



Good, Clinical Pain Practice for Pediatric Procedure Pain: Neurobiologic Considerations

DENNIS PAUL NUTTER, DDS

ABSTRACT The objective of this review is to integrate current knowledge of pediatric procedure pain to develop a conceptual framework of good, clinical pediatric pain practice that can be used to improve the processes and outcomes of the clinical management of pediatric procedure pain in dentistry. This paper will present four characteristics of pain neurobiology that critically influence clinical decisions in pediatric procedure pain management.

AUTHOR

Dennis Paul Nutter, DDS, is in private practice in Fairfield, Calif.

ACKNOWLEDGMENT

The author thanks NorthBay Medical Center, Fairfield, Calif., and librarian Linda Grix for their assistance in the acquisition of many of the relevant journal articles for this paper.

Procedure pain is a brief but frequent, problematic feature of clinical practice encountered by the dental surgeon treating children.^{1,2} How this pain is assessed and managed is inevitably guided by each clinician's concept of good, clinical pediatric pain practice. Advancements in the understanding of the neurobiology of pain have led to pharmacological agents to obtund the nociceptive and central processing dimensions of pain experience.³⁻²⁴ Local anesthetics have historically served as the primary staple of intraoperative pain control in dentistry. However, the articles in this issue will argue that any description of good, clinical pain practice must take

its derivation from both the neurobiology of pain as well as those clinician factors that influence judgments of pain assessment and pain intervention.

This paper discusses the neurobiological characteristics of pediatric procedure pain that critically influence clinical decisions in pediatric procedure pain management. These are pain's subjective nature that defies prediction; its "plastic" nature that facilitates central sensitization; its developmental nature that ensures that children, in the absence of sensitization, will experience more pain for the same medical procedure than they will as adults; and its multidimensional nature that compels an accommodating multidimensional pain technique.



FIGURE 1.



FIGURE 2.



FIGURE 3.

FIGURES 1-3. All of the above children are displaying a type of pain behavior despite the absence of noxious nociceptive stimulation. In the context of a procedural setting, anxiety 1), anger 2), and what some may term “disobedience,” 3) are all examples of pain affect. The child in Figure 3 is not clowning around. He has been asked by both his father and the dental assistant to take his hands away from his face.

The Subjective Nature of Pain

Pediatric pain has a multidimensional ontogeny with contributions from nociceptive, affective (psychological) and stimulus dimensions that occur in a developmental context.^{25-27,2} Through genotypic and phenotypic processes, procedure pain becomes differentiated in each of us so that the magnitude of our pain experience is only partially related to the amount of tissue trauma experienced. The subjective, emotional dimension of pain has been affirmed by the International Association for the Study of Pain, which has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”²⁸ Studies have confirmed that a child’s sensitivity to pain varies from individual to individual.^{29,30}

In a study by Walco and Dampier, et al., experimental pain was applied to a group of children with a history of clinical pain and a group of healthy controls without pain history.³¹ The authors found that there was no uniform pain experience for a given stimulus intensity. They also found that previous pain experience lowers pain threshold levels, a process known as “central sensitization” discussed below. This phenotypic influence on nociceptive pathway development magnifies and further confounds genotypic differences in pain perception.

Given this, it is not possible for a clinician to reliably predict the intensity

of pain experienced by a child based on the clinician’s calculation of the extent of tissue damage or the clinician’s previous experience with the reactions of other children in similar conditions. The clinical and neurobiological evidence supports the idea that only the child can know how much pain they are experiencing.^{32,33} This is the first principle of good, clinical pain practice. It will be further supported by evidence, discussed in another article in this issue that clinicians tend to underestimate the magnitude of pain a child is experiencing as well as the clinical reality that there is no reliable, objective measure of pediatric pain.

The subjective expression of pain has two forms. In the case of procedure pain, the immediate form is the emotional response to the nociceptive-sensory perception of tissue trauma. It may manifest as an obvious, violent, evasive maneuver, or a barely discernable squinting of the eyes. The secondary form known as “pain affect” is the emotional response to its anticipated recurrence.^{26,34-36} Pain affect may appear as an anticipatory response to a consciously recognized external threat (fear), or as a vague but persistent apprehension of danger (anxiety).^{26,37-39} It may also be comprised of feelings such as “annoyance, anger, despair, boredom, or depression” if these moods assist in orienting the patient’s attention toward a pain stimulus.^{26,34,40} This delayed

feature of pain is facilitated by ascending sensory afferents that are heavily interconnected with limbic, emotional centers of the brain that retain information about a pain event’s time and place.^{41,42} Affective pain behavior can be as subtle as an elevated heart rate, as overt as the refusal to sit in the dental chair, or as dramatic as combative hysteria (**FIGURES 1-3**).

Individuals with trait or state anxiety have a pain affect that is positive; it orients their attention toward a pain stimulus resulting in a general hyperalgesia.^{40,43-45} Procedural anxiety’s relationship to increased pain perception is well known.^{46,39,47-50} Nakai and Milgrom et al. have concluded that unresolved preprocedural anxiety is the strongest predictor of poor pain control.¹ Therefore to target pain, a clinician must target for treatment both anticipated nociception and anticipated pain affect.

Central Sensitization

Generally, central sensitization refers to any plastic change in the central nervous system that results in an amplification of pain experience. The most recognizable clinical form is pain affect. This is the secondary emotional response (e.g., anxiety) resulting from the “cognitive appraisal” of a memory of prior pain.²⁶ This clinical observation has led to a “conventional wisdom”; that if children do not consciously remember a painful experience, then there is no lasting harm to them. For many clini-

cians this has served to anchor a chain of logic to rationalize permitting a greater intensity of pain during procedures performed on infants and preschool children while they are completely restrained. Certainly, most circumcision before 1997 falls into this category but arguably much of the current practice of complete immobilization of preschoolers for dental treatment also qualifies.^{51,52}

The idea that young children, even infants, do not remember painful events has been proven wrong by Clifford Woolf. In 1983, Woolf discovered the mechanism for a type of central sensitization that operates below the level of conscious memory by virtue of its location in the spinal cord.⁵² When pain signals travel from a site of tissue trauma to the dorsal horn of the spinal cord, it causes receptive fields to enlarge, reduce conduction thresholds, and amplify their responsiveness.⁵³⁻⁵⁷ As this “centrally located” altered sensory processing represents a form of subconscious memory, it is termed *implicit* memory to differentiate it from memory that is accessible to conscious thought, which is now being referenced as *explicit* memory.⁵⁸⁻⁶⁶ In fact, the processes associated with producing an implicit memory of pain experience appears to be mediated by the same chemical factors that promote learning, memory, and conditioning in the brain.^{67,68}

Much of what is known about the clinical effects of central sensitization in children can be gleaned from a single study of infant surgery by Taddio, Katz, and Ilerisich in 1997.⁵¹ It is a definitive demonstration of the sustained neural sensitization induced by procedure pain that is consistent with other studies, both human and animal.^{63,69-71} The study focused on the behavior of circumcised and uncircumcised infants at their first inoculation. An independent observer who was trained in rating infant pain

behavior, and who was blinded to the infant’s previous exposure to procedure pain, observed that circumcised infants consistently displayed greater distress than their noncircumcised peers.⁵¹

When better clinical pain practice was performed by placing an occlusive dressing of lidocaine-prilocaine cream (Emla) over the affected site for 60 to 80 minutes, these infants still displayed a distress level greater than the noncircumcised infants yet, less than the infants who were not given any pain medication.

**CIRCUMCISED
infants
consistently
displayed
greater distress
than their
noncircumcised peers.**

This study revealed three characteristics of the clinical sequela of procedure pain. First, it clearly demonstrated that a single episode of procedure pain in full-term infants can have a persistent disabling influence. Second, it showed that elevated sensitivity to tissue trauma is transferable to a site distant from the original injury, demonstrating that the sensitization in question is centrally mediated. Finally, it confirmed that pain intervention efforts can mitigate the degree to which a child may become sensitized.

The Hippocratic moral prescription to alleviate suffering has for centuries remained the traditional rationale for preventing pain.⁷² However, evidence that children “remember” pain implicitly compels clinicians to recalibrate

their pain justification scenarios to include the potential risk of a prolonged sensitization injury. The existence of implicit memory voids the idea that the absence of conscious memory for a painful event is proof that no latent harm is done. Procedure pain’s cumulative effect is a repetitive stress injury to developing pain pathways. It leads to a sustained, magnification of pain perception that can debilitate a patient’s compliance with future necessary, medical procedures.^{60,63,74,75} Any attempt to justify permitting pediatric procedure pain is now more difficult due to this increased risk of sensitization injury. From this, it follows that it is better to prevent pain than to treat it after its occurrence.^{32,33}

The Developmental Dimension

Younger children generally experience more pain for the same medical procedure than do older children.^{46,29,76-79} The mechanisms accounting for this observation in children have not been entirely elaborated but the immaturity of both their pain modulating mechanisms and their cognitions are contributors to the phenomenon.

Infants are not born with the endogenous pain control mechanisms that benefit adults.⁸⁰ This includes, but is not limited to, diffuse and descending pain inhibitory controls, voluntary control of attention, and arousal state.⁸¹⁻⁹¹ These pain-limiting mechanisms are absent in the neonate and only gradually develop from nascent, endogenous utility in the preschool child to, putatively, full complement in late adolescence.^{92-94,78} Clinical pain studies demonstrating that younger children experience more pain for the same medical procedure than do older children corroborates these basic science findings.^{29,76} In adults, anxiety alone may be sufficient to produce endogenous opioid analgesia.⁴⁰ Yet, in children this

presumed advantage is lost through the rudimentary functioning of their pain modulating mechanisms that only blossom over time. This makes them more vulnerable to a debilitating, long-term potentiation of their nociceptive pathways as a result of exposure to procedure pain.

It would be important clinically to know the age at which a child's pain modulating mechanisms mature most rapidly. This would be an important milestone in a child's presumptive tolerance to pain. Noteworthy in this respect is the Jay, Ozolins, et al. study that found that children under the age of 7 exhibit five times more distress during bone marrow aspirations than do older children.²⁹ Evidently, 6-year-olds have a rapid maturation of pain inhibitory controls. However, not all children will conform to this developmental schedule. Before applying this rule to children clinically, it would be well to remember that brain imaging studies of children with attention deficit disorder have revealed that the areas of their brains that are responsible for control of attention are three years delayed in their development.⁹⁶ Voluntary control of attention is an endogenous pain control mechanism that will be delayed in these individuals.

The younger the child, the more pain they experience for the same invasive procedure and the greater is their need for pain intervention. This strengthens the credibility of the behavioral pain reports of young children and provides a rationale to modify procedures to lower their noxious stimulation or, when practicable, delay procedures until the child has developed increased pain modulating mechanisms.

The Multidimensional Nature of Pain

Pain's multidimensional nature is facilitated by a convergence of peripheral sensory receptors and a centrally medi-

ated psychological dimension.^{56,83,97,98} Children's pain is differentiated from adult pain by its developmental dimension that is responsible for variations in an individual's pain experience over time.^{93,99} Procedure pain, unlike chronic pain, has an easily recognizable and controlled stimulus dimension.

The stimulus dimension is comprised of those aspects of a procedure's invasiveness that encompasses the full spectrum of sensory receptors. This definition therefore includes not only nociceptive input but also those sensory aspects (touch, smell, sight, hearing, and taste) of a procedure that can be perceived aversively by the patient. The need to include all sensory components in this definition is compelled by the influence on pain affect that non-noxious procedural stimuli may exert. Cotton-roll isolation may not noxiously stimulate nociceptors but it is providing the child's integrated pain neuromatrix with a convergent pattern of somatosensory information that the limbic system may interpret as a threat. The resulting anxiety will orient attentional vigilance onto nociceptive stimuli and elevate pain perception.^{36,43,46}

Reducing procedural invasiveness of all sensory modalities (proprioceptive, mechanoreceptive, chemoreceptive, auditory, olfactory, visual, as well as nociceptive) is a reasonable clinical intervention that should be considered in order to counter the magnification of nociception that occurs with high pain-affect without resorting to a more risky, more expensive or more cumbersome elevated pharmacological option (FIGURE 4). The multiple dimensions of pain compel clinicians to use a multidimensional pain technique that attends to the nociceptive, affective, developmental, and stimulus dimensions of pain.^{32,33}



FIGURE 4. Patients with severe pathology and high pain affect are not usually candidates for a treatment strategy involving lowered operative stimulation. General anesthesia is unavoidable in many of these cases.

Summary

Four characteristics of the neurobiology of pain have been identified and discussed in terms of their influence on clinical decisions in pediatric procedure pain management. The subjective nature of pain prevents clinicians from reliably predicting a child's pain intensity and supports the idea that the first principle of good, clinical pediatric pain practice is for clinicians to accept as credible the pain reports of children that issue from invasive procedures; that only the child knows how much pain they are experiencing.

From the neurobiologic phenomenon of central sensitization the second principle may be derived: It is better to prevent pain than to treat it after its occurrence. The developmental nature of a child's pain inhibitory controls provides further support for the notion that the pain reports of young children should be believed. It also suggests a reason for limiting the invasive, noxious stimulation of children until they have developed increased pain modulating mechanisms. Together, the diverse neurobiologic factors that contribute to pain's ontogeny compel clinician's to a third principle of good, clinical pain practice: Use a multidimensional pain technique that attends to the nociceptive, affective, developmental, and stimulus dimensions of pain. ■■■■

REFERENCES

1. Nakai Y, Milgrom P, et al, Effectiveness of local anesthesia in pediatric dental practice. *J Am Dent Assoc* 131:1699-705, 2000.
2. Versloot J, Veerkamp JS, Hoogstraten J, Children's self-reported pain at the dentist. *Pain* 137(2): 389-94, 2008.
3. Dionne RA, Campbell RA, et al, Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. *J Clin Pharmacol* 23:37-43, 1983.
4. Kohli K, Ngan P, et al, A survey of local and topical anesthesia use by pediatric dentists in the United States. *Pediatr Dent* 23(3):265-9, 2001.
5. Kreider K, Stratmann RG, et al, Reducing children's infection pain: lidocaine patches vs. topical benzocaine gel. *Pediatr Dent* 23(1):19-23, 2001.
6. Oulis CJ, Vadiakas GP, Vasilopoulou A, The effect of mandibular infiltration compared to mandibular block anesthesia in treating primary molars in children. *Pediatr Dent* 18:301-5, 1996.
7. Ram D, Peretz B, Reactions of children to maxillary infiltration and mandibular block injections. *Pediatr Dent* 23:343-6, 2001.
8. McArdle BF, Painless palatal anesthesia. *J Am Dent Assoc* 128:647, 1997.
9. Houpt MI, Limb R, Livingston R, Clinical effects of nitrous oxide conscious sedation in children. *Pediatr Dent* 26:29-36, 2004.
10. Houpt M, Project USAP 2000 - Use of sedative agents by pediatric dentists: a 15-year follow-up survey. *Pediatr Dent* 24(4):289-94, 2002.
11. Primrosch RE, Buzzi IM, Jerrell G, Effect of nitrous oxide-oxygen inhalation with scavenging on behavioral and physiological parameters during routine pediatric dental treatment. *Pediatr Dent* 21:417-20, 1999.
12. Kanagasundaram SA, Lane LJ, et al, Efficacy and safety of nitrous oxide in alleviating pain and anxiety during painful procedures. *Arch Dis Child* 84:492-5, 2001.
13. Hammond NI, Clemens FA, Nitrous oxide analgesia and children's perception of pain. *Pediatr Dent* 6(4):238-42, 1984.
14. Eidelman E, Faibis S, Peretz B, A comparison of restorations for children with early childhood caries treated under general anesthesia or conscious sedation. *Pediatr Dent* 22:33-7, 2000.
15. Acs G, Pretzer S, et al, Perceived outcomes and parental satisfaction following dental rehabilitation under general anesthesia. *Pediatr Dent* 23:419-23, 2001.
16. Adair SM, Schafer TE, et al, Survey of management teaching in predoctoral pediatric dentistry programs. *Pediatr Dent* 26:143-50, 2004.
17. Masek JB, Canion SB, et al, Behavioral procedures to increase cooperation of developmental disabled children with dental treatment. *Pediatr Dent* 4(4):317-21, 1982.
18. Weinstein P, Milgrom P, Ramsay DS, Treating dental fears using nitrous oxide oxygen inhalation and systematic desensitization. *Gen Dent* 36(4):322-6, 1988.
19. Kuhn B, Allen K, Expanding child behavior management technology in pediatric dentistry: a behavioral science perspective. *Pediatr Dent* 16:13-7, 1994.
20. Stokes TF, Kennedy SH, Reducing child uncooperative behavior during dental treatment through modeling and reinforcement. *J Appl Behav Anal* 13(1):41-9, 1980.
21. McKnight-Hanes C, Myers DR, et al, The use of behavior management techniques by dentists across practitioner type, age, and geographic region. *Pediatr Dent* 15:267-71, 1993.
22. Moore PA, Peskin RM, Pharmacologic desensitization for dental phobias: clinical observations. *Anesth Prog* 37:308-11, 1990.
23. Moore PA, Ramsay DS, et al, Pharmacologic modalities in the management and treatment of dental anxiety. *Dent Clin North Am* 32(4):803-16, 1988.
24. Finley AG, Pharmacological management of procedure pain. In: Acute and procedure pain in infants and children, progress in pain research and management, Seattle, IASP Press, vol. 20, pages 57-76, 2001.
25. Fitzgerald M, Howard RF, The neurobiologic basis of pediatric pain. In: Pain in infants, children and adolescents, second edition. Schechter NL, Berde CB, Yaster M, eds., Philadelphia, Lippincott, Williams and Wilkins, pages 19-42, 2003.
26. Price DD, The dimensions of pain experience. In: Psychological mechanisms of pain and analgesia, progress in pain research and management. Seattle, IASP Press, vol. 15, pages 1-14, 1999.
27. Fassler D, The fear of needles in children. *Am J Orthopsychiatry* 55:371-7, 1985.
28. Turk DC, Okifuji A, Pain terms and taxonomies of pain. In: Bonica's management of pain, Loeser JD, Butler SH, et al, eds., Philadelphia, Lippincott Williams and Wilkins, pages 17-25, 2001.
29. Jay SM, Ozolins M, et al, Assessment of children's distress during painful medical procedures. *Health Psychol* 2:133-47, 1983.
30. Diatchenko L, Slade GD, et al, Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 14(1):135-43, 2005.
31. Walco GA, Dampier CD, et al, The relationship between recurrent clinical pain and pain threshold in children. In: Advances in pain research therapy. Tyler DC, Krane EJ, eds., New York, Raven Press, Ltd., vol. 15, pages 333-40, 1990.
32. McGrath P, Dick B, Unruh A, Psychologic and behavioral treatment of pain in children and adolescents. In: Pain in infants, children and adolescents, second ed. Schechter NL, Berde CB, Yaster M, eds., Philadelphia, Lippincott, Williams and Wilkins, pages 303-16, 2003.
33. Goldman A, Frager G, Pomietto M, Pain and palliative care. In: Pain in infants, children and adolescents, second ed. Schechter NL, Berde CB, Yaster M, eds., Philadelphia, Lippincott, Williams and Wilkins, pages 539-62, 2003.
34. Fernandez E, Turk DC, The scope and significance of anger in the experience of chronic pain. *Pain* 61:165-75, 1995.
35. Champion GD, Goodenough B, et al, Measurement of pain by self-report. In: Finley GA, McGrath PJ, eds., Measurement of pain in infants and children. Seattle, IASP Press, pages 123-60, 1998.
36. Sifford L, Psychiatric assessment of the child with pain. *Child Adolesc Psychiatr Clin North Am* 6:745-81, 1997.
37. Vika M, Raadal M, et al, Dental and medical injections: prevalence of self-reported problems among 18-year-old subjects in Norway. *Eur J Oral Sci* 114(2):122-7, 2006.
38. Borszcz GS, Contribution of the ventromedial hypothalamus to generation of the affective dimension of pain. *Pain* 123(1-2):155-68, 2006.
39. Green W, Kowalik S, Psychopharmacologic treatment of pain and anxiety in the pediatric patient. *Child Adolesc Psychiatr Clin North Am* 3(3):465-83, 1995.
40. Janssen SA, Arntz A, Anxiety and pain: attentional and endorphinergic influences. *Pain* 66:145-50, 1996.
41. Craig AD (Bud), Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci* 26:1-30, 2003.
42. Rutishauser U, Schuman EM, Mamelak AM, Activity of human hippocampal and amygdala neurons during retrieval of declarative memories. *Proceedings of the National Academy of Science*, 105(1):329-34, Jan. 8, 2008.
43. Keogh E, Ellery D, et al, Selective attentional bias for pain-related stimuli amongst pain fearful individuals. *Pain* 91(1-2):91-100, 2001.
44. Newton JT, Buck DJ, Anxiety and pain measures in dentistry: a guide to their quality and application. *J Am Dent Assoc* 31(10):1449-57, 2000.
45. Villemure C, Bushnell CM, Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain* 95:195-9, 2002.
46. Baier K, Milgrom P, et al, Children's fear and behavior in private pediatric dentistry practices. *Pediatr Dent* 26(4):316-21, 2004.
47. McGrath PA, Hillier LM, Modifying the psychological factors that intensify children's pain and prolong disability. In: Pain in infants, children and adolescents, second ed. Schechter NL, Berde CB, Yaster M, eds., Philadelphia, Lippincott, Williams and Wilkins 85-104, 2003.
48. Cardona L, Behavioral approaches to pain and anxiety in the pediatric patient. *Child Adolesc Psychiatr Clin North Am* 3:449-64, 1994.
49. Weiser S, Cedraschi C, Psychosocial issues in the prevention of chronic low back pain — a literature review. *Bailliere's Clin Rheumatol* 6:657-84, 1992.
50. Beidel DC, Christ MAG, Long PJ, Somatic complaints in anxious children. *J Abnorm Child Psychol* 19:659-70, 1991.
51. Taddio A, Katz J, et al, Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 349:599-603, 1997.
52. Vargas KF, Nathan JE, et al, Use of restraint and management style as parameters for defining sedation success: A survey of pediatric dentists. *Pediatr Dent* 29(3):220-7, 2007.
53. Woolf CJ, Evidence for a central component of postinjury pain hypersensitivity. *Nature* 306:686-8, 1983.
54. Woolf CJ, King AE, Dynamic alterations in the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat spinal cord. *J Neurosci* 10(8):2717-26, 1990.
55. Cook AJ, Woolf CJ, et al, Dynamic receptive field plasticity in rat spinal cord dorsal horn following C primary afferent input. *Nature* 325:151-3, 1987.
56. Woolf CJ, Thompson SWN, The induction and maintenance of central sensitization is dependent on N-methyl-D-Aspartic acid receptor activation; implications for the treatment of postinjury pain hypersensitivity states. *Pain* 44(3):293-9, 1991.
57. Fitzgerald M, Howard RF, The neurobiologic basis of pediatric pain. In: Pain in infants, children and adolescents, second ed. Schechter NL, Berde CB, Yaster M, eds., Philadelphia, Lippincott, Williams and Wilkins pages 19-42, 2003.
58. Terman GW, Bonica JJ, Spinal mechanisms and their modulation In: Bonica's management of pain Loeser JD, Butler SH, Chapman RC, Turk DC, eds., Philadelphia, Lippincott Williams and Wilkins pages 73-152, 2001.

59. LaMotte RH, Shain CN, et al, Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *J Neurophysiol* 66:190-211, 1991.
60. Lang S, Klein T, et al, Modality-specific sensory changes in humans after the induction of long-term potentiation (LPT) in cutaneous nociceptive pathways. *Pain* 128:254-63, 2007.
61. Afrah AW, Fiska A, et al, Spinal substance P release in vivo during the induction of long-term potentiation in dorsal horn neurons. *Pain* 96:49-55, 2002.
62. Liang YC, Huang CC, Hsu KS, Characterization of long-term potentiation of primary afferent transmission at trigeminal synapses of juvenile rats: essential role of subtype 5 metabotropic glutamate receptors. *Pain* 114:417-8, 2005.
63. Hermann C, Hohmeister J, et al, Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain* 125(3):278-85, 2006.
64. Kim DK, Kwak J, et al, Long-lasting enhancement in the intrinsic excitability of deep dorsal horn neurons. D, Is there a mechanism for the spinal cord to remember pain? In: Bostock H, Kirkwood PA, Pullen AH, eds. *The neurobiology of disease: contributions from neuroscience to clinical neurology*. Cambridge: Cambridge University Press, pages 177-88, 1996.
65. Willis WD, Is there a mechanism for the spinal cord to remember pain? In: Bostock H, Kirkwood PA, Pullen AH, eds. *The neurobiology of disease: contributions from neuroscience to clinical neurology*. Cambridge: Cambridge University Press, pages 177-88, 1996.
66. Woolf CJ, Wall PD, Long-term alterations in the excitability of the flexion reflex produced by peripheral tissue injury in the chronic decerebrate rat. *Pain* 18:325-43, 1984.
67. Bliss TV, Collingridge GL, A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361(6407):31-9, 1993.
68. Morris RG, Anderson E, et al, Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, Ap5. *Nature* 319(27):774-6, 1986.
69. Andrews K, Fitzgerald M, The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation. *Pain* 56:95-101, 1994.
70. Randich A, Uzzell T, et al, Neonatal urinary bladder inflammation produces adult bladder hypersensitivity. *J Pain* 7(7):469-79, 2006.
71. Marsh D, Dickenson A, et al, Epidural opioid analgesia in infant rats II: responses to carrageenan and capsaicin. *Pain* 82:33-8, 1999.
72. Daikos GK, History of medicine: our Hippocratic heritage. *Int J Antimicrob Agents* 29(6):617-20, 2007.
73. Berggren U, Meynert G, Dental fear and avoidance: causes, symptoms and consequences. *J Am Dent Assoc* 109:247-51, 1984.
74. Asmundson GJG, Norton PJ, Allerdings MD, Fear and avoidance in dysfunctional chronic back pain patients. *Pain* 69:231-6, 1997.
75. Milgrom P, Vignehsa H, Weinstein P, Adolescent dental fear and control. *Behav Res Ther* 30:367-73, 1992.
76. Goodenough B, Champion GD, et al, Assessing needle pain severity in children: the correlation between self-report and pain behavior reduces with increasing age. In: Abstracts: eighth world congress on pain. Seattle, IASP Press, pages 184-5, 1996.
77. Fradet C, McGrath PJ, Kay J, et al, A prospective survey of reactions to blood tests by children and adolescents. *Pain* 40:53-60, 1990.
78. Bournaki MC, Correlates of pain-related responses to venipunctures in school-age children. *Nurs Res* 46(3):147-54, 1997.
79. Bachanas PJ, Roberts MC, Factors affecting children's attitudes toward health care and responses to stressful medical procedures. *J Pediatr Psychol* 20(3):261-75, 1995.
80. Fitzgerald M, The development of descending brainstem control of spinal cord sensory processing. In: *The fetal and neonatal brainstem*. Hanson MA, ed. Cambridge, Cambridge University Press, pages 127-36, 1991.
81. Ren K, Dubner R, Enhanced descending modulation of nociception in rats with persistent hindpaw inflammation. *J Neurophysiol* 76:3025-37, 1996.
82. Beeson JM, The neurobiology of pain. *Lancet* 353:1610-5, 1999.
83. Fields HL, Basbaum AI, Heinricher MM, Central nervous system mechanisms of pain modulation. In: *Wall and Melzack's textbook of pain*, fifth ed. McMahon SB, Koltzenburg M, eds. Philadelphia, Elsevier; pages 125-42, 2006.
84. Willer JC, Roby A, Le Bars D, Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain* 107:1095-112, 1984.
85. Falinower S, Willer JC, et al, A C-fiber reflex modulated by heterotopic noxious somatic stimuli in the rat. *J Neurophysiol* 72:194-213, 1994.
86. Killian P, Holmes BB, et al, Cold water swim stress and delta-2 opioid-induced analgesia are modulated by spinal gamma-aminobutyric acids receptors. *J Pharmacol Exp Ther* 274(2):730-4, 1995.
87. Fox NA, Caulkins SD, The development of self-control of emotion: intrinsic and extrinsic influences. *Motiv Emot* 27(1):7-26, 2003.
88. Legrain V, Guerit JM, et al, Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. *Pain* 99:21-39, 2002.
89. Lavelli M, Fogel A, Developmental changes in the relationship between the infant's attention and emotion during early face-to-face communication: The two-month transition. *Dev Psychol* 41(1):265-80, 2005.
90. Calkins SD, Fox NA, Self-regulatory process in early personality development: a multilevel approach to the study of childhood social withdrawal and aggression. *Dev Psychopathol* 14:477-98, 2002.
91. Rothbart MK, Posner MI, Boylan A, Regulatory mechanisms in infant development. In: *The development of attention: research and theory*, Enns J, ed. Amsterdam, Elsevier, pages 47-66, 1990.
92. Boucher T, Jennings E, Fitzgerald M, The onset of diffuse noxious inhibitory controls in postnatal rat pups: A c-fos study. *Neurosci Lett* 257:9-12, 1998.
93. Fitzgerald M, Jennings E, The postnatal development of spinal sensory processing. Proceedings of the National Academy of Sciences of the United States of America. 96(14):7719-22, 1999.
94. Fitzgerald M, Koltzenburg M, The functional development of descending inhibitory pathways in the dorsolateral funiculus of the newborn rat spinal cord. *Brain Res* 389:261-70, 1986.
95. Gjerstad J, Tjolsen A, Hole K, Induction of long-term potentiation of single wide dynamic neurons in the dorsal horn is inhibited by descending pathways. *Pain* 91: 263-8, 2001.
96. Shaw P, Eckstrand K, et al, Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proceedings of the National Academy of Science. 104(49):19649-54, Dec. 4, 2007.
97. Byers MR, Bonica JJ, Peripheral pain mechanisms and nociceptor plasticity. In: *Bonica's management of pain*, Loeser JD, Butler SH, et al, eds. Philadelphia, Lippincott Williams and Wilkins pages 26-72, 2001.
98. Chudler EH, Bonica JJ, Supraspinal mechanisms of pain and nociception. In: *Bonica's management of pain*, Loeser JD, Butler SH, et al, eds. Philadelphia, Lippincott Williams and Wilkins 153-79, 2001.
99. Baccei M, Fitzgerald M, Development of pain pathways and mechanisms. In: *Wall and Melzack's textbook of pain*, fifth ed. McMahon SB, Koltzenburg M, eds. Philadelphia, Elsevier, pages 143-58, 2006.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Dennis Paul Nutter, DDS, 3694 Hilborn Road, Suite 100, Fairfield, Calif., 94534-7994.