1

History and Overview of Neonatal Pain

The study of pain in neonates is relatively new and still evolving. Before the 1980s, pain in the neonate was disputed and often dismissed. The idea that neonates do not experience pain is not new. Charles Darwin, in his famous work *The Expression of the Emotions in Man and Animals*, wrote that even though newborns exhibit pain reactions, these were only reflexive and babies were incapable of experiencing and expressing true pain (Darwin, 1872). Darwin's belief, coupled with research by scientists such as Dr. Flechsig, who equated the absence of myelination in some of the baby's nervous system as the system's inability to function (Cope, 1998). This idea was so widely believed that even operations, including open-heart surgery, were carried out without the use of analgesics or anesthetics (Cope, 1998). It was thought that neonatal nervous systems were so immature that they did not feel pain and that lack of myelination translated into a decreased or disorganized response to pain. It is now known that incomplete myelination only leads to a slower conduction of pain, not an absence of pain. This decreased speed is offset, however, by the shorter distance the impulse needs to travel to reach the neonatal brain. Myelination is usually complete by the second to third trimester. There was a belief that because the infant would not remember the pain, it was not necessary to provide relief from pain. Another common concern was that the risks of pain relief exceeded the benefits when it came to pharmacologic and anesthetic use. Today, it is understood that pain is detrimental to term and preterm infants and that these patients have a worse pain

From: Clinical Handbook of Neonatal Pain Management for Nurses DOI: 10.1891/9780826194381.0001

experience than an adult or older child. This realization began with a landmark paper published by Anand and Hickey in 1987, which was one of the first peer-reviewed trials to study pain in the neonatal population. In this article, it was made clear that even a fetus is capable of experiencing pain and urged clinicians to humanely treat pain in this population as adults and older children would be treated (Anand & Hickey, 1987). In 1987, the American Academy of Pediatrics (AAP) released a statement on neonatal pain control with consensus from three of their committees: the Committee on Fetus and Newborn and the Committee on Drugs, the Section on Anesthesiology and the Section on Surgery. The statement confirmed that there are now ways to safely use anesthesia and analgesia for surgical procedures and such treatment should be given by following the guidelines for any high-risk patient (AAP, 1987). Practice still needed time to catch up though. In 1997, a study was published on neonatal intensive care units (NICUs), which found that 2,134 invasive procedures were performed in 1 week on 239 patients and only 0.8% of these patients received analgesics (Johnson, Collinge, & Henderson, 1997). Then, in 2001, the AAP Committee on Psychosocial Aspects of Children and Family Health, along with the American Pain Society (APS) Task Force on Pain in Infants, Children, and Adolescents, published a call-to-action statement for the treatment of pediatric pain. In this statement, they directly addressed the critical need for pain management with all types of pediatric pain (acute injuries, chronic pain, procedures, surgery, etc.), and some of the barriers keeping patients from receiving the pain control that they deserve (American Academy of Pediatrics, 2001). A few years later a study was published that demonstrated about one third of the study neonates received analgesia for painful procedures (Simons et al., 2003).

Two studies have addressed whether infants can process noxious stimulation at the cortical level. Using real-time, near-infrared spectroscopy to detect changes in cortical blood flow, both studies showed that noxious stimuli activated the primary somatosensory cortex in newborns (Bartocci, Bergqvist, Lagercrantz, & Anand, 2006; Slater et al., 2006). This was

shown to occur in even preterm infants, the youngest of whom were tested at 25 weeks gestational age (Slater et al., 2006).

The current movement is toward pain prevention and treatment, rather than treatment alone. Because of the adverse effects stress can have on the developing neonate, eliminating or minimizing as much stress as possible has become standard practice. Standardized policies and procedures regarding pain management have been put into place in many organizations.

Pain assessment and management are one of the most important components of patient care. Pain is often referred to as the "fifth vital sign" (a phrase introduced by The Joint Commission), along with heart rate, respiration, blood pressure, and temperature, because of the powerful indicator pain is of the patient's current condition.

Pain is a complex topic that is especially difficult to conceptualize in the neonatal population. Practitioners for adult patients typically base treatment on verbal descriptions regarding pain level and tolerance, yet neonates do not yet have the capacity to relay this information. This leads to a high risk of misinterpreted pain responses and inadequate pain relief in this fragile population, who, unfortunately, are most affected by pain. Neonates sometimes offer physiologic cues to signal pain, but this may be masked or confused with concurrent conditions and comorbidities. For this reason, pain should be at the forefront of all clinical practice and pain relief should be administered if any pain signs are noticed or anticipated.

DEFINING PAIN

There are many ways to describe pain. The International Association for the Study of Pain (IASP) definition of *pain* as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" is derived from a 1964 definition by Harold Merskey (1979, p. 250). If the patient is an adult and a good historian, simply asking him or her to describe the pain, its location, quality, duration, exacerbating and relieving factors, whether there

has been previous injury and any other associating symptoms (such as swelling, numbness, erythema, etc.) will give clues as to what is causing the pain and how relief can be provided. But neonates, unlike adults or even older children, are not able to verbalize such sensations. Neonates also give nonspecific and inconsistent cues that may become masked in their underlying pathology (such as a premature infant having an apneic episode in which pain may not be considered as part of the problem). When treating this population, care providers have to be attuned to often subtle or complicated symptoms. In some cases, providers should treat based on the fact that they are performing an invasive procedure known to cause pain. Inability to express pain in a traditional manner in no way negates the fact that pain is being experienced.

ANATOMY AND PAIN PATHWAYS

DEVELOPMENT

Responses to somatic stimuli begin at an early age. Reflex responses to stimuli begin around 7.5 weeks postconception in the perioral skin and continue to develop in the palms of the hands before finally reaching the limbs by about 13 to 14 weeks. Peripheral pain receptors are in place systemically by around 20 weeks postconception (Stevens, 1999). By 21 weeks, there is dendritic arborization. At around 22 weeks postconception, nerve tracts in the spinal cord to the brain stem and connections with the thalamocortical fibers are in place. But it is not until 32 weeks that the descending, inhibitory fibers are complete. These fibers aid in blunting full pain response and experience. Therefore, a lack of neurotransmitters in the descending tract suggests a lack of complete neuromodulating mechanisms in the preterm infant, making the infant more sensitive to pain than older children and adults (Anand et al., 2006).

Nociception is the most common pain pathway. Nociceptors are sensory receptors that are located throughout the body and are activated by physical, chemical, or heat stimuli. First, painful

sensory stimuli are introduced; these can be actual tissue damage, muscle spasms, or even anticipated tissue damage.

Most pain originates from damage to body tissues. A stimulus is introduced, perceived by the nociceptors, then sent through the spinal cord and into the brain for interpretation. A stimulus is transmitted first through tiny afferent nerve fibers in the spinal cord. The fibers that are most responsible for pain are the afferent A-delta and C-fibers (Adriaensen, Gybels, Handwerker, & Van Hees, 1983). These fibers are the first-order neurons and they begin the pain-perception process. A-delta fibers are found primarily in the skin and muscle, and C-fibers are found in muscle, periosteum, and visceral organs. A-delta fibers are myelinated fibers that produce rapid sharp, pricking, and piercing sensations. This pain is usually localized. In contrast, C-fibers are unmyelinated (or poorly so), and conduct temperature, chemical, or strong physical signals. Pain elicited from the C-fibers is a dull, aching, or burning pain that is more diffuse. Of note, there are other fibers responsible for sensation related to pain, such as A-alpha and A-beta fibers. A-alpha and A-beta fibers transmit nonpainful sensations such as pressure, soft touch, and vibration. These nonpainful sensations can be either beneficial or detrimental to pain management by either contributing to stimulation overload or by helping to block painful messages.

The stimuli then travel through to the spinal cord, to the dorsal root ganglia, through to the dorsal horn, and up to the thalamus. This begins the involvement of the second-order neurons. The tract from the dorsal horn to the thalamus is called the spinothalamic tract and it is divided into two pathways: the lateral pathway called the neospinothalamic (NST) tract and the medial pathway called the paleospinothalamic (PST) tract. The NST tract transmits pain directly to the sensory cortex, where it is interpreted. The PST tract synapses in other parts of the brain, such as the limbic system and the reticular formation, which are areas of the brain responsible for emotion and circadian rhythm. A-beta fibers make synapses in the spinal dorsal horn close to synapses of the A-delta and C-fibers. This dorsal horn connection means that input from touch fibers can enter the spinal

cord and synapse or communicate with cells carrying nociceptive input. This is an important reason that techniques, such as massage, light touch, acupuncture/acupressure, and other alternative measures, work to aid in pain management.

Pain stimuli may be influenced by neuroregulators. Neuroregulators are chemicals that inhibit, enable, or even enhance painful stimuli. There are two types: neurotransmitters and neuromodulators. Neurotransmitters, such as epinephrine, norepinephrine, acetylcholine, and dopamine, work to either slow or accelerate postsynaptic nerve activity. Neuromodulators are endogenous opiates and help in pain relief. They consist of large amino acid peptides, such as alpha-endorphins, beta-endorphins, and enkephalins, which act similarly to morphine with increased potency. Endorphins are produced in the anterior pituitary gland and hypothalamus. They are larger peptides and longer acting than enkephalins. Enkephalins are more diffuse throughout the brain and dorsal horn. Several types of endorphins and enkephalins have been identified and each acts on a highly specific opiate receptor in the central nervous system (CNS).

Once the pain signal reaches the brain, it is processed at three levels: the thalamus, midbrain, and cortex. These areas work together to interpret and respond to stimuli. The thalamus relays sensory data from the NST and PST tracts. The midbrain alerts the cortex to be aware of incoming stimuli. Lastly, the cortex discriminates and interprets the stimuli. This demonstrates that the painful stimuli must pass through many areas of the brain, which sometimes includes behavioral and emotional centers. All of this happens in a matter of seconds (Figure 1.1).

Almost all painful stimuli cause some degree of tissue damage (e.g., heel lancing, venipuncture, catheterization, difficult adhesive tape removal). This damage leads to a release of chemicals, such as noradrenaline, bradykinin, histamine, prostaglandins, purines, cytokines, 5-HT, leukotrienes, nerve growth factor, and neuropeptides, which sensitize the receptors. This sensitization occurs to make sure the body is aware of the painful stimuli and can act to stop the stimuli and begin repair. These chemicals can also lead to a decrease in the nociception threshold, ectopic

discharges, and accumulation of sodium (Na) channels, especially with repeated exposure to pain (Devor, 1994).

Pain is processed in four main ways: transduction, transmission, modulation, and perception (Box 1.1).

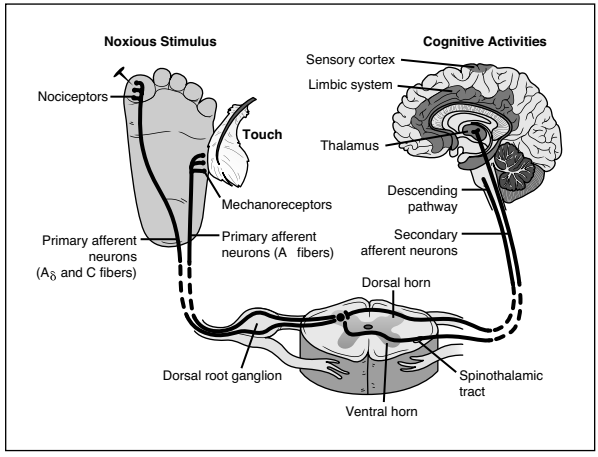

FIGURE 1.1. Noceptive stimulus received at the periphery → travels through the dorsal horn of the spinal cord to the dorsal root ganglia → thalamus → through the spinothalamic tracts (paleospinothalamic [PST] and neospinothalamic [NST]) → NST goes to the sensory cortex → PST goes to limbic system and reticular formation.

BOX 1.1 Processing Pain

Transduction—When nociceptors are exposed to a noxious stimulus

Transmission—Path of the stimulus sent from the site of transduction to the dorsal horn of the spinal cord, then to the brain stem, finally to higher levels of the brain

Modulation—Painful stimuli may be inhibited or enhanced by neurotransmitters on the way to perception

Perception—Pain signals reach their final destination in the brain and are interpreted

PAIN THEORIES

Most information known about pain is related to the adult pain experience. One prominent pain theory is the gate control theory introduced in 1965 by Melzack and Wall. This theory explores the fact that pain is more than just a physiologic response; other variables, such as behavioral and emotional responses, influence perception of pain. Because neonates lack the context to apply the stimuli, this gate is more likely to be open for painful messages to reach the brain. Let us further describe this theory. The gating process occurs in the spinal cord. A-delta and C-fibers send pain impulses from the periphery. These impulses travel to the dorsal horns of the spinal cord, specifically to the substantia gelatinesa. The cells of the substantia gelatinesa either stop or allow pain signals to be transmitted to the T-cells. When T-cell activity is inhibited, the gate is closed and pain signals have a reduced chance of reaching the brain. When the gate is open, pain signals travel directly to the brain (Melzack & Wall, 1965).

Similar "gating" mechanisms exist in the nerve fiber descending from the thalamus and cerebral cortex. These are the areas of the brain that control thoughts and emotions. When pain occurs, a person's thoughts and emotions can modify the perception of pain. Neonates, unfortunately, lack language abilities, life experience, and control over thoughts and emotions to assist in this gating process. Neonates benefit from comfort measures that help to reduce pain by reducing agitation, promoting sleep, and decreasing a feeling of disorganization (AAP and Canadian Paediatric Society, 2006). Other theories have been proposed against the gate control theory, some arguing a more dynamic and less linear path of pain interpretation.

Another theory related to pain that has significant bearing on the neonate is the theory of wind-up. Wind-up is a phenomenon in which repeated exposure to the same noxious stimulus leads to an exaggerated response and this response continues even after the noxious stimulus is withdrawn (McMahon, Koltzenburg, Tracey, & Turk, 2013). With repeated moderate to severe pain, N-methyL-D-aspartate (NMDA) receptors are

activated, which produces a wind-up effect, changing intracellular calcium ion concentrations and creating synaptic buildup of excitatory amino acids. Pain intensity, duration, and surface distribution become greater than expected for a particular stimulus (Coderre, Katz, Vaccarino, & Melzack, 1993).

TYPES OF PAIN (NOCICEPTIVE, NEUROPATHIC, SOMATIC, VISCERAL, ACUTE, CHRONIC)

One of the ways to describe pain is from its source. Pain can originate from several different locations and manifest in many different ways. Nociceptive pain is perceived by afferent nerve fibers (as described in Figure 1.1). This refers to a stimulus activating the nociceptors in body tissue, and then traveling through the spinal cord and brain for interpretation and action. Nociceptors are so named because of their affinity to transmit noxious stimuli (Sherrington, 1906). They perceive all potential risks to body tissues, including thermal, mechanical, and chemical risks. Neuropathic pain is perceived by deafferent nerve fibers. The IASP defines *neuropathic pain* as "pain caused by a lesion or disease of the somatosensory system" (Merskey, Lindblom, Mumford, Nathan, & Sunderland, 1994). This is basically pain not caused by a painful stimulus, but by a dysfunction or defect in the neurological system resulting in pain. This is rare in neonates, but may occur with traumatic brain injury from delivery, meningitis, or some other encephalopathic condition.

Pain can also be described as somatic or visceral. Somatic pain affects the skin, bone, muscle, blood vessels, and connective tissue. Visceral pain affects the vital organs and the linings of body cavities. An example of somatic pain would be a venipuncture. An example of visceral pain would be insertion of a chest or gastrointestinal tube.

Acute pain is temporary pain that is expected to last no longer than 6 months. Examples of this would be procedural pain or pain from an acute injury. Chronic pain is pain that lasts or is expected to last longer than 6 months. Chronic pain is rare in

neonates. Examples of chronic pain would be pain from incurable neurodegenerative diseases or cancer. In the APS's latest statement they indicate the significance of chronic pain in the pediatric population and stress the importance of improving patient functioning and quality of life. The APS also recommends the use of psychological interventions, such as relaxation techniques and parent interventions, for all children with chronic pain.

PHYSIOLOGIC, BEHAVIORAL, AND BIOCHEMICAL RESPONSES TO PAIN

When adults experience acute pain, they exhibit a sympathetic nervous system response that can be observed as an increase in heart rate, blood pressure, respiration, anxiety, hormonal fluctuation, and inflammation. Various studies have found that neonates and preterm infants exhibit similar physiologic responses to pain (Table 1.1).

TABLE 1.1 Effects of Pain

Physiologic Response
Heart rate increase or fluctuation
Blood pressure increase or fluctuation
Increased PO_2 (partial pressure of oxygen), SaO_2 (oxygen saturation; initially)
Decreased PO_2, SaO_2 (prolonged stress)
Increased work of breathing
Apnea
Hypercapnea
V/Q mismatch
Increase in intracranial pressure
Vomiting
Diarrhea, which may result in diaper rash

(*continued*)

TABLE 1.1 Effects of Pain (*continued*)
Diaphoresis
Dilated pupils
Slow weight gain, weight loss, failure to thrive
Ileus
Urinary retention
Behavioral Response
Intense or high-pitched cry
Difficult to console
Constant need to be consoled
Frowning, grimacing, brow furrow
Eye closure or aversion
Disorganized or frantic body movements
Increased tone
Decreased activity, "shutting down" (prolonged stress)
Tremors
Hyperalert state
Erratic sleep pattern
Feeding difficulties or increased feeds, which may result in vomiting
Behavioral Response
Increased plasma renin activity
Increased epinephrine and norepinephrine
Increased cortisol levels
Increased glucose
Increased lactate
Increased pyruvate
Release in growth hormones, aldosterone, and glucagon
Sodium or water retention

(*continued*)

TABLE 1.1 Effects of Pain (*continued*)
Protein catabolism
Decreased immune function
Decreased insulin
Decreased prolactin
Decreased platelet adhesion/hypercoagulability
Long-Term Response
Increased length of stay in the hospital
Higher mortality
Increased sensitivity to pain

Sources: Anand (1990); Anand (1993); Anand and Hickey (1987); Burddeau and Kleiber (1991); Gardner, Carter, Enzman-Hines, and Hernandez (2011); and Hall and Anand (2005).

Tissue damage results in a cascade of events that lead to hyperalgesia or enhanced pain in response to all stimuli, as well as sensitization of nocicepetors at and around the injured area. Hyperalgesia and sensitization occur with most somatic and visceral injuries. For example, in the presence of pharyngitis, mere swallowing is painful (McMahon et al., 2013).

A noxious stimulus leads to action in the nociceptive fibers that propagates not only to the CNS, but also into surrounding areas. There is a release of neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP), and neurokinin A (NKA). These substances can stimulate epidermal cells and immune cells or lead to vasodilation, plasma extravasation, and smooth muscle contraction, which can lead to surrounding areas becoming inflamed, erythemic, and tense (McMahon et al., 2013).

The preterm infant is especially susceptible to negative effects of pain. The preterm infant experiences increased stress and activity in the nociceptive pathways after prolonged periods of exposure to painful stimuli. After repeated painful experiences, the preterm infant exhibits pain responses when exposed to other routine

caregiving activities (e.g., suctioning, repositioning, and diaper changes; Evans, Vogelpohl, Bourguignon, & Morcott, 1997), further illustrating the wind-up theory. A neonate or preterm neonate also begins to develop associations between an action and the painful stimulus. For example, the neonate will elicit a pain response and may cry out or fight when an alcohol wipe is brushed across his heel. The neonate is expecting the painful prick of a lancet to follow. If exposure is especially prolonged or traumatic, aversions may develop. For example, a preterm infant may reject a bottle or the breast because of repeated and prolonged endotracheal intubation. Even with developmentally appropriate care, true oral aversions may take months or even years to correct and a gastrointestinal tube may need to be surgically place until the oral aversion resolves.

Neonates may have a higher pain threshold in the upper extremities than in the lower extremities, leading to increased sensitivity to pain in the lower extremities. The descending inhibitory fibers grow from the supraspinal brainstem nuclei, only reaching the cervical section of the spinal cord by 30 to 32 weeks; they have not reached the lumbar spine by 30 weeks, which allows for an increased sensitivity for pain in the lower extremities (Anand, 2007). This is an important factor to consider from a clinical standpoint when there is choice as to which procedure to perform such as deciding between an intravenous catheter site and a heel stick for blood draw.

REGULATIONS/PROFESSIONAL GUIDELINES

As the discussion and study of pain for all patients grows, many governmental, regulatory, and professional organizations have issue and rules and guidelines regarding pain management. Beginning in 2001, California, for example, mandated that health care professionals document pain assessment whenever they documented vital signs.

According to the National Association of Neonatal Nurses (NANN; 2008) guidelines:

1. Education and competency validation in pain assessment and management shall be conducted during orientation and at regularly defined intervals throughout employment for all nurses delivering care to infants (AAP/Canadian Paediatric Society [CPS], 2000, 2006; IASP, 2005; Joint Commission on Accreditation of Healthcare Organizations [JCAHO], 2001; NANN, 2001).
2. Pain is assessed and reassessed at regular intervals throughout the infant's hospitalization (Agency for Health Care Policy and Research [AHCPR], 1992; AAP/CPS, 2000, 2006; IASP, 2005; JCAHO, 2001; NANN, 2001).
3. Use both nonpharmacologic and pharmacologic therapies to control or prevent pain (AHCPR, 1992; AAP/CPS, 2000, 2006; Anand & International Evidence-Based Group for Neonatal Pain [IEBGNP], 2001; IASP, 2005; NANN, 2001).
4. A collaborative, interdisciplinary approach to pain control should be used by all members of the health care team and infant's family to develop a pain management plan. Include the input of all members of the health care team as well as that of the infant's family whenever possible (AHCPR, 1992; AAP, 1999; IASP, 2005; JCAHO, 2001; NANN, 2001).
5. Pain assessment and management practices should be documented in a manner that facilitates regular reassessment and follow-up intervention (IASP, 2005; JCAHO, 2001).
6. Policies and procedures that support and promote optimal pain assessment and management practices should be established by institutions caring for infants (AHCPR, 1992; AAP/CPS, 2000; JCAHO, 2001).
7. Institutions caring for infants should collect data to monitor the appropriateness and effectiveness of their pain management practices (AHCPR, 1992; IASP, 2005; JCAHO, 2001).

The AAP/APS recommends a comprehensive approach to pediatric pain management, such as increased knowledge of pediatric pain and how to manage it; nonpharmacological measures, such as reducing stimuli and involving the family; using appropriate pain assessment tools and techniques; effective use of pain medication; and increased research and evaluation of analgesics for children (AAP/APS, 2001).

REFERENCES

Adriaensen, H., Gybels, J., Handwerker, H. O., & Van Hees, J. (1983). Response properties of thin myelinated A-delta fibers in human skin nerves. *Journal of Neurophysiology*, *49*, 111–122.

Allegaert, K., van den Anker, J. N., & Naulaers, G. (2007). Determinants of drug metabolism in early neonatal life. *Current Clinical Pharmacology*, *2*(1), 23–29.

American Academy of Pediatrics. (1987). Neonatal anesthesia. *Pediatrics*, *80*(3), 446.

American Academy of Pediatrics and Canadian Paediatric Society. (2006). Prevention and management of pain in the neonate. *Pediatrics*, *118*, 2231.

American Academy of Pediatrics Committee on Drugs. (2002). Uses of drugs not described in the package insert (off-label uses). *Pediatrics, 110*, 181–183.

American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery, Canadian Paediatric Society, and Fetus and Newborn Committee. (2000). Prevention and management of pain and stress in the neonate. *Pediatrics*, *105*(2), 454–461.

American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health, & Task Force on Pain in Infants, Children, and Adolescents. (2001). The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics*, *108*(3), 793–797.

Anand, K. J. S. (1990). Neonatal stress responses to anesthesia and surgery. *Clinics in Perinatology*, *17*, 207.

Anand, K. J. S. (1993). Relationship between stress responses and clinical outcomes in newborns, infants and children. *Critical Care Medicine*, *21*(9), S358.

Anand, K. J. S. (2007). Pharmacological approaches to the management of pain in the neonatal intensive care unit. *Journal of Perinatology*, *27*, S4–S11.

Anand, K. J. S., Aranda, J. V., Berde, C. B., Buckman, S., Capparelli, E. V., Carlo, W., … Walco, G. A. (2006). Summary proceedings from the neonatal pain-control group. *Pediatrics*, *117*(3), S9–S22.

Anand, K. J. S., & Hickey, P. R. (1987). Pain and its effects in the human neonate and fetus. *New England Journal of Medicine*, *317*, 1321–1329.

Bartocci, M., Bergqvist, L. L., Lagercrantz, H., & Anand, K. J. S. (2006). Pain activates cortical areas in the preterm newborn brain. *Pain*, *122*, 109–117.

Burddeau, G., & Kleiber, C. (1991). Clinical indicators of infant irritability. *Neonatal Network*, *9*, 23.

Choonara, I., & Conroy, S. (2002). Unlicensed and off-label drug use in children: Implications for safety. *Drug Safety*, *25*, 1–5.

Coderre, T. J., Katz, J., Vaccarino, A. L., & Melzack, R. (1993). Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. *Pain*, *52*, 259–285.

Cope, D. K. (1998, September). Neonatal pain: The evolution of an idea. *American Association of Anesthesiologists Newsletter.* Retrieved from http://anestit.unipa.it/mirror/asa2/newsletters/1998/09_98/Neonatal_0998.html

Darwin, C. (1872). *The expression of the emotions in man and animals* (1st ed.). London, UK: John Murray.

Devor, M. (1994). The pathophysiology of damaged nerves. In P. D. Wall & R. Melzak (Eds.), *Textbook of pain* (3rd ed., pp. 79–100). New York, NY: Churchill Livingstone.

Devor, M. (1996). Pain mechanisms and pain syndromes. In J. Campbell (Ed.), *Pain 1996: An updated review.* Seattle, WA: IASP Press.

Evans, J. C., Vogelpohl, D. G., Bourguignon, C. M., & Morcott, C. S. (1997). Pain behaviors in LBW infants accompany some "non-painful" caregiving procedures. *Neonatal Network*, *16*, 33.

Food and Drug Administration. (2001). *The pediatric exclusivity provision: January 2001 status report to Congress*. Rockville, MD: Author.

Gardner, S. L., Carter, B. S., Enzman-Hines, M., & Hernandez, J. A. (2011). *Merenstein & Gardner's handbook of neonatal intensive care* (7th ed.). St. Louis, MO: Mosby.

Hall, R., & Anand, K. J. S. (2005). Physiology of pain and stress in the newborn. *NeoReviews*, *6*, 61.

Johnson, C. C., Collinge, J., & Henderson, S. (1997). A cross-sectional survey of pain and pharmacological analgesia in Canadian NICUs. *Clinical Journal of Pain*, *13*, 308.

Le, J. (2014). *Drug absorption*. Retrieved from www.merckmanuals.com

McMahon, S. B., Koltzenburg, M., Tracey, I., & Turk, D. C. (2013). *Wall and Melzack's textbook of pain*. Philadelphia, PA: Elsevier Saunders.

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: A new theory. *Science*, *150*(3699), 971–979.

Merskey, H. (1979). *Pain, 6*, 250. Retrieved from the International Association for the Study of Pain, http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&&navItemNumber=576#Pain

Merskey, H., Lindblom, U., Mumford, J. M., Nathan, P. W., & Sunderland, S. (1994). Part III: Pain terms, a current list with definitions and notes on usage. In H. Merskey & N. Bogduk (Eds.), *Classification of chronic pain* (2nd ed., pp. 209–214). Seattle, WA: IASP Press.

Meyer, R., Campbell, J., & Raja, S. (1994). Peripheral neural mechanisms of nociception. In P. Wall & R. Melzack (Eds.), *Textbook of pain*. Edinburgh, UK: Churchill Livingstone.

Schecter, N., Berde, C., & Yaster, M. (2002). *Pain in infants, children and adolescents* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Sherrington C. S. (1906). *The integrative action of the nervous system*. New Haven, CT: Yale University Press.

Simons, S., vanDijk, M., Anand, K. S., Roofthooft, D., van Lingen, R. A., & Tibboel, D. (2003). Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Archives of Pediatrics and Adolescent Medicine*, *157*, 1058.

Slater, R., Cantarella, A., Gallella, S., Worley, A., Boyd, S., Meek, J., & Fitzgerald, M. (2006). Cortical pain responses in human infants. *Journal of Neuroscience*, *26*, 3662–3666.

Stevens, B. (1999). Pain in infants. In M. McCaffery & C. Pasero (Eds.), *Pain: Clinical manual* (2nd ed.). St. Louis, MO: Mosby.