SPECIAL ARTICLE

PAIN AND ITS EFFECTS IN THE HUMAN NEONATE AND FETUS

K.J.S. Anand, M.B.B.S., D.Phil., and P.R. Hickey, M.D

From the Department of Anesthesia, Harvard Medical School, and Children's Hospital, Boston. Address reprint requests to Dr. Anand at the Department of Anesthesia, Children's Hospital, 300 Longwood Ave., Boston, MA 02115.

THE evaluation of pain in the human fetus and neonate is difficult because pain is generally defined as a subjective phenomenon.[1] Early studies of neurologic development concluded that neonatal responses to painful stimuli were decorticate in nature and that perception or localization of pain was not present.[2] Furthermore, because neonates may not have memories of painful experiences, they were not thought capable of interpreting pain in a manner similar to that of adults.[3,4] On a theoretical basis, it was also argued that a high threshold of painful stimuli may be adaptive in protecting infants from pain during birth.[5] These traditional views have led to a widespread belief in the medical community that the human neonate or fetus may not be capable of perceiving pain.[2,6]

Strictly speaking, nociceptive activity, rather than pain, should be discussed with regard to the neonate, because pain is a sensation with strong emotional associations. The focus on pain perception in neonates and confusion over its differentiation from nociceptive activity and the accompanying physiologic responses have obscured the mounting evidence that nociception is important in the biology of the neonate. This is true regardless of any philosophical view on consciousness and "pain perception" in newborns. In the literature, terms relating to pain and nociception are used interchangeably; in this review, no further distinction between the two will generally be made.

One result of the pervasive view of neonatal pain is that newborns are frequently not given analgesic or anesthetic agents during invasive procedures, including surgery.[7-12] Despite recommendations to the contrary in textbooks on pediatric anesthesiology, the clinical practice of inducing minimal or no anesthesia in newborns, particularly if they are premature, is widespread.[7,8,12] Unfortunately, recommendations on neonatal anesthesia are made without reference to recent data about the development of perceptual mechanisms of pain and the physiologic responses to nociceptive activity in preterm and full-term neonates. Even Robinson and Gregory's landmark paper demonstrating the safety of narcotic anesthesia in preterm neonates cites "philosophic objections" rather than any physiologic rationale as a basis for using this technique.[9] Although methodologic and other issues related to the study of pain in neonates have been discussed,[5,13] the body of scientific evidence regarding the mechanisms and effects of nociceptive activity in newborn infants has not been addressed directly.

ANATOMICAL AND FUNCTIONAL REQUIREMENTS FOR PAIN PERCEPTION

The neural pathways for pain may be traced from sensory receptors in the skin to sensory areas in the cerebral cortex of newborn infants. The density of nociceptive nerve endings in the skin of newborns is similar to or greater than that in adult skin.[14] Cutaneous sensory receptors appear in the perioral area of the human fetus in the 7th week of gestation; they spread to the rest of the face, the palms of the hands, and the soles of the feet by the 11th week, to the trunk and proximal parts of the arms and legs by the 15th week, and to all cutaneous and mucous surfaces by the 20th week.[15,16] The spread of cutaneous receptors is preceded by the development of synapses between sensory fibers and interneurons in the dorsal horn of the spinal cord, which first appear during the sixth week of gestation.[17,18] Recent studies using electron microscopy and immunocytochemical methods show that the development of various types of cells in the dorsal horn (along with their laminar arrangement, synaptic interconnections, and specific neurotransmitter vesicles) begins before 13 to 14 weeks of gestation and is completed by 30 weeks.[17]

Lack of myelination has been proposed as an index of the lack of maturity in the neonatal nervous system[2] and is used frequently to support the argument that premature or full-term neonates are not capable of pain perception.[5,6] However, even in the peripheral nerves of adults, nociceptive impulses are carried through unmyelinated (C-polymodal) and thinly myelinated (A-delta) fibers.[19] Incomplete myelination merely implies a slower conduction velocity in the nerves or central nerve tracts of neonates, which is offset completely by the shorter interneuron and neuromuscular distances traveled by the impulse.[20] Moreover, quantitative neuroanatomical data have shown that nociceptive nerve tracts in the spinal cord and central nervous system undergo complete myelination during the second and third trimesters of gestation. Pain pathways to the brain stem and thalamus are completely myelinated by 30 weeks; whereas the thalamocortical pain fibers in the posterior limb of the internal capsule and corona radiata are myelinated by 37 weeks.[14]

Development of the fetal neocortex begins at 8 weeks gestation, and by 20 weeks each cortex has a full complement of 10^9 neurons.[21] The dendritic processes of the cortical neurons undergo profuse arborizations and develop synaptic targets for the incoming thalamocortical fibers and intracortical connections.[22,23] The timing of the thalamocortical connection is of crucial importance for cortical perception, since most sensory pathways to the neocortex have synapses in the thalamus. Studies of primate and human fetuses have shown that afferent

neurons in the thalamus produce axons that arrive in the cerebrum before mid-gestation. These fibers then "wait" just below the neocortex until migration and dendritic arborization of cortical neurons are complete and finally establish synaptic connections between 20 and 24 weeks of gestation (Fig. 1).[9-38]

Functional maturity of the cerebral cortex is suggested by fetal and a neonatal electroencephalographic patterns, studies of cerebral metabolism, and the behavioral development of neonates. First, intermittent electroencephalographic bursts in both cerebral hemispheres are first seen at 20 weeks gestation; they become sustained at 22 weeks and bilaterally synchronous at 26 to 27 weeks. By 30 weeks, the distinction between wakefulness and sleep can be made on the basis of electroencephalo- graphic patterns. Cortical components of visual and auditory evoked potentials have been recorded in preterm babies (born earlier than 30 weeks of gestation), whereas olfactory and tactile stimuli may also cause detectable changes in electroencephalograms of neonates. Second, in vivo measurements of cerebral glucose utilization have shown that maximal metabolic activity in located in sensory areas of the brain in neonates (the sensorimotor cortex, thalamus, and mid brain- brain-stem regions), further suggesting the functional maturity of these regions. Third, several forms of behavior imply cortical function during fetal life. Well-defined periods of quiet sleep, active sleep, and wakefulness occur in utero beginning at 28 weeks of gestation. In addition to the specific behavioral responses to pain described below, preterm and full-term babies have various cognitive, coordinative, and associative capabilities in response to visual and auditory stimuli, leaving no doubt about the presence of cortical function.

Several lines of evidence suggest that the complete nervous system is active during prenatal development and that detrimental and developmental changes in any part would affect the entire system. In studies in animals, Ralston found that somatosensory neurons of the neocortex respond to peripheral noxious stimuli and proposed that "it does not appear necessary to postulate a subcortical mechanism for appreciation of pain in the fetus or neonate." Thus, human newborns do have the anatomical and functional components required for the perception of painful stimuli. Since these stimuli may undergo selective transmission, inhibition, or modulation by various neurotransmitters, the neurochemical mechanisms associated with pain pathways in the fetus and newborn are considered below.
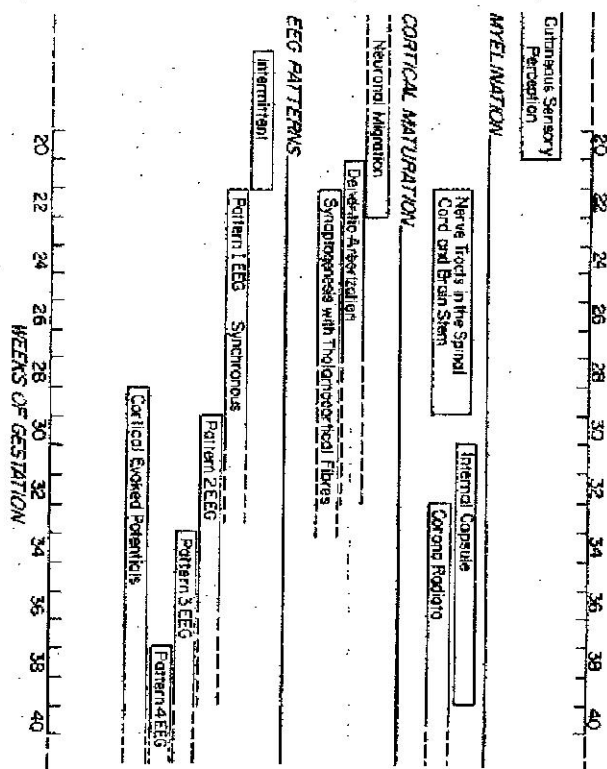

Figure 1. Schematic Diagram of the Development of Cutaneous Sensory Perception, Myelination of the Pain Pathways, Maturation of the Fetal Neocortex, and Electroencephalographic Patterns in the Human Fetus and Neonate.

NEUROCHEMICAL SYSTEMS ASSOCIATED WITH PAIN PERCEPTION

The Tachykinin System

Various putative neurotransmitters called the tachykinins (substance P, neurokinin A, neuromedin K, and so forth) have been identified in the central nervous system, but only substance P has been investigated thoroughly and shown to have a role in the transmission and control of pain impulses. Neural elements containing substance P and its receptors appear in the dorsal-root ganglia and dorsal horns of the spinal cord at 12 to 16 weeks of gestation. A high density of substance P fibers and cells have been observed in multiple areas of the fetal brain stem associated with pathways for pain perception and control and visceral reactions to pain. Substance P fibers and cells have also been found in the hypothalamus, mammillary bodies, thalamus, and cerebral cortex of human fetuses early in the development. Many studies have found higher densities of substance P and it receptors in neonates than in adults of the same species, although the importance of this finding is unclear.

The Endogenous Opioid System

With the demonstration of the existence of stereospecific opiate receptors[9][10] and their endogenous ligands,[9] the control of pain was suggested as a primary role for the endogenous opioid system.[9] Both the enkephalinergic and the endorphinergic systems may modulate pain transmission at spinal and supraspinal levels.[70][71] In the human fetus, however, there are no data on the ontogeny and distribution of specific cells, fibers, and receptors (mu-, delta-, and kappa opiate receptors) that are thought to mediate the antinociceptive effects of exogenous and endogenous opioids.[73] However, functionally mature endorphinergic cells in fetal pituitary glands have been observed at 15 weeks of gestation and possibly earlier.[75][76] Beta-endorphin and beta-lipotropin were found to be secreted from fetal pituitary cells at 20 weeks in response to in vitro stimulation by corticotropin-releasing factor.[77] In addition, more production of beta-endorphin may occur in fetal and neonatal pituitary glands than in adult glands.[78][79]

Endogenous opioids are released in the human fetus at birth and in response to fetal and neonatal distress.[80] Umbilical-cord plasma levels of beta-endorphin and beta-lipotropin from healthy full-term neonates delivered vaginally or by cesarean section have been shown to be three to five times higher than plasma levels in resting adults.[81][82] Neonates delivered vaginally by breech presentation or vacuum extraction had further increases in beta-endorphin levels, indication beta-endorphin secretion in response to stress at birth.[83] Plasma beta-endorphin concentrations correlated negatively with umbilical-artery pH and partial pressure of oxygen and positively with base deficit and partial pressure of carbon dioxide, suggesting that birth asphyxia may be a potent stimulus to the release of endogenous opioids.[83][84][85] Cerebrospinal fluid levels of beta-endorphin were also increased markedly in newborns with apnea of prematurity,[86] infections, or hypoxemia.[87][88][89] These elevated values may have been caused by the "stress" of illness,[90] the pain associated with these clinical conditions, or the invasive procedures required for their treatment. However, these high levels of beta-endorphin are unlikely to decrease anesthetic or analgesic requirements,[91] because the cerebrospinal fluid levels of beta-endorphin required to produce analgesia in human adults have been found to be 10,000 times higher than the highest recorded levels in neonates.[92]

The high levels of beta-endorphin and beta-lipotropin in cord plasma decreased substantially by 24 hours after birth[82][83] and reached adult levels by five days, whereas the levels in the cerebrospinal fluid fell to adult values in 24 hours.[87][92][93] In newborn infants of women addicted to narcotics, massive increases in plasma concentrations of beta-endorphin, beta-lipotropin, and metenkephalin occurred within 24 hours, with some values reaching 1000 times those in resting adults. Markedly increased levels persisted for up to 40 days after birth.[94] However, these neonates were considered to be clinically normal, and no behavioral effects were observed (probably because of the development of prenatal opiate tolerance).

PHYSIOLOGIC CHANGES ASSOCIATED WITH PAIN

Cardiorespiratory Changes

Changes in cardiovascular variables, transcutaneous partial pressure of oxygen, and palmar sweating have been observed in neonates undergoing painful clinical procedures. In preterm and full-term neonates undergoing circumcision[95][96][97] or heel lancing,[13][14][98] marked increases in the heart rate and blood pressure occurred during and after the procedure. The magnitude of changes in the heart rate was related to the intensity and duration of the stimulus[14] and to the individual temperaments of the babies.[98] The administration of local anesthesia to full-term neonates undergoing circumcision prevented the changes in heart rate and blood pressure,[95][96][100] whereas giving a "pacifier" to preterm neonates during heel-stick procedures did not alter their cardiovascular or respiratory responses to pain.[101] Further studies in newborn and older infants showed that noxious stimuli were associated with an increase in heart rate, whereas non-noxious stimuli (which elicited the attention or orientation of infants) caused a decrease in heart rate.[102][103][104]

Large fluctuations in transcutaneous partial pressure of oxygen above and below an arbitrary "safe" range of 50 to 100 mm Hg have been observed during various surgical procedures in neonates.[105][106] Marked decreases in transcutaneous partial pressure of oxygen also occurred during circumcision,[106][107] but such changes were prevented in neonates given local analgesic agents.[106][108][109] Tracheal intubation in awake preterm and full-term neonates caused a significant decrease in transcutaneous partial pressure of oxygen, together with increases in arterial blood pressure[110][111] and intracranial pressure.[99] The increases in intracranial pressure with intubation were abolished in preterm neonates who were anesthetized.[110] In addition, infants' cardiovascular responses to tracheal suctioning were abolished by opiate-induced analgesia.[99]

Palmar sweating has also been validated as a physiologic measure of the emotional state in full-term babies and has been closely related to their state of arousal and crying activity. Substantial changes in palmar sweating were observed in neonates undergoing heel-sticks for blood sampling, and subsequently, a mechanical method of heel lancing proved to be less painful than manual methods, on the basis of the amount of palmar sweating.[112]

Hormonal and Metabolic Changes

Hormonal and metabolic changes have been measured primarily in neonates undergoing surgery, although there are limited data on the neonatal responses to venipuncture and other minor procedures. Plasma renin activity increased significantly 5 minutes after venipuncture in full-term neonates and returned to basal levels 60 minutes thereafter, no changes occurred in the plasma levels of cortisol, epinephrine, or norepinephrine after venipuncture.[113] In preterm neonates receiving ventilation therapy, chest physiotherapy and endotracheal suctioning produced significant increases in plasma epinephrine and norepinephrine; this response was decreased in sedated infants.[114] In neonates undergoing circumcision without anesthesia, plasma cortisol levels increased markedly during and after the procedure.[95][96] Similar changes in cortisol levels were not inhibited in a small number of neonates given a local anesthetic,[123] but the efficacy of the nerve block was questionable in these cases.

Further detailed hormonal studies[124] in preterm and full-term neonates who underwent surgery under minimal anesthesia documented a marked release of catecho-lamines,[125] growth hormone,[126] glucagon,[127] cortisol, aldosterone, and other corticosteroids,[129][130] as well as suppression of insulin secretion.[131] These responses resulted in the breakdown of carbohydrate and fat stores,[125][128] leading to severe and prolonged hyperglycemia and marked increases in blood lactate, pyruvate, total ketone bodies, and nonesterified fatty acids. Increased protein breakdown was documented during and after surgery by changes in plasma amino acids, elevated nitrogen excretion, and increased 3-methyl-histidine:creatinine ratios in the urine (Anand KJS, Aynsley-Green A: unpublished data). Marked differences also occurred between the stress responses of premature and full-term neonates (Anand KJS, Aynsley-Green A: unpublished data) and between the responses of neonates undergoing different degrees of surgical stress.[132] Possibly because of the lack of deep anesthesia, neonatal stress responses were found to be three to five times greater than those in adults, although the duration was

shorter.[?] These stress responses could be inhibited by potent anesthetics, as demonstrated by randomized, controlled trials of halothane and fentanyl. These trials showed that endocrine and metabolic stress responses were decreased by halothane anesthesia in full-term neonates 35 and abolished by low-dose fentanyl anesthesia in preterm neonates.[?] The stress responses of neonates undergoing cardiac surgery were also decreased in randomized trials of high-dose fentanyl and sufentanil anesthesia.[?] These results indicated that the nociceptive stimuli during surgery performed with minimal anesthesia were responsible for the massive stress responses of neonates. Neonates who were given potent anesthetics in these randomized trials were more clinically stable during surgery and had fewer postoperative complications as compared with neonates under minimal anesthesia.[?] There is preliminary evidence that the pathologic stress responses of neonates under light anesthesia during major cardiac surgery may be associated with an increased postoperative morbidity and mortality (Anand KJS, Hickey PR: unpublished data). Changes in plasma stress hormones (e.g., cortisol) can also be correlated with the behavioral states of newborn infants,[?] which are important in the postulation of overt subjective distress in neonates responding to pain.

BEHAVIORAL CHANGES ASSOCIATED WITH PAIN PERCEPTION

Simple Motor Responses

Early studies of the motor responses of newborn infants to pinpricks reported that the babies responded with a "diffuse body movement" rather than a purposeful withdrawal of the limb,[?] whereas other studies found reflex withdrawal to be the most common response.[?] More recently, the motor responses of 24 healthy full-term neonates to a pinprick in the leg were reported to be flexion and adduction of the upper and lower limbs associated with grimacing, crying, or both, and these responses were subsequently quantified.[?] Similar responses have also been documented in very premature neonates, and in a recent study, Fitzgerald et al. found that premature neonates (<30 weeks) not only had lower thresholds for a flexor response but also had increased sensitization after repeated stimulation.[?]

Facial Expressions

Distinct facial expressions are associated with pleasure, pain, sadness, and surprise in infants.[?] These expressions, especially those associated with pain, have been objectively classified and validated in a study of infants being immunized.[?] With use of another method of objectively classifying facial expressions of neonates, different responses were observed with different techniques of heel lancing and with different behavioral states[?] (and Grunau RVE, Craig KD: unpublished data). These findings suggest that the neonatal response to pain is complex and may be altered by the behavioral state and other factors at the time of the stimulus.[?]

Crying

Crying is the primary method of communication in newborn infants and is also elicited by stimuli other than pain.[?] Several studies have classified infant crying according to the type of distress indicated and its spectrographic properties.[?] These studies have shown that cries due to pain, hunger, or fear can be distinguished reliably by the subjective evaluation of trained observers and by spectrographic analysis.[?] This has allowed the cry response to be used as a measure of pain in numerous recent studies.[?]

The pain cry has specific behavioral characteristics and spectrographic properties in healthy full-term neonates.[?] Pain cries of preterm neonates and neonates with neurologic impairment, hyperbilirubinemia, or meningitis are considerably different, thereby indicating altered cortical function in these babies.[?] Changes in the patterns of neonatal cries have been correlated with the intensity of pain experienced during circumcision and were accurately differentiated by adult listeners.[?] In other studies of the painful procedures, neonates were found to be more sensitive to pain than older infants (those 3 to 12 months old) but had similar latency periods between exposure to a painful stimulus and crying or another motor response.[?] This supports the contention that slower conduction speed in the nerves of neonates is offset by the smaller inter-neuron distances traveled by the impulse.

Complex Behavioral Responses

Alterations in complex behavior and sleep-wake cycles have been studied mainly in newborn infants undergoing circumcision without anesthesia. Emde and coworkers observed that painful procedures were followed by prolonged periods of non-rapid-eye-movement sleep in newborns and confirmed these observations in a controlled study of neonates undergoing circumcision without anesthesia.[?] Similar observations have been made in adults with prolonged stress. Other subsequent studies have found increased wakefulness and irritability for an hour after circumcision, an altered arousal level in circumcised male infants as compared with female and uncircumcised male infants, and an altered sleep-wake state in neonates undergoing heel-stick procedures.[?] In a double-blind, randomized controlled study using the Brazelton Neonatal Behavioral Assessment Scale, 90 percent of neonates had changed behavioral states for more than 22 hours after circumcision, whereas only 16 percent of the uncircumcised infants did.[?] It was therefore proposed that such painful procedures may have prolonged effects on the neurologic and psychosocial development of neonates.[?] A similar randomized study showed the absence of these behavioral changes in neonates given local anesthesia for circumcision.[?] For two days after circumcision, neonates who had received anesthetics were more attentive to various stimuli and had greater orientation, better motor responses, decreased irritability, and a greater ability to quiet themselves when disturbed. A recent controlled study showed that intervention designed to decrease the amount of sensory input and the intensity of stressful stimuli during intensive care of preterm neonates was associated with improved clinical and developmental outcomes.[?] Because of their social validity and communicational specificity, the behavioral responses observed suggest that the neonatal response to pain is not just a reflex response.[?]

MEMORY OF PAIN IN NEONATES

The persistence of specific behavioral changes after circumcision in neonates implies the presence of memory. In the short term, these behavioral changes may disrupt the adaptation of newborn infants to their postnatal environment,[?] the development of parent-infant bonding, and feeding schedules.[?] In the long term, painful experiences in neonates could possibly lead to psychological sequelae,[?] since several workers have shown that newborns may have a much greater capacity for memory than was previously thought.[?]

Pain itself cannot be remembered, even by adults[?]; only the experiences associated with pain can be recalled. However, the question of memory is important, since it has been argued that memory traces are necessary for the "maturation" of pain perception,[?] and a painful experience may not be deemed important if it is not remembered. Long-term memory requires

the functional integrity of the limbic system and diencephalon (specifically, the hippocampus, amygdala, anterior and mediodorsal thalamic nuclei, and mamillary nuclei)[158]; these structures are well developed and functioning during the newborn period.[15] Furthermore, the cellular, synaptic, and molecular changes required for memory and learning depend on brain plasticity, which is known to be highest during the late prenatal and neonatal periods.[192,196] Apart from excellent studies in animals demonstrating the long-term effects of sensory experiences in the neonatal period,[192] evidence for memories of pain in human infants must, by necessity, be anecdotal.[193,94] Early painful experiences may be stored in the phylogenically old "procedural memory,"[1] which is not accessible to conscious recall. Although Janov[195] and Holden[196] have collected clinical data that they claim indicate that adult neuroses or psychosomatic illnesses may have their origins in painful memories acquired during infancy or even neonatal life, their findings have not been substantiated or widely accepted by other workers.

Conclusions

Numerous lines of evidence suggest that even in the human fetus, pain pathways as well as cortical and subcortical centers necessary for pain perception are well developed late in gestation, and the neurochemical systems now known to be associated with pain transmission and modulation are intact and functional. Physiologic responses to painful stimuli have been well documented in neonates of various gestational ages and are reflected in hormonal, metabolic, and cardiorespiratory changes similar to but greater than those observed in adult subjects. Other responses in newborn infants are suggestive of integrated emotional and behavioral responses to pain and are retained in memory long enough to modify subsequent behavior patterns.

None of the data cited herein tell us whether neonatal nociceptive activity and associated responses are experienced subjectively by the neonate as pain similar to that experienced by older children and adults. However, the evidence does show that marked nociceptive activity clearly constitutes a physiologic and perhaps even a psychological form of stress in premature or full-term neonates. Attenuation of the deleterious effects of pathologic neonatal stress responses by the use of various anesthetic techniques has now been demonstrated. Recent editorials addressing these issues have promulgated a wide range of opinions, without reviewing all the available evidence.[197-201] The evidence summarized in this paper provides a physiologic rationale for evaluating the risks of sedation, analgesia, local anesthesia, or general anesthesia during invasive procedures in neonates and young infants. Like persons caring for patients of other ages, those caring for neonates must evaluate the risks and benefits of using analgesic and anesthetic techniques in individual patients. However, in decisions about the use of these techniques, current knowledge suggests that humane considerations should apply as forcefully to the care of neonates and young, nonverbal infants as they do to children and adults in similar painful and stressful situations.