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LOCATING THE BEGINNINGS OF PAIN

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ABSTRACT

This paper examines the question of whether a fetus can feel pain. The question is divided into four sub questions: What is pain? What is the neurology of pain processing? What is the fetus? Are there good reasons for holding that fetuses feel pain? Pain is suggested to be a multi-dimensional phenomenon drawing on emotional and sensory processes – a consequence of a gradual development involving a number of noxious events rather than an automatic consequence of injury or disease. The non-automaticity of pain is emphasised in the discussion of pain neurology that defies explanations based on a specialised neuronal 'pain-centre'. The development of the fetus is considered with respect to developmental neurobiology, behavioural and neurological responses to stimulation, and hormonal and neurochemical responses to noxious stimulation. While acknowledging that the development of the fetus is complex, especially after 26 weeks gestation, considerable development is still to occur, even after birth. The fetal pain literature is criticised for tending to exaggerate fetal development. Finally, the difficulty of explaining the subjectivity of pain in materialist terms is discussed. Pain is suggested to arise with development of the necessary neurological, cognitive and emotional structures. Pain experience is placed at approximately 12 months of age, though this is within the context of a continuum of awareness rather than a straight 'on-off' switch. The major moral implication of this stance is to place the burden of proof for analgesic use onto clinical measures, rather than relying upon the, so far, poorly supported assumption of pain awareness.

An important paper by Burgess and Tawia published recently attempted to tackle the question of when a fetus can be first said to *feel*.[1] An accompanying *Bioethics* editorial praised and

[1]Burgess J.A. and Tawia S.A.: 'When did you first begin to feel it? – Locating the beginning of human consciousness', *Bioethics*, 10, 1996: pp. 1–26.

supported the article: 'there is, to our knowledge, no comparable study of this question that is anywhere near so well informed both philosophically and physiologically'.[2] Burgess and Tawia concluded that conscious feeling emerges at 30-35 weeks gestation. This conclusion was based upon interpretation of anatomical data indicating that the central structures necessary for feeling have 'attained a critical minimal level of structural organisation' and upon EEG recordings of the underlying neuronal activity which indicate the first waking-state at 30–35 weeks gestation. The authors rightly acknowledged that such a conclusion has 'morally important practical consequences'. Establishing, within reasonable doubt, that the fetus does feel pain means there is a moral imperative to use analgesia or anaesthesia when performing operations on premature infants or *in utero*. This imperative remains regardless of any potential dangers associated with such an intervention.

Not surprisingly, the medical literature has also discussed the question of whether the fetus can feel pain.[3] Unlike Burgess and Tawia, medical researchers largely concluded that the fetus could not feel pain, regardless of gestational age. This conclusion was based upon an understanding of what pain is, rather than upon an understanding of the biological development of the fetus. As two of the contributors put it: 'So can a fetus feel pain? Given the definitions of feeling and pain the answer must be no.'[4] These authors suggested that the use of analgesia may still be advisable during fetal procedures to avoid possible detrimental effects, other than pain, following noxious stimulation.

Debate about whom, when or what can feel pain has also had an impact on basic scientific research. The journal *Pain* recently carried an editorial challenging the current definition of pain[5] because the definition 'does not apply to living organisms that

[2]Kuhse H. and Singer P.: 'From the editors', *Bioethics*, 10, 1996: pp. iii–iv.

[3]Giannakoulopoulos X., Sepulveda W., Kourtis P., Glover V. and Fisk N.M.: 'Fetal plasma cortisol and β-endorphin response to intrauterine needling', *Lancet*, 344, 1994: pp. 77–81; Derbyshire S.W.G.: 'Fetal stress responses', *Lancet*, 344, 1994: pp. 615; Derbyshire S.W.G. and Furedi A.: 'Fetal pain' is a misnomer', *British Medical Journal*, 313, 1996: pp. 795; Glover V. and Fisk N.: 'We don't know; better to err on the safe side from mid-gestation', *British Medical Journal*, 313, 1996: pp. 796; Szawarski Z., 'Probably no pain in the absence of "self", *British Medical Journal*, 313, 1996: pp. 796–797; Lloyd-Thomas A.R. and Fitzgerald M.: 'Reflex responses do not necessarily signify pain', *British Medical Journal*, 313, 1996: pp. 797–798.

[4]Lloyd-Thomas A.R. and Fitzgerald M., *op. cit.*, note 3.

[5]Merskey H.: 'The definition of pain', *European Journal of Psychiatry*, 6, 1991: pp. 153–159.

are incapable of self report'.[6] The debate around the editorial raised the problem of clinical practice.[7] Is it morally acceptable to introduce potentially dangerous and difficult anaesthetic or analgesic procedures in a situation where there is no definitive understanding of what it is that is being treated? While philosophers and bench scientists have the luxury of being able to rest on probabilities, medical practitioners have to work with binary absolutes, 'do I use this analgesic or not?' A thorough review of the issues surrounding fetal pain is imperative in the face of continuous advances in fetal medicine, which currently allow the placement of valves into the fetal heart and blood transfusion directly into the fetal liver. While various important attempts have been made, in this author's opinion, that review has barely begun. In order to answer the question of whether or not the fetus feels pain, the following four questions need addressing:

(1) What is pain?
(2) What is the underlying neurology of pain processing?
(3) What is the fetus?
(4) Are there good reasons for holding that fetuses feel pain?

1. WHAT IS PAIN?

To answer the question 'does the fetus feel pain?', it is necessary to first have a conception of what pain is. The definition of pain is crucial, without a definition of what pain is the conclusion as to whether or not the fetus feels pain tends towards circularity.[8] Pain becomes a behavioural response or a neurological response in the presence of a stimulus that is labeled 'painful' precisely because it elicits the said response. It is a tautology based upon subjective interpretation, rather than being a conclusion based upon empirically verifiable observation. A definition of pain, in

[6]Anand K.J.S. and Craig K.D.: 'New perspectives on the definition of pain', *Pain*, 67, 1996: pp. 3–6

[7]Anand K.J.S. and Craig K.D.: 'Reply to letters to the Editor from Merskey & Wall', *Pain*, 67, 1996: pp. 210; Derbyshire S.W.G.: 'Comment on Editorial by Anand and Craig', *Pain*, 67, 1996: 210–211.

[8]Wall P.D.: 'Why the definition of pain is crucial', in Wall P. and Melzack R., eds, *Textbook of Pain*, Churchill Livingstone, 1989, pp. 1–18; Wall P.D.: 'Definition of pain needs clarification', *British Medical Journal*, 314, 1997: pp. 1201; Derbyshire S.W.G.: 'Analgesic and anaesthetic procedures are being introduced because of shoddy sentimental argument', *British Medical Journal*, 314, 1997: pp. 1201.

itself, will not solve this problem but it will at least provide a target for the investigation.

Pain is usually defined as a sort of amalgam of cognition, sensation and affective processes, this amalgam is commonly described under the rubric of the 'biopsychosocial' model of pain.[9] Pain is no longer regarded as merely a physical sensation of noxious stimulus and disease, but is seen as a conscious experience which may be modulated by mental, emotional and sensory mechanisms and includes both sensory and emotional components. Pain has been described as a multidimensional phenomena for some time[10] and this understanding is reflected in the current IASP (International Association for the Study of Pain) definition of pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.[11]

Leventhal has proposed a model of pain processing that is unique in that it posits parallel processing of the informational and emotional aspects of the sensory experience as well as beginning an explanation of how pain evolves.[12] According to Leventhal once stimulus information passes through the spinal 'gate'[13] it is organised and elaborated with respect to three hierarchical mechanisms in the central nervous system. Affect is considered to arise independently and virtually simultaneously with the noxious sensation following the same hierarchical mechanism.

[9]Waddell G.: 'A new clinical model for the treatment of low-back pain', *Spine*, 12, 1987: pp. 632–644.

[10]Melzack R. and Casey K.L.: 'Sensory, motivational and central control determinants of pain', in Kenshalo D., ed, *The Skin Senses*, Springfield Ill: Thomas, 1968, pp. 423–443.

[11]Merskey, *op. cit.*, note 5.

[12]Leventhal H.: 'A perceptual-motor theory of emotion', *Advances in Experimental Social Psychology*, 17, 1984: pp. 117–175; Leventhal H. and Scherer K.: 'The relationship of emotion to cognition: A functional approach to a semantic controversy', *Cognition and Emotion*, 1, 1987: pp. 3–28.

[13]Melzack R. and Wall P.D.: 'Pain mechanisms: a new theory', *Science*, 150, 1965: pp. 971–979 – 'Gate control theory' is a hypothesised system for the regulation of nociceptive information within the dorsal horn of the spinal cord. The theory was a major step forward in understanding the physiological correlates of psychological interventions in pain, such as the modification of one sensation by another, and was successful in persuading investigators to relinquish ideas that were already known to be wrong but were retained for their simplicity. It shifted attention away from the peripheral nerve fibres and towards the central nervous system. The details of the theory can be found in accessible form in Melzack R. and Wall P.D., *The Challenge of Pain*, Penguin Books, 1988. As this article is mainly concerned with central mechanisms, the gate theory will not be considered in further detail.

The first two levels in the hierarchy are perceptual-motor processing followed by schematic processing. Both these levels are considered preconscious. Perceptual-motor processing involves the activation of an innate set of expressive motor reactions to environmental stimuli: schematic processing involves the automatic encoding in memory of the experience to produce a categorical structure representing the general informational, emotional and sensory aspects of pain experiences.

At a higher level still, a set of abstract rules about emotional episodes and associated voluntary responses are proposed to arise over time because of self observation and voluntary efforts to cope with emotion provoking situations. These rules are highly variable with experience. For example a long history of pain (chronic pain) appears to lead to a shift in emphasis from a belief in psychological factors influencing pain towards a more organic view of pain.[14]

The biopsychosocial model and Leventhal's elaboration teach us that pain does not, so to speak, spring forth 'from the depths of the person's mind' prior to any experience, but is gradually formed as a consequence of general conscious development. Thus pain requires the support of a sophisticated neurological and cognitive architecture.

2. WHAT IS THE UNDERLYING NEUROLOGY OF PAIN PROCESSING?

The inability to derive any subjective report from the fetus means that all comments about the psychological experience of the fetus are drawn from inference. Virtually all discussion of fetal pain draws on the developing neurobiology of the fetus as an indirect indication of fetal pain experience. If it can be shown that pain experience is always contingent upon the activity of some neurological structure (a 'pain centre'), and further shown that this structure is developed in the fetus, then an argument can be made that activity in that structure should be taken in itself as indicating fetal pain experience. Section 4, *Are there good reasons for holding that fetuses feel pain?*, will discuss the problems with this argument in relation to the psychology of pain. This section discusses the current neurological understanding of pain and shows that, 'regardless of any philosophical view on con-

[14]Edwards L.C., Pearce S.A., Turner-Stokes L. and Jones A.: 'The pain beliefs questionnaire: an investigation of beliefs in the causes and consequences of pain', *Pain*, 51, 1992: pp. 267–272.

sciousness and "pain perception",[15] the neurology of pain itself does not conform to such a straightforward interpretation.[16]

'Specificity theory' and the hypothesis of a centralised 'pain centre' dominated early research into the central mechanisms of pain.[17] A series of experiments to uncover the location of the pain centre, initially believed to be seated in the cerebral cortex, were carried out. Penfield stimulated 800 areas of somatosensory cortex but found only 11 to elicit pain.[18] Despite this finding, special effort was made to place the pain centre in the somatosensory cortex. Consequently somatosensory projection areas from phantom limb pain were excised in many patients, with no effect at all on their pain.[19] During neurosurgical operations the stimulation of many other areas of cortex generally failed to produce pain. Such infrequent reports of pain led to the belief that the pain centre was not located in the cortex[20] but was instead a thalamic function. Electrical stimulation of the somatosensory thalamus sometimes relieves

[15]The quote is taken from: Anand K.J.S. and Hickey P.R.: 'Pain and its effects in the human neonate and fetus', *New England Journal of Medicine*, 317, 1987: pp. 1321–1329.

[16]As with the definition of pain, if we want to make a judgment as to whether the fetus has the biological capacity for pain, then we must be in a position to say what the biological requirement for pain is. However, because so much of the argument that the fetus feels pain rests upon the discussion of the biological development of the fetus, this section is not entirely necessary for the flow of the argument and can be bypassed if the reader wishes. The biological story will be picked up in section 3. At this point it is sufficient to know that there is no central pain processor which can be taken as a proxy for pain experience. More skeptical readers, or those with a desire to understand the mysteries of pain neurology in more detail, should read on.

[17]The traditional theory of pain, first proposed by Descartes in 1664, is generally known as 'specificity theory'. Descartes suggested that a painful stimulus transferred energy to 'threads' running through the body which opened pores in the head and signaled pain. Thus pain was produced just as pulling at one end of a rope causes a bell, connected at the other end, to strike. Although the theory is over 300 years old it is still described in many textbooks on neurology, neurophysiology and medicine (e.g., Mountcastle, V.B. (1980) 'Pain and temperature sensibilities', in V.B. Mountcastle (Ed) *Medical Physiology*, Vol 1, C.V. Mosby Company: St. Louis, pp. 391–427) and is widely accepted by professional and lay people alike as fact rather than theory. The theory is discredited because it cannot account for the variability between injury and pain and because it has failed to produce a useful treatment as discussed in the text.

[18]Penfield W. and Bolder E.: 'Somatic motor and sensory representations in the cerebral cortex of man as studied by electrical stimulation,' *Brain*, 60, 1937: pp. 389–443.

[19]Melzack R. and Wall P.D.: *The Challenge of Pain*, Penguin Books, 1988.

[20]White J.C and Sweet W.H.: *Pain and the Neurosurgeon*, C.C. Thomas, Springfield, Illinois, 1969.

chronic pain,[21] while stimulation of the intralaminar and medial thalamic nuclei elicits intense pain during neurosurgery for chronic pain.[22] Thalamic neurons have also been destroyed in an attempt to abolish pain. This procedure may produce pain relief, but often does not,[23] and can make the pain worse.[24] Many other medical procedures have drawn on the logic of a specific pain system, destroying selected peripheral nerves or pathways in the central nervous system in an attempt to control pain. For a long time it was believed that the ventrolateral spinal cord contained the specific 'pain pathway' to the thalamus, resulting in the clinical procedure of cordotomy which severs the axons from this part of the cord. Although immediate relief of pain was common, the effects faded after a few months. Additionally, patients would often be left with the burden of incontinence as the control fibres for the bladder and rectum also run in the ventrolateral spinal cord. The failure of spinal cord lesions encouraged the surgeon to move more centrally. The spinothalamic fibres have been cut immediately prior to their entrance into the thalamus in the mid-brain. As for cordotomy, this procedure often results in the return of pain a few months later. Unlike cordotomy, this procedure was incredibly difficult, 42 percent of patients died on the operating table. Other lesions have been placed in the cingulum bundle, frontal white matter, pulvinar, amygdala, frontothalamic tracts, pituitary and hypothalamus in an attempt to produce pain relief. Lesions of these sites are sometimes effective in controlling chronic pain, but are ineffective for acute pain.[25] The basic failure of medical techniques based on specificity theory has led to the widespread abandonment of ideas based on a specific pain centre and led instead to the suggestion that there is a widespread pain system involving many different neural structures.

Based on psychological and physiological observations pain can be classified into two types: fast pain and slow pain.[26] The psychological observation is that pain can be

[21]Turnbull I.M., Shulman R. and Woodhurst W.B.: 'Thalamic stimulation for neuropathic pain', *Journal of Neurosurgery*, 52, 1980: pp. 486–493.

[22]Hassler R.: 'The division of pain conduction into systems of pain sensation and pain awareness', in *Pain*, R. Jansen (ed).

[23]Spiegal E.A. and Wycis H.T.: 'Present status of stereocephalotomies for pain relief', *Confinia Neurologica*, 27, 1966: pp. 7–17.

[24]Mauguiere F. and Desmedt J.E.: 'Thalamic pain syndrome of Dejerine–Roussy; Differentiation of four subtypes assisted by somatosensory evoked potentials data', *Archives of Neurology*, 45, 1988: pp. 1312–1320.

[25]Bouckoms A.J.: 'Psychosurgery', in *The Textbook of Pain*, Wall P.D. and Melzack R., eds, Churchill Livingstone, 1989, pp. 666–676.

separated into two broad categories: acute pain and chronic pain, each with a characteristic pattern of description.[27] The physiological observation is the transmission of nociceptive signals to the brain by multiple ascending pathways, each with distinctive conduction velocities and terminations in the brain.[28] Two major systems can be distinguished: the phylogenetically old pathways that course medially through the brainstem, and the newer pathways that maintain a lateral course in the brainstem.

The medial pathways ascend in the ventrolateral spinal cord, which have multiple synaptic connections along their route, and terminate widely in the brain stem, including the reticular formation and the periaqueductal grey matter, before projecting to the amygdala and other limbic structures. Most fibres of the medial system pass all the way to the medial and intralaminar nuclei of the thalamus. The major projections of the medial thalamus include the prefrontal cortex, anterior cingulate cortex and the basal ganglia. The medial system is polysynaptic, transmitting impulses to the brain slowly, and exhibits only gross somatotopic organisation meaning it is very poor at localisation.[29]

The pathways that make up the lateral system pass upward to the brain through the anterolateral white matter with no synaptic connections on the way ('monosynaptic').[30] The lateral system terminates predominantly in the ventrobasal complex of the thalamus with a major projection to the somatosensory cortex. In contrast to the medial system, the lateral system consists of rapidly conducting pathways that are somatotopically highly organised.

The categorisation of the fast Aδ and the slow C fibres complements this central dissociation of the medial and lateral systems.[31] The Aδ fibres are believed to be concerned with the

[26]Guyton A.C.: *Basic Neuroscience: Anatomy and Physiology*. W.B. Saunders Company, 1991.

[27]Melzack R. 'The McGill pain questionnaire: major properties and scoring methods', *Pain*, 1, 1975: pp. 277–299.

[28]Kerr D.I.B., Haugen F.P. and Melzack R.: 'Responses evoked in the brain stem by tooth stimulation.' *American Journal of Physiology*, 183, 1955: pp. 253–258; Bowsher D. and Albe–Fassard D.: 'The anatmophysiological basis of somatosensory discrimination', *International Review of Neurobiology*, 8, 1965: pp. 35–75.

[29]Soper W.Y. and Melzack R.: 'Stimulation-produced analgesia: evidence for somatotopic organization in the midbrain', *Brain Research*, 51, 1982: pp. 307–311.

[30]Apkarian A.V. and Hodge C.J.: 'Primate spinothalamic pathways: 1. A quantitative study of the cells of origin of the spinothalamic pathway', *Journal of Comparative Neurology*, 288, 1989, pp. 447–473.

rapid transmission of phasic discriminative information regarding the onset, location, intensity and duration of a stimulus bringing about responses preventing further damage. Hence the association with fast or acute pain. Whereas the C fibres are believed to signal actual peripheral damage by transmitting tonic information about the state of the organism determining the arousal and behavioural responses necessary to foster rest, thereby promoting recovery. Hence the association with slow or chronic pain. The well-documented involvement of the spinothalamic tract in the transmission of pain and the dissociation of the transmission systems suggests that the involvement of the cerebral cortex in pain processing should be well understood. All pain should result in thalamic activation with additional somatosensory cortex activation with acute, transient pains, and anterior cingulate cortex and prefrontal cortex with longer lasting, chronic pains.[32] Figure 1 describes this distinction. In reality even this expanded framework for understanding pain neurology is controversial and there is surprisingly little consensus regarding the involvement of the cerebral cortex in pain processing.[33]

Recent advances in brain imaging techniques mean that it is now possible to investigate the brain systems regulating pain information in a direct, dynamic and non-invasive manner. These techniques all rely on measurement of regional cerebral blood flow (rCBF) in the brain, because rCBF is the major carrier of energy for neural activities, rCBF reflects activation of large neural networks. Several monographs describe the theoretical and technical background of rCBF measurement.[34] In summary, rCBF is measured by recording the distribution of cerebral

[31]The Aδ fibres are partially myelinated which means that they have a higher conduction rate than the non–myelinated C fibres.

[32]Albe-Fassard D., Berkley K.J., Kruger L., Ralston H.J. and Willis, W.D.: 'Diencephalic mechanisms of pain sensation', *Brain Research Review*, 9, 1985: pp. 217–296.

[33]Stea R.A. and Apkarian A.V.: 'Pain and somatosensory activation', *Trends in Neuroscience*, 15, 1992: pp. 250–251; Roland P.E.: 'Cortical representation of pain', *Trends in Neuroscience*, 15, 1992: pp. 3–5; Evans A.C., Meyer E. and Marret S.: 'Pain and activation in the thalamus', *Trends in Neuroscience*, 15, 1992: pp. 252; Roland P.E.: 'Reply', *Trends in Neuroscience*, 15, 1992: pp. 252–253; Jones A.K.P.: 'Do pain centres' exist?', *British Journal of Rheumatology*, 31, 1992: pp. 290–292.

[34]Deshmukh V.D. and Meyer J.S.: *Noninvasive measurement of regional cerebral blood flow in man*, Spectrum, NY, 1978: pp. 177–182; Woods J.H.: *Cerebral blood flow: Physiologic and clinical aspects*, McGraw, NY, 1987; Resicgno A. and Boicelli A.: *A Cerebral blood flow: Mathematic models, instrumentation and imaging techniques.* Plenum, NY, 1988; Knezevich S.: *Handbook of regional cerebral blood flow.* Erlbaum, Hillsdale, NJ, 1988.

radioactivity following infusion of the freely diffusible positron emitting ^{15}O-labeled tracer, $H_2{}^{15}O$. The physical basis of PET is the localisation of the position of positron annihilation. Positrons are sub-atomic particles emitted from the radioactively decaying nuclei of tracer substances, and have the same mass as electrons but are of opposite charge. A positron will lose its kinetic energy after traveling less than 2–3mm in tissue. During or after this movement the positron will encounter a negatively charged free electron. The result of this encounter is the annihilation of both particles and the emission of electromagnetic radiation. Coincidence detection of the two simultaneously released gamma rays (each of 511 keV energy), which travel in

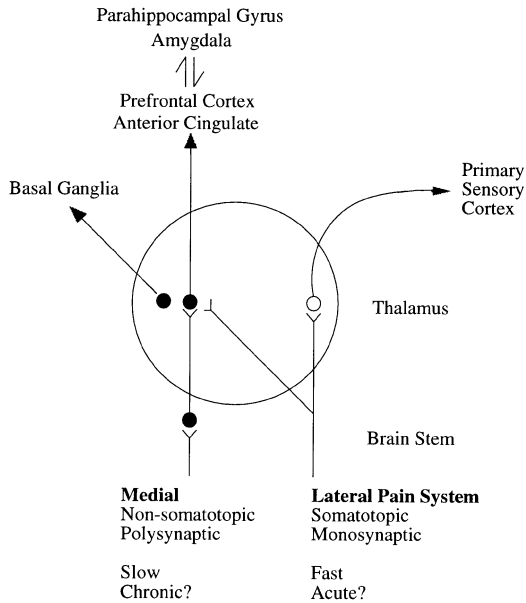

Figure 1. *A schematic representation of the medial and lateral pain system. The medial system is a slow system with poor ability to localise. The projections of the medial system are to areas associated with emotional and cognitive processes. In contrast the lateral system is a very fast system with somatotopic organisation at each level meaning it is well organised for localising incoming stimulation. The lateral system projects predominantly to the somatosensory cortex. Classically, the medial system was believed to be responsible for processes associated with chronic pain whereas the lateral system is associated with acute pain. Such presumptions are discussed in the text as incorrect.*

approximately opposite directions (180°±0.5°), enables localisation of the radioactive source.

On either side of the subject are detectors connected in a coincidence circuit to register photons in coincidence within a time window (12–25 ns). The intersection between lines connecting detector pairs defines the location of a source inside the subject.

Collection of about $\frac{1}{2}$–1 million coincident events, by a circumferential array of multiple paired detectors (100–4000) placed in one or more (7–17) rings, will allow the reconstruction of an image of a heterogeneously-distributed, positron emitting nuclide within the detector array. Using a standard computerised reconstruction algorithm, it is possible to map the spatial and temporal distribution of the nuclide, and tomographic images in one or more planes can be reconstructed in a manner similar to that used for computerised tomography (CT) and magnetic resonance imaging (MRI).[35] An image is produced to represent the radiotracer distribution. In principle, the pixel values in the image should be directly proportional to the radioisotope concentration inside the subject.

rCBF studies of brain processes during painful experience have provided diffuse results similar to the findings with neurosurgery. In response to acute and chronic noxious experience changes in rCBF have been demonstrated in: (i) the anterior cingulate cortex, present in all recently published experiments where assessed; (ii) the insula cortex, present in 75%; (iii) the thalamus (50%); (iv) the prefrontal cortex (47%); (v) the primary somatosensory cortex (47%); (vi) the lentiform nucleus (42%) and; (vii) the secondary somatosensory cortex (31%). More occasional findings have also been reported in the inferior parietal cortex, brain stem and amygdala.[36] Further division of the cortical areas is possible (and is discussed in detail

[35]Brooks R.A.: 'Principles of CAT in radiographic and radioisotopic imaging', *Physics in Medicine and Biology*, 24, 1976: pp. 689.

[36]Casey K.L., Minoshima S., Berger K.L., Koeppe R.A., Morrow T.J. and Frey K.A.: 'Positron Emission Tomographic Analysis of Cerebral Structures Activated Specifically by Repetitive Noxious Heat Stimuli', *Journal of Neurophysiology*, 71, 1994: pp. 802–807; Coghill R.C., Talbot J.D., Evans A.C., Meyer E., Gjedde A,. Bushnell M.C. and Duncan G.H.: 'Distributed processing of pain and vibration by the human brain' *Journal of Neuroscience*, 14, 1994: pp. 4095–4108; Derbyshire S.W.G., Jones A.K.P., Devani P., Friston K.J., Feinmann C., Harris M., Pearce S., Watson J.D.G. and Frackowiak R.S.J.: 'Cerebral responses to pain in patients with atypical facial pain measured by Positron Emission Tomography', *Journal of Neurology Neurosurgery and Psychiatry*, 57, 1994: pp. 1166–1173; Di Piero V., Jones A.K.P., Iannotti F., Powell M., Perani D., Lenzi G.L. and Frackowiak R.S.J.:

for anterior cingulate below) increasing the central variability in response to pain. The basis for the variability in the results between groups is far from understood, however it is becoming clear that the projections of the medial pain system, especially to the anterior cingulate cortex, are more consistently activated during any pain experience than is the lateral projection to the somatosensory cortex. Based on this observation it has been suggested that the anterior cingulate cortex could be responsible for the cortical representation of the aversive aspects of pain.[37] Observations of chronic pain patients following a neurosurgical procedure to cut the white matter tract underlying the anterior cingulate cortex ('cingulotomy') support this view. Although such patients remain aware of their pain and are still able to

'Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy', *Pain*, 46, 1991: pp. 9–12; Di Piero V., Ferracuti S., Sabatini U. Pantano P., Cruccu G. and Lenzi G.L.: 'A cerebral blood flow study on tonic pain activation in man', *Pain*, 56, 1994: pp. 167–173; Hsieh J.C., Stahl–Backdahl M., Hagermark O., Stone-Elander S., Rosenquist G. and Ingvar M. 'Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study', *Pain*, 64, 1995: pp. 303–314; Hsieh J.C., Belfrage M., Stone-Elander S., Hansson P. and Ingvar M.: 'Central representation of chronic ongoing neuropathic pain studied by positron emission tomography', *Pain*, 63, 1995: pp. 225–236; Iadarola M.J., Max M.B., Berman K.F., Byas-Smith M.G., Coghill R.C., Gracely R.H. and Bennett G.J.: 'Unilateral decreases in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain', *Pain*, 63, 1995: pp. 55–64; Jones A.P.K., Brown W.D., Friston K.J., Qi L.Y. and Frackowiak R.S.J.: 'Cortical and subcortical localization of response to pain in man using Positron Emission Tomography', *Proceedings of the Royal Society (London)*, 244, 1991: pp. 39–44; Jones A.K.P. and Derbyshire S.W.G.: 'Cerebral mechanisms operating in the presence and absence of inflammatory pain', *Annals of the Rheumatic Diseases*, 55, 1996: pp. 411–420; Rosen S.D., Paulesu E., Frith C.D., Frackowiak R.S.J., Davies G.J., Jones T. and Camici P.G.: 'Central nervous pathways mediating angina pectoris', *Lancet*, 344, 1994: pp. 147–150; Talbot J.D., Marret S., Evans A.C., Meyer E., Bushnell M.C. and Duncan G.H.: 'Multiple representations of pain in human cerebral cortex', *Science*, 251, 1991: pp. 1355–1358; Vogt B.A., Derbyshire S.W.G. and Jones A.K.P.: 'Pain processing in four regions of human cingulate cortex localized with coregistered PET and MR imaging', *European Journal of Neuroscience*, 8, 1996: pp. 1461–1473; Weiller C., May A., Limmroth V., Juptner M., Kaube H., Schayck R.V., Coenen H.H. and Diener H.C.: 'Brain stem activation in spontaneous human migraine attacks', *Nature Medicine*, 7, 1995: pp. 658–660; Craig A.D., Reiman E.M., Evans A. and Bushnell M.C.: 'Functional imaging of an illusion of pain', *Nature*, 384, 1996: pp. 258–260; Rainville P., Duncan G.H., Price D.D., Carrier B. and Bushnell M.C.: 'Pain affect encoded in human anterior cingulate but not somatosensory cortex', *Science*, 277, 1997: pp. 968–971; Di Piero V., Fiacco F., Tombari D. and Pantano P.: 'Tonic pain: a SPET study in normal subjects and cluster headache patients', *Pain*, 70, 1997: pp. 185–191.

[37]See the references from Jones, Derbyshire and Vogt, *op. cit.*, note 36.

discriminate noxious stimuli their pain no longer bothers them.[38] Furthermore, lesions of the anterior cingulate cortex of rabbits have been shown to undermine the negative reinforcing quality of a painful stimulus.[39] These behavioural changes which result from cingulate cortex ablation may be interpreted as demonstrating the role of cingulate cortex in producing affective responses to noxious stimuli. However the anterior cingulate cortex is a functionally very heterogeneous region that can be activated by word association, the detection of visual targets and other cognitive tasks.[40] Posner and Rothbart have suggested that the anterior cingulate cortex is the fundamental structure for 'attention'.[41] As virtually all rCBF measurement tasks require attentional resources this interpretation may explain the wide functional heterogeneity of anterior cingulate cortex. It may also explain why pain loses its bothersome quality following cingulotomy. Presumably the patients are now able to ignore their pain as a side effect of their inability to focus attention. This view, however, has recently been demonstrated to be at least simplistic.[42] A full account of cingulate responses to noxious stimulation must incorporate the variability in its structure and connections.

[38]Gybels J.M. and Sweet W.H.: *Neurosurgical Treatment of Persistent Pain*, Karger, Basel, 1989; Santo J.L., Arias L.M., Barolat G., Schwartzman R.J. and Grossman K.: 'Bilateral cingulotomy in the treatment of reflex sympathetic dystrophy', *Pain*, 41, 1990: pp. 55–59.

[39]Gabriel M., Vogt B.A., Kubota Y., Poremba A. and Kang E.: 'Training stage related neuronal plasticity in limbic thalamus and cingulate cortex during learning: a possible key to mnemonic retrieval', *Behavioural and Brain Research*, 46, 1991: pp. 175–185.

[40]Petersen S.E., Fox P.T., Posner M.I., Mintun M. and Raichle M.E.: 'Positron emission tomographic studies of the cortical anatomy of single-word processing', *Nature*, 331, 1988: pp. 585–589; Corbetta M., Meizin F.M., Dobmeyer S., Shulman G.L. and Petersen S.E. 'Selective and divided attention during visual discriminations of shape, color, and speed: Functional anatomy by positron emission tomography', *Journal of Neuroscience*, 11, 1990: pp. 2383–2402; Pardo J.V., Pardo P.J., Janer K.W. and Raichle M.E. 'The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm', *Neurobiology*, 87, 1990: pp. 256–259; Bench C.J., Frith C.D., Grasby P.M., Friston K.J., Paulesu E., Frackowiak R.S.J. and Dolan R.J.: 'Patterns of cerebral activation during the Stroop colour word interference task: A positron emission tomography study', *Neuropsychologica*, 31, 1992: pp. 907–922.

[41]Posner M.I. and Rothbart M.K.: 'Attentional mechanisms and conscious experience', in *The Neuropsychology of Consciousness*, D. Milner & M. Rugg (Eds), Academic press, 1991.

[42]Derbyshire S.W.G., Vogt B.A. and Jones A.K.P.: 'Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex', *Experimental Brain Research*, 118, 1998: pp. 52–60.

Vogt defines the midcingulate region as the ventral division of the anterior cingulate cortex, denoted area 24′.[43] The division of the anterior cingulate cortex into midcingulate and rostral cingulate (the more anterior portion of cingulate cortex – also called perigenual cingulate) is motivated by the different cytoarchitecture and connections of these regions. These differences are described in detail elsewhere.[44] In summary, there is a transition region at the border between the agranular rostral cingulate and the granular midcingulate. From a connection point of view, rostral area 24 in the rat receives most mediodorsal thalamic and amygdala afferents.[45] Area 24′ has major and reciprocal connections with cingulate premotor areas, the pontine nuclei and area 46 of the prefrontal cortex.[46] Also, neurons in midcingulate show a plasticity that allows discrimination between positive and negative conditioning tone stimuli.[47] Thus the midcingulate region is liable to be involved in executive functions such as response selection during divided attention tasks.[48] Processes associated with affect, by contrast, are liable to involve the perigenual cingulate region. Electrical stimulation in the perigenual region can evoke fear and other emotional responses and perigenual cingulate has been

[43]Vogt B.A.: 'Structural organization of cingulate cortex: Areas, neurons, and somatodendritic transmitter receptors', in Vogt B.A. and Gabriel M., eds, *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Treatise*, Birkhauser, Boston 1993: pp. 19–70.

[44]Vogt B.A., Finch D.M. and Olson C.R.: 'Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions'. *Cerebral Cortex*, 2, 1992: pp. 435–443; Vogt 1993, *op. cit.*, note 43; Devinsky O., Morrel M.J. and Vogt B.A.: 'Contributions of anterior cingulate cortex to behaviour', *Brain*, 118, 1995: pp. 279–306.

[45]Krettek J.E. and Price J.L.: 'The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat', *Journal of Comparative Neurology*, 84, 1977: pp. 157–192; Sripanidkulchai K., Sripanidkulchai B. and Wyass J.M.: 'The cortical projections of the basolateral amygdaloid nucleus in the rat: A retrograde fluorescent dye study', *Journal of Comparative Neurology*, 229, 1984: pp. 419–431.

[46]Vogt, *op. cit.*, note 44.

[47]Gabriel M.: 'Functions of anterior and posterior cingulate cortex during avoidance learning in rabbits,' in *Progress in Brain Research*, H. Uylings, C. Van Eden, J. De Bruin, M. Corner and M. Feenstra, eds, NY: Academic press, 85, 1990: pp. 467–483; Gabriel M. Foster K. and Orona E.: 'Interaction of laminae of the cingulate cortex with the anteroventral thalamus during behavioural learning', *Science*, 208, 1980: pp. 1050–1052; Gabriel M., Foster K., Orona E., Saltwick S.E. and Stanton M.: 'Neuronal activity of cingulate cortex, anteroventral thalamus, and hippocampal formation in discriminative conditioning', *Progress in Psychobiology and Physiological Psychology*, 9, 1980: pp. 125–231.

[48]Pardo *et al.*, Bench *et al.*, Corbetta *et al.*, *op. cit.*, note 40.

reported with PET when subjects recalled sad events during the scan.[49] Thus, cingulate cortex as a whole has the necessary properties to be a key area in attention, discrimination, avoidance and affect.

The functional heterogeneity of anterior cingulate cortex and the plasticity of its neuronal structure is in contrast to the relative functional specificity of somatosensory cortex and its highly somatotopic structure. The information about noxious stimuli that travels via the spinothalamic tract to excite the lateral group of thalamic nuclei interconnected with somatosensory cortex, undergoes few alterations between the spinal cord and cortex.[50] Excitatory responses in monkey somatosensory cortex are generally restricted to both innocuous and noxious mechanical and thermal stimuli. Somatosensory neurons have receptive fields that are small or at least confined to one limb and always contralateral.[51] Such a system is ideal for providing detailed information about the location and characteristics of particular noxious stimuli but is not well suited for processes associated with affective and cognitive responses to noxious stimuli.

In summary, the conscious appreciation of pain cannot be explained as the consequence of an active 'pain centre'. Instead a 'neuromatrix'[52] of regions, incorporating structures such as the anterior cingulate cortex which shows a plasticity with learning and development, is proposed as necessary for the experience of pain. Parallel interacting areas, many of which are in a dynamic relationship with experience, each of which add a component to the experience of pain but none of which define it in its entirety make it impossible to infer pain on the basis of any single active 'centre'.

[49]Bancaud J. and Talairach J.: 'Clinical semiology of frontal lobe seizures', in Chauvel, P., Delgado-Escueta, A.V., Halgren, E. and Bancaud, J. (eds), *Frontal Lobe Seizures and Epilepsies*. Raven Press, New York, 1992: pp. 3–58; George M.S., Ketter T.A., Parekh P.I., Horowitz B., Herscovitch P. and Post R.M.: 'Brain activity during transient sadness and happiness in healthy women', *American Journal of Psychiatry*, 152, 1995: pp. 341–351.

[50]Vogt B.A., Sikes R.W. and Vogt L.J.: 'Anterior cingulate cortex and the medial pain system', in Vogt B.A. and Gabriel M., eds, *Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Treatise*, Birkhauser, Boston 1993: pp. 330–360.

[51]Kenshalo D.R. and Isensee O.: 'Responses of primate S1 cortical neurons to noxious stimuli', *Journal of Neurophysiology*, 50, 1983: pp. 1479–1496.

[52]Melzack R.: 'Phantom limbs, the self and the brain: The D.O. Hebb memorial lecture', *Canadian Psychology*, 30, 1989: pp. 1–16.

3. WHAT IS THE FETUS?

While the definition of pain has received little attention within the fetal pain literature, the corresponding discussion of what the fetus is has received abundant discussion and has dominated the suggestion that the fetus may be able to feel pain. There is a considerable amount of research examining development of the pathways thought to be fundamentally involved in the processing of pain,[53] examining the development of behavioural responses to noxious stimulation[54] and examining other aspects of fetal neuronal and hormonal responses to stimulation.[55]

From the studies that have been carried out it is now known that the innervation of the skin by the free nerve endings responsible for initial registration of noxious stimulation and which eventually give rise to the C fibre projection system, begins in fetal life.[56] Studies with rats suggest that the C-fibre cells should mature in their firing frequencies and response patterns

[53]Fitzgerald M.: 'Spontaneous and evoked activity of foetal primary afferents in vivo', *Nature*, 326, 1987: pp. 603–605; Fitzgerald M.: 'The prenatal growth of fine diameter afferents into the rat spinal cord – a transganglionic study', *Journal of Comparative Neurology*, 261, 1987: pp. 98–104; Fitzgerald M.: 'Neurobiology of fetal and neonatal pain', in Wall P. and Melzack R., eds, *The Textbook of Pain*, Churchill Livingstone, 1994, pp. 153–163; Mrzljak L., Uylings H.B.M., Kostovic I. and van Eden C.G.: 'Prenatal development of neurons in prefrontal cortex: a qualitative Golgi study', *Journal of Comparative Neurology*, 271, 1988: pp. 355–386; Chugani H.T. and Phelps M.E.: 'Maturational changes in cerebral function in infants determined by 18FDG positron emission tomography', *Science*, 231, 1986: pp. 840–843.

[54]Craig K.D., Whitfield M.F., Grunau R.V.E., Linton J. and Hadjistavropoulos H.D.: 'Pain in the preterm neonate: behavioural and physiological indices', *Pain*, 52, 1993: pp. 287–299; Fitzgerald M., Millard M. and McIntosh N.: 'Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia', *Pain*, 39, 1989: pp. 31–36; Stevens B.J., Johnston C.C. and Horton L.: 'Factors that influence the behavioural pain responses of premature infants', *Pain*, 59, 1994: pp. 101–109; Johnston C.C., Stevens B., Craig K.D. and Grunau R.V.E.: 'Developmental changes in pain expression in premature, full term, two- and four-month-old infants', *Pain*, 52, 1993: 201–208.

[55]Giannakoulopoulos X, *et al*, *op. cit.*, note 3; Teixeira J., Fogliani R., Giannakoulopoulos X., Glover V. and Fisk N.: 'Fetal haemodynamic stress response to invasive procedures', *Lancet*, 347, 1996: pp. 624; Hughes J.R., Fino J. and Gagnon L.: 'Periods of activity and quiescence in the premature EEG', Neuropediatrics, 14, 1983: pp. 66–72; Torres F. and Anderson C.: 'The normal EEG of the human newborn', *Journal of Clinical Neurophysiology*, 2, 1985: pp. 89–103.

[56]Fitzgerald M., *op. cit.*, note 53; Fitzgerald M.: 'Development of pain mechanisms', *British Medical Bulletin*, 47, 1991: 667–675.

in the human fetus by 24–28 weeks gestation, the A-fibre cutaneous receptors, although active, mature later.[57] The rate at which the afferent terminals – i.e., the spinal cord terminations projected from the periphery – mature in the spinal cord is not known. There are, however, two known phases of intense neuronal development in the human cord at 9–10 weeks and again at 17–21 weeks. By 25 weeks the neurons of the first layer of the spinal cord, laminae I, are mature and there is clear evidence of nociceptive afferent input.[58] By 30 weeks the main features of the adult spinal cord are present. There is, however, considerable interneuronal development yet to occur which will not be complete until after birth.

From 26–29 weeks gestation the fetal cortex has six recognisable layers similar to that seen in the adult cortex.[59] However, the fetal cortex still displays immature characteristics including a densely packed layer II and migrating or immature neurons. From 26–34 weeks there is penetration of the thalamo-cortical fibres into the cortical plate completing the connection from periphery to cortex.

Thus at around 30 weeks gestation, the fetus has a complete neurological connection from the peripheral tissue through the brain stem and the thalamus to the cerebral cortex of the brain.

Behavioural responses to stimulation reflect the changing maturity of the fetal nervous system. At 7.5 weeks gestation reflex responses to somatic stimuli begin. At this point touching the peri-oral region results in a contralateral bending of the head. The palms of the hands become sensitive to stroking at 10.5 weeks and the rest of the body and hindlimbs become sensitive at approximately 13.5 weeks. Although these responses may look purposive, they are in fact spinal reflex responses not dependent on central activity.

Shortly after the development of sensitivity, repeated skin stimulation results in hyperexcitability and a generalised movement of all limbs. This hyperexcitability also indicates the

[57]Fitzgerald M.: 'Cutaneous primary afferent properties in the hindlimb of the neonatal rat', *Journal of Physiology*, 383, 1987: pp. 79–92.

[58]Andrews K.A. and Fitzgerald M.: 'The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation', *Pain*, 56, 1994: 95–101.

[59]Mrzljak L. *et al.*, *op. cit.*, note 46. This data is derived from studies using Golgi staining techniques to examine neuronal development and connectivity with material obtained from 12 fetuses of 10–34 weeks gestation and from two full-term newborn babies. The material originated from legal or spontaneous abortions or from perinatal cases of respiratory distress syndrome in premature infants. The full-term newborn babies died of sarcoma and pneumonia.

immature nature of the spinal cord sensory neurons, which still have large receptive fields, and the lack of descending inhibitory control over behaviour.[60] After 26 weeks this generalised movement gradually gives way to more defined actions that indicate improved organisation within the nervous system. Infants delivered at 26–31 weeks, for example, show coordinated facial actions in response to heel prick that are not present in younger infants.[61] The anatomical changes also correlate well with changes in cortical activity as measured by EEG.

Burgess and Tawia describe EEG.[62] By placing electrodes onto the scalp of the subject the electrical activity generated by neuronal firing can be indirectly recorded. Although there are problems in accounting for attenuation through the scalp, and through brain tissue if the signal originates deep in the brain, and artifacts generated by eye and scalp movement, EEG is well recognised as measuring something associated with brain function. EEG studies have demonstrated that the distinct electrical discharges associated with the arrival of sensory impulses at a cortical level are detectable after 29 weeks gestation.[63] In general EEG studies have demonstrated that the pattern of EEG activity in response to somatic stimulation, and the patterns of quiescent activity, come to resemble those of a mature adult after about 29 weeks gestation.[64] Figure 2 shows the EEG pattern observed in response to a somatic stimulus at 25 and 29 weeks gestation, birth and adulthood, adapted from Hrbek et al (1973), Klimach and Cooke (1988) and Chen et al (1999).[65] Although it is true that the early negative evoked potential begins to develop from 25 weeks, the differences between the pattern of the adult evoked response and the developing fetus and newborn are striking. There are also other

[60]Lloyd-Thomas A.R. and Fitzgerald M, *op. cit.*, note 3.

[61]Craig K. *et al.*, *op. cit.*, note 54.

[62]Burgess and Tawia, *op. cit*, note 1.

[63]Klimach V.J. and Cooke R.W.I.: 'Maturation of the neonatal somatosensory evoked responses in preterm infants', *Developmental Medicine and Child Neurology*, 30, 1988: pp. 208–214.

[64]Spehlman R.: 'The normal EEG from premature age to the age of 19 years', in *EEG Primer*, Amsterdam: Elsevier/North Holland-Biomedical Press, 1981; Hrbek A., Karlberg P. and Olsson T.: 'Development of visual and somatosensory evoked responses in pre–term and newborn infants', *Electroencephalography and Clinical Neurophysiology*, 34, 1973: pp. 225–232; Hughes *et al*; Torres and Anderson, *op. cit*, note 55; Klimach and Cooke, *op. cit.*, note 63.

[65]Hrbek *et al*, *op. cit.*, note 64; Klimach and Cooke, *op. cit.*, note 63; Chen A.C.N., Derbyshire S.W.G., Dickens C.M., Bentley D.E., Clark S., Jayson M.I.V., Campbell F. and Jones A.K.P.: 'Spatiotemporal dynamic brain mapping of laser–evoked potentials during normal pain processing', under review, 1999.

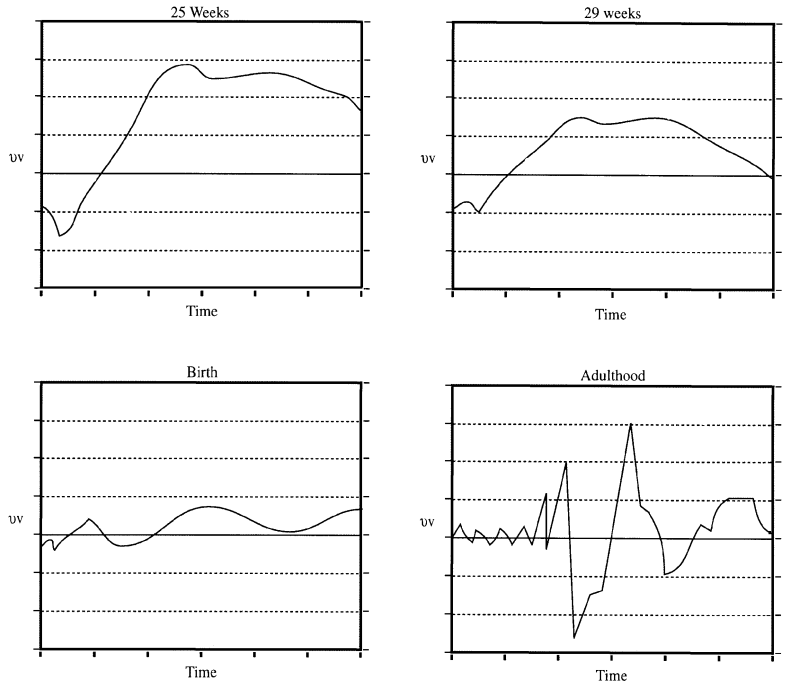

Figure 2. *EEG responses recorded in response to stimulation at 25 weeks and 29 weeks gestation, birth and adulthood. Along the abscissa is time with uv shown on the ordinate, the actual time points and voltages are displayed arbitrarily to indicate the variable pattern formations only.*

important differences in the EEG responses of the fetus compared to the newborn. Periods of quiescent EEG activity occur in all infants up to 32 weeks conceptional age, the incidence drops to 50% at 36 weeks and to 8% at full term.[66] Between about 6 and 8 weeks of age, daytime sleep patterns in full-term babies go through various important changes, among these is the disappearance of the tracé alternant (TA) EEG pattern, change of REM sleep onset to quiet sleep onset and the appearance of clearly defined EEG sleep spindles.[67]

The demonstration that actual neuronal activity in the neonate undergoes considerable maturation during the first year of life mirrors the differences in EEG activity evident in the fetus and newborn. Chugani and Phelps examined the neuronal activity of neonates from birth to 18 months using

[66]Torres and Anderson, *op. cit*, note 55.
[67]Hughes *et al*, *op. cit*, note 55.

PET in conjunction with radio-labeled fluorodeoxyglucose (^{18}FDG).[68] Unlike $H_2{}^{15}O$, ^{18}FDG is actively metabolised during synaptic activity allowing the recorded radioactive measures to be used as a direct indication of neuronal activation. Using this method Chugani and Phelps demonstrated that the neuronal function of the cerebral cortex, especially the somatosensory cortex, the prefrontal cortex and the anterior cingulate cortex, increased by a third from birth to 18 months.

Further evidence suggesting a similarity between a mature response to pain and that of the fetus comes from a study of the hormonal and neurochemical response of the fetus to noxious stimulation. Giannakoulopoulos *et al* reported that blood sampling at 20–34 weeks gestation via the intrahepatic vein, which is innervated with free nerve endings, produced an increased cortisol and β-endorphin response compared with the usual technique of taking blood from the placenta which is not innervated.[69] This is typical of a response to a noxious stimulus that might be expected of someone complaining of pain. Cortisol release is known to prevent inflammation of a wound while β-endorphin acts to suppress the flow of noxious information and dampens pain experience. Moreover, the response is indicative of a developed central mechanism (the hypothalamic-pituitary adrenal axis) for hormonal regulation. However it should be noted that the increases in cortisol and β-endorphin responses recorded were much smaller than those usually seen in adult populations.[70] Furthermore, high cortisol concentrations in adults following surgery can be associated with *lower* pain

[68]Chugani and Phelps, *op. cit*, note 53.

[69]Giannakoulopoulos *et al*, *op. cit.*, note 3.

[70]This under-reported fact bears upon the suggestion that the cortisol response indicates a developed hypothalamic-pituitary adrenal axis. Cortisol is released from the adrenal cortex under the regulation of adrenocorticotropic hormone (ACTH) which is in turn regulated by corticotrophin-releasing factor (CRF). CRF is released from the hypothalamus according to the balance of instructions sent from the amygdala and hippocampus. The amygdala induces CRF production while the hippocampus inhibits CRF production. Very little is known about the development of these neuronal structures, however it is known that the amygdala develops before the hippocampus (Rudy J.W. and Morledge P.: 'Ontogeny of contextual fear conditioning in rats: Implications for consolidation, infantile amnesia, and hippocampal system functioning', *Behavioural Neuroscience*, 108, 1994: pp. 227–234), thus it should be expected that there would be greater cortisol release under the differential influence of the amygdala, rather than less. Alternatively, the hypothalamic–pituitary adrenal axis is less well developed than implied.

ratings.[71] In summary it can be said with confidence that at 30 weeks gestation the human fetus has a well-developed system for the projection of noxious information from the periphery (the skin) to the central nervous system. It is known that activation of this system results in coordinated behavioural responses, regulated neuronal discharge and up-regulation of the endogenous anti-inflammatory agent cortisol and the endogenous pain analgesic β-endorphin. However, while there are similarities between the fetal nervous system and the adult, it is important to remember that the real explosion of events in the cortex occurs postnatally between the third and sixth months of life.[72] The basic connections may develop early on in the fetus, but the subsequent neuronal development needed to create a sophisticated nervous system comes much later.[73]

4. ARE THERE GOOD REASONS FOR HOLDING THAT FETUSES FEEL PAIN?

The sophisticated development of the fetal biology outlined above, combined with the observations of fetal behaviour in response to invasive practice and the recorded improvement in neonatal survival following the use of analgesics during surgery, has led many commentators to suggest that the fetus and neonate may feel pain.[74] Too often, however, this suggestion relies on assertion rather than argument with neurological and behavioural measures suggested as a proxy for psychological experience.[75] The strong

[71]Salmon P.: 'Anxiety and stress in surgical patients', *British Journal of Hospital Medicine*, 48, 1992: pp. 531–532.

[72]Ottoson D.: *Physiology of the Nervous System*, Macmillan: London, 1983.

[73]I am grateful to Professor Maria Fitzgerald for this insight.

[74]Giannakoulopoulos *et al*; Glover and Fisk, *op. cit.*, note 3; Teixeira *et al*, *op. cit.*, note 55; Anand K.J.S., Sippel W.G. and Aynsley-Green A.: 'Randomised trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response', *Lancet*, 1, 1987: pp. 243–248; Rogers M.C.: 'Do the right thing: Pain relief in infants and children', *New England Journal of Medicine*, 326 1992: pp. 55–56; Anand and Hickey, *op. cit.*, note 15.

[75]For example, Francis Crick has the following to say about experience: 'The Astonishing Hypothesis is that "You," your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules'. Crick F.: *The Astonishing Hypothesis: The Scientific Search for the Soul*, Simon & Schuster, 1994: pp. 3. The inadequacy of this position is easily recognisable once one tries to explain *how* it is that a system of neurons and chemicals can bring about conscious awareness. This is discussed here in section 4, good general discussions of this problem can be found in: Penrose R.:

argument is that psychological experience is a higher order consequence of neural biology. The implication is that once an experience is correlated with a specific neurological activity or neurochemical response then that experience can be directly inferred from the neurology without resort to the less exact techniques of subjective report. Unfortunately, although all of these phenomena are associated with the notion of 'pain', none of them adequately describe or explain the phenomenological experience of 'pain'. These phenomena may exist independently of conscious experience. The relationship between the physiological responses of nociceptors, the hormonal and other responses of the CNS and the behavioural outcome of these changes to the psychological response has yet to be determined.[76]

Is it logical to suggest that the fetal responses to stimulation post 26 weeks gestation represent conscious appreciation as opposed to complex *reflex* responses, similar in quality to the responses prior to 26 weeks? Despite the importance of providing evidence for the conscious appreciation of pain, the fetal and neonatal literature largely tries to ignore this issue. Anand, for example, highlighted the clinical findings with neonates as being of greater importance than 'any philosophical view on consciousness and "pain perception".[77] Giannakoulopoulos *et al* distanced themselves from any implied fetal pain experience with the statement 'a hormonal response cannot be equated with the perception of pain'.[78] In a report for the British Department of Health (Foetal pain: an update of current scientific knowledge. A paper for the Department of Health, May 1995) Fitzgerald even went so far as to say that 'true pain experience [develops] postnatally along with memory, anxiety and other cognitive brain functions' leaving confusion as to what the 'untrue' pain experience of a fetus may be.[79]

Such equivocation is perhaps not surprising in view of the general failure of material interpretations, i.e., interpretations

The Emperor's New Mind Concerning Computers, Minds, and the Laws of Physics, Vintage, 1989; Penrose R.: *Shadows of the Mind*, Vintage, 1994; Chalmers D.J.: 'Facing up to the problem of consciousness', *Journal of Consciousness Studies*, 2, 1995: 200–219; Chalmers D.J.: *The Conscious Mind*, New York: Oxford, 1996.

[76]Wall P.D. and McMahon S.B.: 'The relationship of perceived pain to afferent nerve impulses', *Trends in Neuroscience*, 9, 1986: pp. 254–255.

[77]Anand and Hickey, *op. cit.*, note 15.

[78]Giannakoulopoulos *et al*, *op. cit.*, note 3.

[79]This paper is available in the House of Commons Library, London, UK. Professor Fitzgerald's comments should be compared with her view, published later in the *British Medical Journal* (note 3), that the fetus cannot be said to feel pain if feeling and pain are properly understood.

that focus specifically upon the biological properties of human beings,[80] to deliver a coherent account of human consciousness.[81] In the current author's view, the key to understanding consciousness lies in the relationship of the individual to the world in which she exists rather than within biology *per se*. For example, as the child develops she will inevitably build up an extensive memory of motor responses based on instinct. But, if this (computer) analogy is valid, then she would, like a computer programmed to make a robotic movement, still not necessarily be aware of anything. In fact, if left entirely alone, a human being might operate in an unconscious computational manner. This speculation is, unfortunately, difficult to verify empirically. There are, thankfully, no documented cases of children being reared in such obscene circumstances. Thus, an entirely 'naturalised awareness' that develops independently, or irrespectively, of all nurturing influence remains a possibility. Theoretically, however, the idea is difficult to sustain.

Daniel Dennett has approached this issue through a consideration of what animals might 'think' or be aware of:[82]

> if a lion could talk, we could understand him just fine with the usual sorts of effort required for translation between different languages – but our conversations with him would tell us next to nothing about the minds of ordinary lions, since his language – equipped mind would be so different. It *might* be that adding language to a lions 'mind' would be *giving* him a mind for the first time! Or it might not. In either case, we should investigate the prospect and not just assume, with tradition, that the minds of non-speaking animals are really like ours. [Quoted from Dennett, pp. 18, emphasis in the original].[83]

[80]Crick, *op. cit.*, note 75.

[81]Chalmers, *op. cit.*, note 75; Derbyshire S.W.G.: 'Toward a science of consciousness: Journey to the centers of the mind – Review', *British Medical Journal*, 313, 1996: pp. 1090–1091.

[82]Dennett D.C.: *Kinds of Minds: Towards an Understanding of Consciousness*, Basic Books, New York, 1996.

[83]Dennett, *op. cit.*, note 82. Dennett's argument raises an intriguing and contentious issue which is whether it is logical to talk about a 'restrained consciousness', i.e., can an organism be said to experience 'pain' without being able to reflect upon that experience? Can there be such a thing as an 'ouch' without any reference to the self or any other form of conceptual anchor? Dennett explicitly states it thus: 'For such states to matter – whether we call them pains, or conscious states, or experiences – there must be an enduring subject to *whom* they matter because they are a source of suffering'. These are

Dennett raises a number of issues that are pertinent to the discussion at hand. Given the physiology of the lion, what kind of 'mind' is it likely to have? If you add language, or other cognitive constructs, how might that alter the 'mind'? Dennett warns that conceptualising the problem of an animal's 'mind' can easily become a tautology that assumes precisely what it is that needs to be explained. If something thinks then it must think particular thoughts. Particular thoughts, however, are composed of particular concepts. 'Ouch', for example, is not just a reflexive response, but is a mindful state that includes the sensation and the associated cognitions and emotion. How might we express, in whatever form, the precise 'experience' of pain (or 'ouch') that the fetus is experiencing? Dennett suggests that this is actually impossible and that it might, therefore, either be the case that the fetus does not have thoughts at all or that fetal thoughts must be systematically inexpressible – 'and hence beyond our ken'.

A further consideration is the consequences of having thought. If a thought is conscious or 'mindful' it seems reasonable to propose that the thought will result in action that has a directed or purposive nature. In other words, if a something is thinking in a conscious manner that something would be expected to act in a conscious manner. Deciding whether a given behaviour is purposive is difficult because it is always unclear whether the action just *looks* intentional as opposed to *being* intentional. Nevertheless, we would be surprised if a group of somethings that we took to be conscious consistently acted in a random or stereotypical manner that was actively detrimental to their well being – even if other aspects of their behaviour looked purposive. Dennett uses the example of dolphins trapped in tuna nets. For all their apparent intelligence, dolphins are strangely unable to figure out that they could leap the tuna net to safety – a physical act that is well within their capability.[84]

Conceptual and symbolic abilities along with purposive, directed awareness are suggested as the core components of consciousness. Conscious growth is here suggested as being

very difficult questions. Regardless, an inability to be self aware suggests conscious experience to be impoverished.

[84]As one of the anonymous referees pointed out, the argument regarding fetal pain has obvious implications for an argument regarding animal pain. The suggestion that animals feel pain loses strength if it is accepted that the fetus cannot feel pain. However, the difference in physiology and development of animals, compared with humans, does change the argument and a detailed discussion would take the current article beyond its scope and focus. A separate article on the topic of animal pain is planned.

contingent upon biological development within a social world that exchanges thoughts and ideas through common language (in whatever form). This social interaction changes the nature of development itself; it ceases to be a purely biological process and becomes a biosociohistorical one. The pressure of having to place ideas into a common conceptual framework forces the subordination of our instinctual, reflexive biology to our conscious will. This is a view that lifts us beyond a narrow biological determinism escaping a prescriptive human nature or a metaphysical influence.[85]

One attempt at describing this process of subordination comes from Susan Greenfield.[86] Her description of consciousness is 'based on a triggering epicenter which sets in motion nonlinear concentric associations. The more extensive or sustained they are, the more consciousness will be experienced' (page 97). Rather than seeing consciousness as an all or nothing affair, Greenfield suggests that consciousness is rather like a dimmer switch, gradually moving from fully off to fully on.

The dimmer switch is a useful analogy but it requires elaboration. What parameters need to be in place before the switch can be declared partly on? How can the degree of 'on' be assessed? Figure 3 explores the analogy of a dimmer switch.

Figure 3 shows pain development on the left, as defined by Leventhal, associated with child development on the right.[87] Leventhal suggests that pain is elaborated through the development of innate expressive-motor mechanisms into schematic processing and finishing with a conscious abstract

[85]John Eccles is often mocked in materialist circles for being the only scientist who maintains that there is a metaphysical influence over human thought. However the condemnation is too quick as his devastating attack on the failings of materialism illustrate. See Eccles J.C.: *How the Self Controls its Brain*, Springer Verlag, 1994. Eccles consistently points to the failure of materialism to explain *how* neurology produces conscious experience. This is the 'hard problem' as described by Chalmers (*op. cit.*, note 75) which Eccles 'solves' by introducing divine intervention. Chalmers also explores a form of idealism to resolve the 'hard problem'.

[86]Greenfield S.A.: *Toward a Science of Consciousness: Journey to the Centers of the Mind*, W.H. Freeman & Company, New York, 1996.

[87]The ages at which the various cognitive, emotional and behavioural processes come 'on–line' as it were, have been assessed using a variety of sources. Where there was disagreement, the speed of development was taken as being faster rather than slower: Zelazo P.D.: 'Towards a characterization of minimal consciousness', *New Ideas in Psychology*, 14, 1996: pp. 63–80; Mussen P.H., Conger J.J., Kagan J. and Huston A.C.: *Child Development and Personality*, Harper and Row Publishers, New York, 1984; Leventhal., *op. cit.*, note 12.

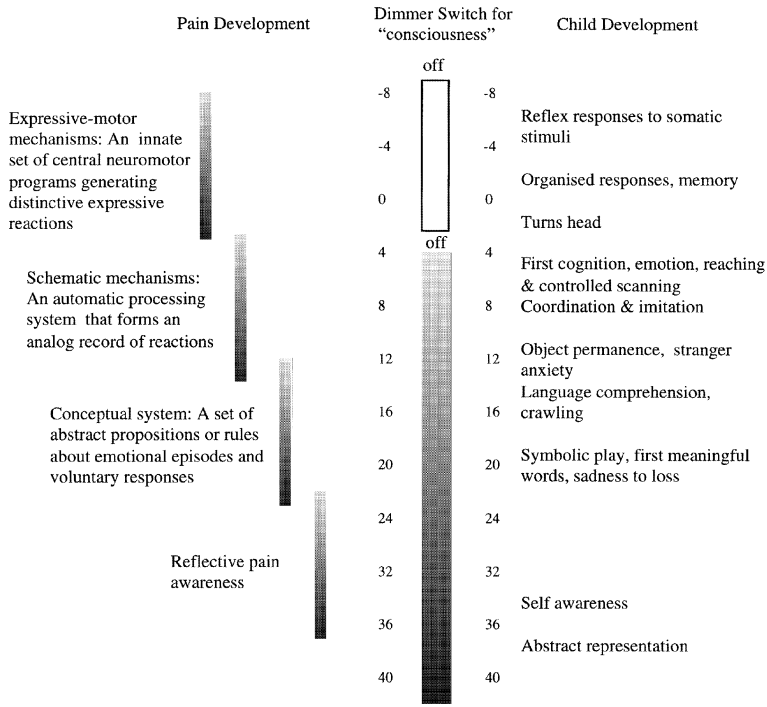

Figure 3. *The dimmer switch. Shown on the left is the hierarchical development of pain as described by Leventhal. Expressive-motor and schematic mechanisms are both considered pre-conscious, however the main consciousness switch is activated from 4 months of age. On the right is the corresponding cognitive development deemed to be necessary for the increasing complexity of Leventhal's pain hierarchy. The numbers represent age in months, the first 'off' is conception and '0' is birth. Detail is indicated in the text.*

conceptual system. These systems form the substance of the four 'pain dimmer switches'. The hierarchy advances as the development of the fetus and newborn makes it feasible to move forward. This judgment has been made entirely by the current author and no doubt others will feel that the switch should move more or less quickly.[88]

[88]The advantage of the dimmer analogy is its capacity to deal with points of transition. However, this is also its weakness. The distinction between points of transition and discontinuity is elided. There is also the tendency to view the psychological transition as a natural unfolding of the biological process of complexification which is precisely the problem under discussion.

Expressive motor mechanisms are introduced with the first signs of movement in response to sensory stimulation, i.e., at 7–14 weeks gestation. Schematic processing is not introduced until 4 months of age. It is possible that aspects of schematic processing become available earlier than this, between 26–30 weeks gestation when the first memory functions become available and the first organised responses to stimulation become apparent. The organisation and categorisation of responses corresponding to a primitive memory structure is certainly the minimal requirement for schematic processing. However, Leventhal is insistent that schematic processing also includes the encoding of emotional processing with the general sensory and behavioural processes. As the first emotion is not considered to occur until around 4 months of age, schematic processing is held until that time.

Leventhal considers neither expressive-motor nor schematic processing to indicate a conscious process. In terms of the conscious development of the fetus it is reasonable to suggest the fetus has nociceptive responses but no pain experience. The conscious conceptual system begins from 12 months of age. This corresponds with the cognitive landmarks of object permanence and symbolic play. The developing infant now has the capacity for continuous processing of the outside world. People and objects no longer exist one moment at a time, as there is conscious awareness during their absence. Symbolic play and the attempt to make meaningful utterances is further evidence for an internal, abstract, representation. The infant is going beyond the innate dictates of expressive-motor functions, and the stereotypical responses associated with schematic processing, and can respond in a voluntaristic or directed manner. The main switch representing consciousness is 'on' and an experience of pain is now clearly possible.

This does not rule out the possibility of a rudimentary, or impoverished, awareness, at an earlier stage. However, it does make apparent the cognitive and conscious development of a human being. This places us in the position of having to define what is different about the fetal or neonatal experience – if there is any experience at all. Given what pain is understood to be (section 1), the complex neurology that pain processing requires (section 2) and the limited neurological and cognitive development of the fetus (sections 3 and 4), I would reject the characterisation of any such experience as 'pain'. It would be better to characterise any neonatal experience, and present a theory of what it is and what to do about it, on its own terms.

Whatever we may conclude, the lack of self-awareness and conceptual and symbolic abilities means we can be certain that any fetal or early neonatal 'experiences' will be of a lesser significance.[89]

5. THE MORAL SIGNIFICANCE OF A DIMMER SWITCH

This paper has argued that the fetal pain literature largely fails to address the fetus as being at one stage in a process of development. Both neurologically and cognitively there is much that is yet to occur. It is inconceivable that the change from fetus to neonate to child has no implications for experience – including pain. The concept of fetal pain and the implied equivalence between our own experience of pain and that of the fetus is therefore misguided. Only by leveling down the current understanding of pain so that it becomes nothing more than a physical sensation of noxious stimulation, distorting the biological maturity of the fetus and exaggerating the sensory, cognitive, emotional and general psychological life of the fetus can such an equivalence be drawn.[90] It is an obvious concern that the complexity of pain is being underestimated while the biological development of the fetus is being exaggerated. It is also worrying that changes in clinical practice may be introduced where they are not necessary, potentially causing harm both to the unborn infant and to the pregnant woman.

At this stage it would be inappropriate for the debate about fetal pain to affect clinical practice involving the fetus. Only when it is shown to be clinically beneficial should analgesic and

[89]The process of development does not stop at 12 months. At 32 months of age, Gerald Edelman suggests that a new form of memory, which he sees as a consequence of a reentrant loop connecting the hippocampus with the cortex, results in 'semantic bootstrapping' and a 'conceptual explosion'. 'Consciousness of consciousness' becomes possible with a resultant surge in mental activity and awareness. (Edelman G.: *Bright Air, Brilliant Fire: On the Matter of the Mind*, Penguin Books, 1992). An example of the usefulness of 'consciousness of consciousness' and evidence for its late appearance in development is provided by Vygotsky L.S.: *Mind in Society: The Development of Higher Psychological Processes*, Harvard University Press, 1978: 'Even a child of two years , when asked to repeat the sentence 'Tanya is standing up' when Tanya is sitting in front of her, will change it to 'Tanya is sitting down.'' pp. 97.

[90]The absence of any conceptual framework to account for a fetal/neonatal experience of pain means the fetal literature tends towards the discredited ideas of 'specificity' and 'pain centres' and argues for a change in the current definition of pain. Changing what we know, and find useful, to fit what we believe, rather than what we can prove, is the wrong way to do science.

anaesthetic intervention be carried out during fetal operations. The seminal paper by Anand and Hickey clearly demonstrated that analgesic intervention during neonatal operations improved clinical outcome.[91] This is in itself sufficient to place an ethical premium upon the use of analgesics during invasive procedures with the neonate. Although it is likely that similar mechanisms may be operative in the fetus, meaning that the fetus may also benefit clinically from analgesic practice, this should not be assumed. Full clinical assessment of analgesic practice for fetal operations is a proper requirement in the evaluation of any new procedure. Speculation as to what the fetus may or may not feel and extrapolation from our own experience or from experiences with neonates should not be used as a replacement.[92]

Fetal pain is obviously an important issue for those carrying out fetal operations and other invasive practices, but it is also of interest for those involved in abortion procedure and for those motivated to restrict, or liberalise, the current abortion legislation. The broadly accepted conclusion that recorded responses to noxious stimulation prior to 26 weeks gestation are *reflex* responses, not dependent on conscious appreciation, is important as it eliminates much of the generated concern regarding abortion. In 1994 just 94 abortions, out of more than 160,000 carried out in the UK, were later than 24 weeks.[93]

Recent guidelines on the termination of pregnancy for fetal abnormality issued by the UK Royal College of Obstetricians and Gynaecologists (RCOG) draws on the work of Fitzgerald (1995) which suggests strongly that the immaturity of the fetal nervous system prevents conscious awareness of pain before 26 weeks gestation. The document argues that 'it follows that up to this gestation the method of abortion should be selected to minimise the physical and emotional trauma to the woman'.[94]

Regardless of one's own views on whether late term induced abortions may cause pain to the fetus, the issue warrants special

[91]Anand and Hickey, *op. cit.*, note 15.

[92]Dr. Lloyd-Thomas brought a sober reminder of the need for carefully controlled trials with thorough follow up to my attention at a recent meeting. Dr. Lloyd-Thomas indicated that in the wake of neonates receiving 'pain-relief' during operational procedures, he was becoming increasingly concerned at the possible detrimental effects of opioid analgesia on the developing nervous system.

[93]*Abortion Statistics Series AB*, 19, 1995 (HMSO).

[94]*Royal College of Obstetricians and Gynaecologists, Termination of Pregnancy for Fetal Abnormality in England, Wales and Scotland*, 1996: pp. 12.

attention because almost all late terminations are of wanted pregnancies where the putative parents may be emotionally vulnerable. Often, during counseling, they express concern about what the fetus may 'feel' during an abortion. In these circumstances it is common for the putative parents to think of the fetus as a 'baby' and to attribute to it the qualities that they anticipated their child would have were it to be born. In such cases good sympathetic clinical practice would require steps to be taken to reduce the concerns of the woman.

In the UK, the RCOG recommends taking measures to stop the fetal heart in all terminations after 21 weeks gestation. This is to ensure that there is no possibility of the abortion resulting in a live birth.[95] After 26 weeks the guidelines suggest that it is not possible to know the extent to which the fetus is aware and so after this gestation it is suggested that 'methods used during abortion to stop the fetal heart should be swift and involve a minimum of injury to fetal tissue'. Whether or not the fetus is aware, these guidelines are appropriate to avoid unnecessary distress to the woman.

The paramount interest of the woman in abortion procedures is an important principle. An argument that with viability the fetus becomes a patient draws on the view that the fetus has equivalent experience to the pregnant woman. This view remains controversial.[96] The view that the pregnant woman is the patient while the fetus is cared for on behalf of the woman endures among many clinicians and should remain the ethical stance.[97]

The response of the fetus to invasive practice is a valuable research area that should lead to better clinical practice in the future. Basing this research upon the assumption that there is pain experience, however, is unjustified in view of what pain is understood to be, the complex neurological circuitry that is believed to process pain, the limited and immature development of the infants neurology, even at full term, and the apparently 'dim' nature of any conscious experience which can be logically said to be present. It is not overstating the case to say it would be irresponsible to introduce potentially dangerous and

[95] *ibid.*, note 94.

[96] McCullough L.B. and Chervenak F.A.: *Ethics in Obstetrics and Gynaecology*, Oxford University Press, New York, 1994; Chervenak F.A., McCullough L.B. and Campbell S.: 'Is third trimester abortion justified?', *British Journal of Obstetrics and Gynaecology*, 103, 1995: pp. 187–189; 'Sentence will test fetal rights', *New York Times*, 23 October 1996.

[97] Sirisena J.: 'Correspondence. Is third trimester abortion justified?', *British Journal of Obstetrics and Gynaecology*, 103, 1996: pp. 187–189.

problematic anaesthetic procedures without evidence for actual clinical benefit. Increasing the distress faced by those women who seek abortion and placing paediatric surgeons at risk of lawsuit on the basis of what is currently known regarding fetal responses to stimulation is also morally dubious.[98]

There are many questions left unanswered by this review.[99] However the structure for the theoretical examination of 'fetal pain' outlined here is believed to be useful in clarifying the approach towards an answer.[100]

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[98]I am grateful to Naomi Tsujimura, *The Medical Mutual Group*, for informing me of lawsuits relating to fetal pain.

[99]I have, for example, not discussed in detail the developing neurotransmitter or inflammatory mechanisms. Also, much research remains to be done before we can be confident regarding the neurobiology of a fetus.

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