EXPERT REPORT OF KANWALJEET S. ANAND, M.B.B.S., D.Phil.

I am a pediatrician specialized in the care of critically ill newborns and children. For more than 20 years, I have conducted intensive research and study on the development of pain and stress in the human newborn and fetus. The U.S. Department of Justice has asked me to provide this expert report, describing the capacity of the fetus to feel pain and the effects of maternal anesthesia on that capacity, to assist the Court in its assessment of the Partial-Birth Abortion Ban Act of 2003.

Background and Qualifications

I received an M.B.B.S. (Bachelor of Medicine/Bachelor of Surgery, equivalent to an M.D.) from Mahatma Gandhi Memorial Medical College in Indore, India. After post-doctoral training in Pediatrics, I received a Rhodes Scholarship to study at the University of Oxford, England. For research performed at Oxford, on the hormonal and metabolic responses of premature and full-term newborns to the pain/stress caused by surgical operations and the effects of anesthesia in neonates, I received a D.Phil. (Doctor of Philosophy) from the Faculty of Medicine. Additional post-doctoral training was acquired in England, at Children's Hospital, Boston and at Massachusetts General Hospital, where I completed a fellowship in pediatric critical care medicine.

I have held academic appointments at the University of Oxford, Harvard Medical School, Emory University School of Medicine, and the University of Arkansas for Medical Sciences, where I served as Director of Critical Care Medicine in the Department of Pediatrics (1997-2003) and remain presently employed. I currently occupy the Morris & Hettie Oakley Endowed Chair in Pediatric Critical Care Medicine and serve as a tenured Professor of Pediatrics, Anesthesiology, Pharmacology and Neurobiology at the University of Arkansas for Medical Sciences. I serve as Director of the Pain Neurobiology Laboratory at Arkansas Children's Hospital Research Institute, where I study the effects of repetitive pain in early development. I am currently conducting a long-term study funded by the National Institutes of Health examining the effect of morphine on premature neonates from 23 to 32 weeks gestation. I also serve on the

Board of Directors of Arkansas Children's Hospital Research Institute. My clinical appointment at Arkansas Children's Hospital, as an Attending Physician, allows me to provide care for the patients admitted to the Pediatric Intensive Care Unit. I am a diplomate of the American Board of Pediatrics and the Sub-Board of Pediatric Critical Care Medicine, and licensed to practice medicine in the State of Arkansas. I have previously held medical licenses in Massachusetts, Georgia, in the United Kingdom and India.

I am the author or co-author of approximately 200 publications, and recipient of the Dr. Michael Blacow Award from the British Paediatric Association (1986), a Pediatric Resident Research Award from the American Academy of Pediatrics (1992), the first Young Investigator Award in Pediatric Pain from the International Association for the Study of Pain (1994), the Jeffrey Lawson Award from the American Pain Society (2000), and numerous other awards and honors. My research efforts have been focused on examining the immediate and long-term effects of pain in premature and full-term newborn infants, the development of a functional pain system during fetal and neonatal life, and the treatment of pain at these ages.

I am being compensated by the U.S. government at the rate of $450.00 per hour for my work on this case, plus the reimbursement of travel expenses.

During the past four years, I have testified as an expert witness in the following cases:

1. State of Texas vs. Kim Laird (pt. Michael Andrews); 9-24-2003 in Cass County Court, Texas.

2. State of Arkansas vs. Roshonda Smith (pt. Christian Cogshell); 11-4-2003 in Pulaski County Court, Jacksonville, Arkansas.

3. State of Arkansas vs. Efrem Burke (pt. Madison Crofford); Dec. 12-14, 2001 in Craighead County Court, Jonesboro, Arkansas.

4. Marilyn & Leon Espinoza vs. Morristown Memorial Hospital, S.E. Finch and others (pt. Alexandra Espinoza), Aug.-Sept., 2000 in Newark Federal Court, Newark, New Jersey.

Attached as Appendix A is my Curriculum Vitae, which lists in more detail my academic background, positions, research and publications. In forming the opinions contained in this Expert Report, I have considered the following materials, attached as Appendix B:

1. International Association for the Study of Pain; IASP Pain Terminology. A sample list of frequently used terms from: Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy, edited by H. Merskey and N. Bogduk, IASP Press, Seattle, 1994, pp. 209-214. (Website: http://www.iasp-pain.org/terms-p.html)

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3. Ward-Platt M, Anand KJS, Aynsley-Green A. Ontogeny of the stress response to surgery in the human fetus, neonate and child. Intensive Care Medicine (1989) 15:844-945.

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13. Smith RP, Gitau R, Glover V, Fisk NM. Pain and stress in the human fetus. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2000; 92:161-5.

14. Partsch CJ, Sippell WG, MacKenzie IZ, Aynsley-Green A. The steroid hormonal milieu of the undisturbed human fetus and mother at 16-20 weeks gestation. Journal of Clinical Endocrinology & Metabolism 1991; 73:969-74.

15. Teixeira JM, Glover V, Fisk NM. Acute cerebral redistribution in response to invasive procedures in the human fetus. American Journal of Obstetrics & Gynecology 1999; 181:1018-25.

16. Fitzgerald M. Spontaneous and evoked activity of fetal primary afferents in vivo. Nature 1987; 326:603-5.

17. Kinney HC, Ottoson CK, White WF. Three-dimensional distribution of 3H-naloxone binding to opiate receptors in the human fetal and infant brainstem. Journal of Comparative Neurology 1990; 291:55-78.

18. Teixeira J, Fogliani R, Giannakoulopoulos X, Glover V, Fisk NM. Fetal haemodynamic stress response to invasive procedures. Lancet 1996; 347:624.

19. Kopecky EA, Ryan ML, Barrett JF, et al. Fetal response to maternally administered morphine. American Journal of Obstetrics & Gynecology 2000; 183:424-30.

20. Giannakoulopoulos X, Sepulveda W, Kourtis P, Glover V, Fisk NM. Fetal plasma cortisol and beta-endorphin response to intrauterine needling. Lancet 1994; 344:77-81.

21. Gitau R, Fisk NM, Teixeira JM, Cameron A, Glover V. Fetal hypothalamic-pituitary-adrenal stress responses to invasive procedures are independent of maternal responses. Journal of Clinical Endocrinology & Metabolism 2001; 86:104-9.

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Summary of Opinion

It is my opinion that the human fetus possesses the ability to experience pain from 20 weeks of gestation, if not earlier, and the pain perceived by a fetus is possibly more intense than that perceived by term newborns or older children. The process of (a) grasping the lower extremity of the fetus with a forceps or other surgical instrument, (b) manipulating or rotating the fetal position within the uterus, (c) forcible extraction of the fetal legs and lower body through the uterine cervix, (d) surgical incision of the fetal cranium/upper neck area of the fetus, and (e) entrance into the cranial vault (followed by vacuum suctioning of the fetal brain) during an abortion procedure will result in prolonged and intense pain experienced by the human fetus, if that fetus is at or beyond the neurological maturity associated with 20 weeks of gestation. Anesthetic agents that are routinely administered to the mother during this procedure would be insufficient to ensure that the fetus does not feel pain, and higher doses of anesthetic drugs, enough to produce fetal anesthesia, would seriously compromise the health of the mother. Thus, it is my opinion that the fetus would be subjected to intense pain, occurring prior to fetal demise, from the abortion procedures described in the Partial-Birth Abortion Ban Act of 2003.

The Capacity of the Fetus to Experience Pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment." The human fetus is obviously incapable of verbal expression and, therefore, the evidence for fetal pain must be based on surrogate markers, including anatomical, functional, physiological and behavioral indicators that are correlated with pain, from studies of pain in children or adults. Multiple lines of scientific evidence converge to support the conclusion that the human fetus can experience pain from 20 weeks of gestation, and possibly as early as 16 weeks of gestation.

Anatomical Development:

The neural pathways for pain include sensory receptors in the skin connected to nerve fibers, which lead to pain processing in the dorsal horn of the spinal cord. Nerve tracts from these spinal cord areas transmit the signals of pain to supraspinal centers located primarily in the brainstem, thalamus, and cerebral cortex of the brain.

Fully-functioning sensory receptors appear in the skin around the mouth of the fetus at 7 weeks and spread to all skin and mucous surfaces before 20 weeks of gestation. Nerve fibers precede the appearance of these skin receptors, and are capable of transmitting sensory stimuli from the periphery to the spinal cord at all times. Until the maturation of connections between unmyelinated pain-specific fibers and spinal cord neurons is complete, pain impulses are transmitted by a population of nerve fibers that only carry the touch sensation in later life. Dorsal horn neurons in the spinal cord begin to develop in the first trimester (before 13 weeks), with increasing anatomical complexity and functional maturation throughout fetal life. The pattern of functional maturation is such that incoming painful impulses are readily transmitted to the brain, but modulation or inhibition of these impulses does not develop until late gestation (36 to 40 weeks) or even 6-8 weeks after birth.

The architectonic organization and differentiation of the neuronal cell types in the fetal brainstem (including the medulla, pons, and midbrain) and fetal thalamus occurs during the first and second trimesters of pregnancy. Transient developmental characteristics appear during early maturation in these areas; for example, the reticular thalamic nucleus plays a major role in the fetal brain, but is not visible in the adult brain. Cellular development in these areas reveals highly diverse, bipolar, multipolar or polymorphous, transmitter-reactive neurons, with highly elaborate branching of dendrites during fetal development. Specific molecular markers in these neurons are correlated with the functional receptors, chemical transmitters, and enzymes that are expressed in the adult human brain. These diverse neuronal types, their elaborate dendrites and axons, as well as their neurochemical development imply a functional role in early development. The brainstem and thalamic areas serve as intermediate targets for the sensory axons growing centrally from different levels of the spinal cord, which are sorted and directed towards different cortical and sub-cortical targets.

The imaging of glucose metabolic rates in the neonatal brain shows the highest functional activity in the thalamus and brain stem, in addition to sensory cortical areas. Magnetic resonance imaging (MRI) scans also show that the earliest myelination occurs in the posterior brainstem and the ventrolateral nuclei of the thalamus, which are the areas associated with pain processing during fetal development.

The cerebral cortex starts to form at about 8-10 weeks of human gestation, although early cortical neurons have few axonal or dendritic connections. Maturation and differentiation of these neurons occurs in the second trimester and the sub-plate zone is formed at around 15 weeks. Massive increases in dendritic arborization and synaptogenesis begin at 18-20 weeks of gestation, with sub-plate neurons serving as a signaling station for axonal connections from the sub-cortical areas. The fetal neocortex is penetrated by the fibers from sensory thalamic nuclei by 20 weeks, whereas other fibers (not routed through the thalamus) have penetrated the sub-plate zone by 13 weeks and reached the cortical plate by 16 weeks of gestation, providing the final anatomical link for inputs to reach the developing cortex. Structural data for fetal brains at 17-40 weeks of gestation showed that cortical layer thickness increases linearly with age, while the number of cortical neurons (corrected for surface and gyral growth) increases 10-fold from 12 to 28 weeks, reaching a peak at 28 to 32 weeks. Cortical columns (functional units of the cerebral cortex) increase in the fetal sensory cortex; the number of dendritic connections varies with age and the body-map representation for each column, which may provide a structural basis for the relationships between stimulus intensity and perception. Numerous studies show that the time course of developmental gene expression critically depends on afferent (sensory) activity entering the cortex. Thus, "neurons that fire together wire together" or activity-dependent effects on gene expression lead to the establishment of cortical maps during development.

Physiological Responses:

Fetuses have been observed to exhibit hormonal stress responses to painful stimuli from as early as 16 weeks of gestation, which provide additional evidence that the fetus can experience pain. Studies have demonstrated that certain stress hormones (plasma cortisol, catecholamines and β-endorphin) increased significantly in fetuses given blood transfusions through a needle

placed, under ultrasound guidance, in the intra-hepatic vein (reached by piercing the fetus's abdominal wall), whereas no consistent responses occurred in the fetuses transfused via a needle placed at the insertion of the umbilical cord (which is not innervated). The magnitude of the stress hormone responses was correlated with the duration of the painful stimulation. In addition, these hormonal responses were reduced when fentanyl (a pain-relieving opiate drug) was administered directly to the fetus.

Other studies have examined the redistribution of blood flow within the fetus caused by invasive procedures such as fetal blood sampling, body cavity aspirations, and insertion of feto-amniotic shunts. These studies revealed that the blood flow to the brain decreased within 70 seconds after painful stimulation in fetuses from as early as 16 weeks of gestation. Hormonal or circulatory responses from the fetus may not vouchsafe conscious pain perception, although their absence would be more likely if sensory stimuli from these invasive procedures were not reaching the thalamus and hypothalamus.

Increased Sensitivity to Pain in the Fetus:

The highest density of pain receptors per square inch of skin in human development occurs *in utero* from 20 to 30 weeks gestation. During this period, the epidermis is still very thin, leaving nerve fibers closer to the surface of the skin than in older neonates and adults. Even though the fetus possesses excitatory pain mechanisms (receptors and fibers that recognize and respond to painful stimuli) before 20 weeks of gestation, the pain inhibitory mechanisms (fibers which dampen and modulate the experience of pain) do not begin to develop until 32-34 weeks of gestation. Thus, a fetus at 20 to 32 weeks of gestation would experience a much more intense pain than older infants or children or adults, when these age groups are subjected to similar types of injury or handling. Other mechanisms supporting an increased sensitivity to pain during fetal life are reviewed in the accompanying materials (Appendix B).

The Question of Fetal Consciousness:

More than 3 decades of research shows that preterm infants are actively perceiving, learning, and organizing information, and are constantly striving to regulate themselves, their

environment and their experiences. All preterm infants actively approach and favor experiences that are developmentally supportive and actively avoid experiences that are developmentally disruptive. These behaviors are designed to support the conservation of energy, the organization of sleep-wake cycles, and the achievement of successive, age-related developmental milestones.

If preterm neonates from 23 weeks can respond to and organize their experiences, it is likely that rudimentary forms of these abilities are present *in utero*, which raises the question of fetal consciousness. Consciousness is associated with shifting patterns of activity of the cerebral cortex, but its mechanisms are not completely understood even in the adult brain. Thus, it may not be possible to obtain unequivocal evidence for fetal consciousness. A British Commission of Inquiry into Fetal Sentience declared that fetuses may be conscious from six weeks of gestation, whereas a committee from the Royal College of Obstetrics and Gynaecology countered that fetuses cannot be sentient before 26 weeks of gestation.

If cortical activity is considered as a marker for fetal consciousness, the electroencephalogram (EEG) signals such activity from 19 to 20 weeks of gestation and sustained EEGs can be recorded from fetuses of 23 weeks gestation. From about 20 weeks, fetuses start responding to light, sound, touch and taste, with progressive increases in the complexity of their spontaneous movements at this time. Somatosensory evoked potentials can be recorded from the sensory cortex after 24 weeks of gestation.

Similar to the physiological responses of preterm neonates, fetuses greater than 16-20 weeks respond to painful procedures with hormonal stress responses, noted from changes in plasma cortisol, catecholamines and β-endorphin, and from changes in the pulsatility index of the middle cerebral artery within 70 seconds after stimulation. Experimental findings show that human fetuses can acquire distinct verbal memories from prenatal experiences (studied only in the third trimester of pregnancy), which supports the concept that consciousness appears before birth. All the lines of evidence reviewed above suggest the presence of consciousness from about 20-22 weeks of fetal life.

The Effect of Maternal Anesthesia on the Fetus

The effect of maternal anesthesia on the fetus' capacity to experience pain depends on the type of anesthetic, the dosage given, and the method of administration. To reach the fetus, a drug administered to the mother would have to avoid metabolism by the maternal liver, enter the maternal bloodstream, cross the placental membrane, reach the fetal circulation in sufficient concentrations, and cross the fetal blood/brain barrier to produce significant clinical effects on the fetus. Methods that are routinely applied, for example, a pudendal nerve block, epidural anesthesia, or other methods of local/regional anesthesia would provide no protection against pain to the fetus. General anesthetics (inhalational anesthetics and certain opiates, such as fentanyl and sufentanyl) can provide some degree of pain relief to the fetus, because they readily cross the placental barrier and fetal blood/brain barrier. Nevertheless, studies of drug efficacy using anesthetic agents show that the fetus would require a higher concentration of anesthetics in the fetal circulation to achieve the same clinical anesthetic effects as occurring on the mother. Thus, doses of anesthesia that would be toxic to the mother will be required to ensure that the fetus experiences no pain during a surgical procedure.

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