obata H, Saito S, Fujita N, Fuse Y, Ishizaki K, Goto F: Epidural block with mepivacaine before surgery reduces long-term post-thoracotomy pain. Can J Anaesth 1999; 46:1127–32
18. Vinik HR, Kissin I: Rapid development of tolerance to analgesia during remifentanil infusion in humans. Anesth Analg 1998; 86:1307–11
19. Chia YT, Liu K, Wang JJ, Kuo MC, Ho ST: Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999; 46:872–7
20. Celerier E, Rivat C, Jun Y, Laulin J-P, Larcher A, Reynier P, Simonnet G: Long-lasting hyperalgesia induced by fentanyl in rats: Preventive effects of ketamine. ANESTHESIOLOGY 2000; 92:465–72
21. Mersky H: Classification of chronic pain: Descriptions of chronic pain syndromes and definitions. Pain 1986; 3(suppl):S1–225