shorter.[122] 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.[126] The stress responses of neonates undergoing cardiac surgery were also decreased in randomized trials of high-dose fentanyl and sufentanil anesthesia.[126,127,128] 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.[126,129] 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major cardiac surgery may be associated with an increased postoperative morbidity and mortality (Anand KJS, Hickey PR: unpublished data).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,[125,130,131] 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,[2] whereas other studies found reflex withdrawal to be the most common response.[111,114] 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.[111,115] 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.[116]

Facial Expressions

Distinct facial expressions are associated with pleasure, pain, sadness, and surprise in infants.[147] These expressions, especially those associated with pain, have been objectively classified and validated in a study of infants being immunized.[132,148] 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[137] (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.[150]

Crying

Crying is the primary method of communication in newborn infants and is also elicited by stimuli other than pain.[151] Several studies have classified infant crying according to the type of distress indicated and its spectrographic properties.[152-158] 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.[152,159] This has allowed the cry response to be used as a measure of pain in numerous recent studies.[22,69,110,152,160,161]

The pain cry has specific behavioral characteristics and spectrographic properties in healthy full-term neonates.[69,160] Pain cries of preterm neonates and neonates with neurologic impairment, hyperbilirubinemia, or meningitis are considerably different, thereby indicating altered cortical function in these babies.[69,160] 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.[160] In other studies of the painful procedures, neonates were found to he 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.[96,110,160,162,170] 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.[171] 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.[172-174] 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.[171] It was therefore proposed that such painful procedures may have prolonged effects on the neurologic and psychosocial development of neonates.[175] A similar randomized study showed the absence of these behavioral changes in neonates given local anesthetics for circumcision.[126] 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.[176] 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.[178-181]

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,[134,176] the development of parent-infant bonding, and feeding schedules.[182,183] In the long term, painful experiences in neonates could possibly lead to psychological sequelae,[2] since several workers have shown that newborns may have a much greater capacity for memory than was previously thought.[184-189]

Pain itself cannot be remembered, even by adults[190]; 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,[3] 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)[188]; these structures are well developed and functioning during the newborn period.[43] 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.[192,193] Apart from excellent studies in animals demonstrating the long-term effects of sensory experiences in the neonatal period,[121] evidence for memories of pain in human infants must, by necessity, be anecdotal.[178,192,193] Early painful experiences may be stored in the phylogenically old "procedural memory," which is not accessible to conscious recall.[182,183,191] 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.[197-200] 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.