With the demonstration of the existence of stereospecific opiate receptors[69,70] and their endogenous ligands,[71] the control of pain was suggested as a primary role for the endogenous opioid system.[72] Both the enkephalinergic and the endorphinergic systems may modulate pain transmission at spinal and supraspinal levels.[46,73] 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.[74] 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.[78-82]

Endogenous opioids are released in the human fetus at birth and in response to fetal and neonatal distress.[83] 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.[78,81] 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.[82] 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.[81,83-87] Cerebrospinal fluid levels of beta-endorphin were also increased markedly in newborns with apnea of prematurity,[88,89] infections, or hypoxemia.[84,91,92] These elevated values may have been caused by the "stress" of illness,[93] 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,[94] 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.[95]

The high levels of beta-endorphin and beta-lipotropin in cord plasma decreased substantially by 24 hours after birth[82,96] and reached adult levels by five days, whereas the levels in the cerebrospinal fluid fell to adult values in 24 hours.[87,97,98] 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.[87] 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[99,100] or heel lancing,[101-105] 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[101] and to the individual temperaments of the babies.[105] The administration of local anesthesia to full-term neonates undergoing circumcision prevented the changes in heart rate and blood pressure,[99,100,106] 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.[22,107,108]

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.[109-111] Marked decreases in transcutaneous partial pressure of oxygen also occurred during circumcision,[100,112] but such changes were prevented in neonates given local analgesic agents.[100,106,112] 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[113-115] and intracranial pressure.[116] The increases in intracranial pressure with intubation were abolished in preterm neonates who were anesthetized.[117] In addition, infants' cardiovascular responses to tracheal suctioning were abolished by opiate-induced analgesia.[118]

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.[120]

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.[121] 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.[122] In neonates undergoing circumcision without anesthesia, plasma cortisol levels increased markedly during and after the procedure.[123,124] Similar changes in cortisol levels were not inhibited in a small number of neonates given a local anesthetic,[125] but the efficacy of the nerve block was questionable in these cases.

Further detailed hormonal studies[126] in preterm and full-term neonates who underwent surgery under minimal anesthesia documented a marked release of catecho- lamines,[127] growth hormone,[128] 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,[127,132,133] 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.[131] 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