FETAL SENTIENCE

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Mrs Ann Winterton, M.P.
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"A fisherman once told me that fish have neither sense nor sensation but how he knew this, he could not tell me."

Bertrand Russell
“HUMAN KNOWLEDGE” “Its Scope and Limitations”
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SUMMARY

There is no direct, objective method of assessing pain or suffering in another subject, human or non-human, prenatal or postnatal.

Indirect methods of assessing pain include:

a) questioning the subject, assuming the subject to possess both the capacity to remember and to communicate,

b) observing the type of stimulus and the subject’s response to it.

c) confirming the presence and integrity of the anatomical structures subserving the appreciation of pain.

Any stimulus capable of being interpreted as painful must activate sensory receptors and initiate the transmission of this activation to that part of the brain where the appreciation of pain occurs. Coincidentally the painful stimulus may also activate a spinal reflex mechanism which results in withdrawal from the painful stimulus by reflex muscle action.

Since no direct objective method of assessing fetal pain exists, the crucial question with regard to fetal sentience is:

At what stage of human prenatal development are those anatomical structures subserving the appreciation of pain present and functional?

The balance of evidence at the present time indicates that these structures are present and functional before the tenth week of intrauterine life.
INTRODUCTION

At present, no known method exists whereby we can directly assess or observe pain in another subject (human or non-human) with absolute certainty.

Our knowledge of pain is subjective. For example, if we see an animal kicked, we are confident in assuming it will feel pain because we know that if we were kicked we would feel pain.

In addition, we can deduce or infer that a subject is suffering or has suffered pain from a number of lines of indirect evidence.

1) Interrogation of Subject

The most informative method rests on interrogation of the subject. To achieve this, the subject must possess the capacity to feel pain, as well as the capacity to communicate. If the pain is to be described at a later time, the subject must also be able to remember.

Lack of either of the two latter capacities precludes the subject from reporting pain.

Animals and fetal, neonatal and some mentally impaired humans lack the capacity to communicate and/or the capacity to remember. As a New England Journal of Medicine editorial stated: "...of course infants are not able to complain later about their case".1

Some paralysed patients are unable to vocalise their complaints of pain.

People with Alzheimer's Disease certainly experience pain and may be able to describe it at the time, but lack capacity to remember and to give an account of it later.

Thus we see that to claim, as have Members of Parliament,2 that "awareness of pain" depends upon "ability to remember", is scientifically untenable.

2) Physical Reactions to Stimuli and the Central Nervous System

i) When it is impossible to interrogate a subject about experience of pain, other types of information must be relied upon. The most obvious additional information is response to the suspected painful stimulus: the commonest form of response is movement. In addition, recent research into hormonal responses (carried out at Queen Charlotte's Hospital in London) has shown changes in fetal plasma following intrauterine needling similar to those found in mature humans experiencing pain.3

ii) A second source of information that may help to gauge the likelihood of pain is the nature and intensity of the presumed painful stimulus. Would one expect such a stimulus to cause pain? (This is the subjective assessment.)

iii) A third, less evident, requirement in assessing the likelihood that a subject is experiencing pain, is knowledge about the structure of the nervous system in that class of subject. Is the degree of development of the nervous system consistent with the requirement for pain awareness? (The latter is as yet little understood.)

None of these types of information is likely to provide irrefutable evidence that the subject is feeling pain.
Consequently the practice in veterinary and human medicine is to presume that the subject may be able to feel pain from any given procedure, unless this can be excluded with reasonable confidence.
CHANGES IN GOOD MEDICAL PRACTICE

It is, of course, necessary for both veterinarians and doctors to bear in mind that our scientific knowledge regarding the identity of those nervous-system structures responsible for pain awareness is incomplete and changing as research progresses (see below). In recent times our knowledge about the minimal structure necessary for pain awareness by the nervous-system increasingly suggests that lower levels of complexity are required: for a subject to feel pain, development need not be as advanced as was previously thought.

Consequently, there have been changes in good medical practice in different areas such as:

i) At one time surgery was carried out on newborn and premature infants with minimal anaesthesia. Since 1986 this has been considered unacceptable as it is recognised that neonatal subjects can experience severe pain.

ii) In 1991 the Scientific Advisers to the Bundesarztekammer (Federal Medical Council) in Germany advised that sedation, analgesia or anaesthetics should be used during operations carried out on the unborn infant.

iii) Another example is the increasing tendency of animal experimentation codes of practice to require administration of analgesics to animals that are being used in experiments. In Australia this includes the fetus of any given species.
NEUROPHYSIOLOGICAL CONDITIONS FOR THE EXPERIENCE OF PAIN

The debate about fetal sentience focuses principally on the question of the fetus’s capacity to experience pain. It is therefore necessary briefly to review what can be reliably said about the neurophysiological requirements for the existence and exercise of this capacity.

Nerve Structures Involved In Pain Awareness

1) The anatomical structures involved in pain awareness consist of:
   i) sensory receptors capable of responding to a painful stimulus;
   ii) nerves to conduct the impulses generated in these receptors to the spinal cord;
   iii) nerve fibres within the spinal cord which transmit these pain impulses to the brain;

2) Two factors related to the transmission of impulses following the application of a noxious and/or potentially painful stimulus must also be explained:
   i) the relevance of reflex responses in assessing pain awareness;
   ii) the identity of brain structures for pain awareness.

A reflex response, in its simplest form, is a movement following a stimulus: it is an automatic reaction such as a child withdrawing her hand from a hot object.

The reflex response to a painful stimulus uses those nerves responsible for the transmission of the impulse to the spinal cord (1 ii). In addition, the nerves which emerge from the spinal cord to activate the muscles involved in the reflex movements must also be present. Thus a reflex action requires that all of these nerves be intact and functional.

It is important, however, to recognise that such a reflex movement does not necessarily require the transmission of an impulse to the brain structure responsible for pain awareness (1 iii). The reflex response of movement and pain awareness may both follow a single noxious/painful stimulus but they are quite separate events.

One can see this distinction in common everyday experiences. For instance, if one puts a hand into very hot water, it will be withdrawn immediately, to be followed within a split second by severe pain.

The significant difference between the reflex withdrawal and the awareness of pain is that while the reflex movement can be reliably observed by another individual, pain awareness can only be experienced by the subject and may only be deduced by the observer.

Reflex Movement Without Pain

In specific situations, either the reflex movement or the pain can occur on its own in response to a noxious stimulus. The reflex movement may occur – without being followed by pain – if the nervous-system pathways which transmit impulses to the brain centres responsible for pain awareness have been blocked by surgery or drugs. The same thing would apply in the case of a subject who had broken his neck: the reflex reaction would occur, but he would not be able to feel pain.
This might also occur in the fetus if the nerves which bring about the reflex action have developed before those of the pain pathways.

It is on this basis that some MPs have claimed that the fetus cannot feel pain.2

However, such a claim can only be scientifically sustained if we can confidently exclude beyond reasonable doubt that the stimulus which brought about the reflex movement does not also reach any centre in the brain concerned with pain awareness. To claim that a fetal movement in response to noxious stimulus is not accompanied by pain is warranted only if this exclusion can be firmly established.

The argument that “it’s only a reflex” would carry little weight if advanced in the context of animal experimentation. For example, the claim that “withdrawal of the dog’s leg when immersed in boiling water was only a reflex and not to be taken as an indication that the dog experienced pain” would not be acceptable.

**Development Of The Cerebral Cortex And The Thalamus**

Inexplicably, in the discussion of fetal pain awareness, the possibility that a fetus may feel pain and yet show no reflex response seems to have been overlooked. Yet, when one considers fetal development, this may well occur.

The fetus will not manifest reflex movements until the nerve fibres which emerge from the spinal cord have formed the necessary connections with those muscles which bring about movement.

Only if we assume that the development of the nerves responsible for muscle-movement occurs before that of the sensory nerves which ascend to the brain centres responsible for pain awareness can we conclude that there will be a period when there will be reflex action without the fetus actually being aware of pain. However, there is considerable evidence to the contrary suggesting that it is more likely for the fetus to experience pain before it has the capacity to move.

The anatomical structures involved in awareness of pain in the mature animal or human have not been completely identified. The programme of development of these structures in fetal animals or humans is even less completely understood.

Nevertheless, current information suggests that many functions which were originally assumed to be exclusively located in the cerebral cortex can be undertaken by lower centres in the brain. Those who claim that “sentience is a function of the cerebral cortex” seem to overlook this scientific evidence.

**i) Anencephaly**

Much of the information relating to the role of lower centres of the brain (eg the thalamus) has come from clinical experience of infants suffering from anencephaly (an abnormality in which the cerebral cortex fails to develop) and a related condition, hydranencephaly. The latter is compatible with prolonged survival whereas anencephaly is not.

Commenting upon the common assumption that anencephalic infants “have to be” incapable of feeling pain because of the lack of development of the cerebral cortex, a group of clinicians from the University of California, Los Angeles Medical Centre (UCLA) stated: “...it neither logically, nor physiologically follows that anencephalic infants by definition can neither feel nor experience pain” (see also footnote A, page 12). The UCLA group made the further point that to ignore actual pain reaction of anencephalic infants on the basis that a cerebral cortex was required amounted to begging the question of where pain was experienced.
ii) Hydrocephaly

Equally dramatic suggestions that many functions hitherto attributed to the cerebral cortex can be effectively accomplished by centres lower in the brain have emerged from research by Professor John Lorber of Sheffield University.  

Lorber has used scanning techniques to study a number of individuals with hydrocephalus who in other respects appear and behave normally. He has demonstrated that reduction of the thickness of the cerebral hemisphere (normally about 45 millimetres) to a “millimetre or so” had occurred in one otherwise normal university student.

Thus Lorber concluded that “the cortex is probably responsible for a great deal less than most people imagine” and he inferred that many assumed cortical functions in this person were located in primitive deep brain structures unaffected by hydrocephalus6 (see footnote B, page 12).

There are indications that awareness of unpleasant sensations may occur in one of these deeper structures, the thalamus.

iii) PVS and Damage to the Thalamus

Damage to the upper parts of the brain does not generate pain (the brain can be operated on after local anaesthesia of the scalp and overlying skin), but the “thalamic syndrome” which occasionally follows damage to the blood supply to the thalamus is characterised by intractable, burning pain.

Another important observation emerged from the findings at the post mortem examination of the American PVS victim, Karen Quinlan, who lived for over 10 years in a comatose state. This examination established that there was comparatively slight damage to the cerebral cortex (in which some MPs have been led to believe consciousness resides) whereas the thalamus had suffered very substantial damage. These findings suggest that the thalamus plays a more crucial role in consciousness and awareness than was previously thought.7

Anatomical observations of the human fetus have indicated that some parts of the thalamus have developed by 9 weeks gestation and that the nerves responsible for carrying sensation from the skin to the spinal cord develop by 6-7 weeks.

Apart from the inferences concerning fetal capacity for pain that can be drawn from these anatomical studies, a number of direct observations of the response of the human fetus to stimulation ex utero (removed from the womb) have been reported. A report from Fitzgerald and Windle8, who made some of the most striking observations, stressed that many other reports were based on assessments of fetuses which were adversely affected by maternal anaesthesia and oxygen deficiency. They attribute the failure of those reports to observe fetal movements after stimulation to the effects of narcosis and lack of oxygen (anoxia) after placental separation (separation from the mother).

They reported that sensory and motor nerves were functioning in the eighth week of gestation, as indicated by muscular contraction in response to stimulation.9 There can be little doubt, on anatomical grounds, that some sensory nerves mature at 6-7 weeks and, therefore, do so before their motor nerves which cause muscle movement. Hence, observations of very early fetal reactions to stimuli are limited by the slower development of motor nerves.

Thus when MPs equate the movements of a human fetus at this stage of development (possessing as it does a nervous system that is already quite extensive) with the
reactions of a single cell amoeba in which any equivalent nervous system is totally lacking they parody science in the best tradition of W.S. Gilbert's derivation of Poo-Bah's ancestry from an amoeba.

Footnote A
The paper also states: "In experimental animals, brain stem structures have been shown to mediate complex behaviours, sometimes traditionally assumed to be cortical, including binocular depth perception, habituation, learning and discriminative conditioning. Similarly, decerebrate (anencephalic or hydramencephalic) human newborns with relatively intact brain stems can manifest a surprising repertory of complex behaviours, including distinguishing their mothers from others, consolability, conditioning and associative learning although irritability and decreased ability to habituate are also common."

Footnote B
In the central nervous system cerebro-spinal fluid (CSF) flows freely through a system of interconnecting spaces called ventricles within the brain. The largest of these spaces, the lateral ventricles, are situated one within each of the cerebral hemispheres. In hydrocephalus the free flow of cerebral spinal fluid (CSF) is blocked, usually during fetal life or early infancy, and it accumulates within and dilates the lateral ventricles. As a result, the overlying brain tissue including the cortex is significantly reduced in thickness.
RESPONSIBILITY IN ASSESSING PAIN IN SUBJECTS

1) As indicated previously, the question of whether a subject, who lacks the capacity to communicate, is feeling pain can only be deduced. Essentially then, any decision about the likelihood that any subject (animal or human) feels pain requires society to decide what is an acceptable risk of error.

How confident must we be that our actions will not inflict pain on a sentient creature? In this type of situation, it is generally required that the burden of proof (of non-sentience) rests on the person who is undertaking the action.

That this is recognised in analogous situations may be seen in the various codes of practice under which experimentation on animals may be conducted.

For what is reflected in those codes is the recognition not of a remote but of a very strong possibility that fetal animals can experience pain.

For instance, the code of the Australian National Health and Medical Research Council, explicitly requires that "unless there is specific evidence to the contrary, investigators must assume fetuses have the same requirements for anaesthesia and analgesia as adult animals of the species".

We can also see a similar concern to avoid the possibility of causing pain, in guidelines on human experimentation. For example, in testimony before a Committee of the European Parliament enquiring into time limits on human embryo experimentation, a French researcher explained:

"Other proposals have been based on the ability of the embryo to experience pain, but at the present state of scientific knowledge, the exact point in time when this occurs is not known.

"Day 17, when the first signs of the formation of the nervous system are visible, has been proposed by The Royal College of Obstetricians & Gynaecologists."99

This is reflected in the Warnock Committee Report (paras 11.20-11.21) which states:

"...the strictly utilitarian view...suggests that the ethics of experiments on embryos must be determined by the balance of benefit over harm or pleasure over pain. Therefore, as long as the embryo is incapable of feeling pain, it is argued that its treatment does not weigh in the balance. According to this argument the time limit for in vitro development, and for research on the embryo could be set either when the first beginnings of the central nervous system can be identified or when functional activity first occurs....The Royal College of Obstetricians & Gynaecologists suggested that embryos should not be allowed to develop in vitro beyond a limit of seventeen days, as this is the point at which early neural development begins."10

Therefore, considerations about the capacity of the fetus to experience pain should be based on the best scientific information currently available. At the very least, these should match the standards in relation to burden of proof that apply to experimental use of animals.

Such a view was recently expressed succinctly by Professor Christopher Hull (Vice President of the Royal College of Anaesthetists and Professor of Anaesthesia at the University of Newcastle) during a BBC World At One news item on the dilation-and-extraction abortion technique (in which fetuses from about 13 weeks gestation are dismembered). He commented:
“So far as I am concerned I would be prepared to accept that the fetus does not feel pain when somebody proves to me that they don’t feel pain. But, until that time I would have to assume that they do.”

Indeed, the burden of proof, surely, should rest upon those who accept the principles of the British Abortion Act, to show that the fetus does not feel pain rather than to demand conclusive proof that s/he does, which is at present the case. In a more general context, the point can be made that many in the community would recognise that the obligation not to harm other human subjects extends considerably beyond that of not causing pain.
AN OPINION GIVEN TO THE DEPARTMENT OF HEALTH

Since 1988 Professor Maria Fitzgerald has been adviser to the Department of Health on fetal pain. She produced one paper in 1988 and an update in 1995 on the neural pathways and reactions of the fetal and neonatal rat compared with the human fetus.12

However, there are a number of points which need to be made:

1) In view of the fact that the central nervous system and its development in the primate is far closer to that of homo sapiens, one should ask why it was decided to compare the human fetus with rats rather than with primates? It is, surely, at least as wrong to risk inflicting pain on the human fetus as it may be to carry out pain studies on primates.

In her paper Professor Fitzgerald states that “Animal models are essential for understanding neural pathways and the fetal and neonatal rat have proved to be excellent models for the study of pain development”12.

But she then compares the reflex to somatic stimuli which begin at 7.5 weeks in the human fetus with those occurring at 15 days in the rat fetus; she goes on to compare those at 10.5 weeks with those at 16 days in the rat and those at 13.5 – 14 weeks in the human with those at 17 days in the rat (the complete gestational period for which is only 22 days). Thus since the events which take some 6 weeks to develop in the human are compared with those occurring over 3 days in the rat and, further, since those in the human occur during the first half of gestation and those in the rat occur in the second half of gestation the rat would not appear to be the appropriate model for the study of pain development in the human.

2) Professor Fitzgerald asserts (as we have done on page 1) that behavioural responses form “the most common ways in which most people judge the reaction to pain in infants (and indeed in domestic animals) and form the basis of standard pain assessment in clinical practice.”12 She also acknowledges that such responses may not adequately reflect the perception of pain since for these responses to do so would require the integrity and maturity of the somatic motor system as well as requiring that the motor output reliably reflects the sensory input. Neither of these assumptions, she admits, are entirely justified.

Thus she recognises that such responses may indicate the presence of pain but that one cannot assume that pain is not present when such responses are absent, a point made in this paper (see page 6, “Development of Cerebral Cortex and the Thalamus”). Furthermore, in her conclusions Professor Fitzgerald states that “The evidence for early exposure to inappropriate sensory stimuli or tissue trauma leading to adverse effects on future neural development is increasing,” adding that “noxious stimulation may not need to penetrate the consciousness in order to substantially alter the normal course of sensory development. If a fetus or preterm infant is to survive and mature into an adult, it is essential to consider this issue.”12 (our emphasis.)

In view of the fact that Professor Fitzgerald’s paper clearly shows that the human fetus reacts in many ways to tactile stimuli from a very early stage, it is surely the duty of those opposed to its protection to prove beyond reasonable doubt that it cannot feel pain, rather than to demand evidence that it can.

3) Professor Fitzgerald’s description of the function of the cortex (that perception or conscious reaction are related solely to the cortex) does not take account of much recent research. Her paper ignores the work of Lorber (see page 7); of the studies of anencephalic infants carried out at the University of California, Los Angeles Medical Centre (see page 7); and of the post mortem examination of American PVS patient, Karen Quinlan (see page 9).
REFERENCES


2) Amendment to Early Day Motion 636 House of Commons Notices of Motions 1.3.95. (See Appendix I).


4) Australian National Health and Medical Research Council “Code of Practice for the care and use of animals for scientific purposes”.


11) BBC World At One, 29.4.1996.

That this House understands concern and non-violent protest about the inhumane treatment of sentient creatures, including the export of veal calves; notes that consistent scientific research since that of I. D. Hogg in 1941 clearly shows that the human fetus reacts to painful stimuli from five to six weeks' gestation when touched around the mouth and that this extends to an almost complete range of cutaneous responses at 12 weeks; notes that the perception of pain is principally within those parts of the thalamus which develop between nine and 12 weeks' gestation; further notes that the cortex which develops after the thalamus influences pain perception by reducing its intensity; thus notes that in these early stages of development the fetus could be subjected to an intensity of pain greater than that experienced by born humans; recalls that Professor Sir William Liley, renowned internationally as the father of fetal medicine, comparing attitudes towards animals and the human fetus, recorded his unhappiness that we withhold from the human fetus a charitable consideration we extend to animals; and calls for changes to the Abortion Act to give protection to the human fetus who has less legal protection than laboratory animals and less charitable consideration from the 'politically correct' than they extend to livestock.

As an Amendment to Mr Joe Benton's proposed Motion (Treatment of Sentient Creatures).

Mr Harry Cohen

Line 2. leave out from 'calves' to end and add 'but disassociates itself from the opinion that the human fetus is sentient, at least before the 24th week of pregnancy; notes that animals ranging in complexity from the one-cell amoeba to the human respond by movement when stimulated; notes that such a response does not imply the awareness necessary for sentience; notes that sentience is a function of the cerebral cortex and that this part of the brain increases greatly in bulk and complexity after the 24th week of pregnancy and its development is not complete until some months after birth; notes that awareness of pain and of the emotions associated with being hurt is a function of consciousness which depends not only on the maturity of the brain but also on the ability to remember and understand information received through the senses; notes that the fetus may have some small degree of consciousness in the last weeks of pregnancy but that full development occurs after birth; notes that the Abortion Act recognises that the protection of the health of the woman has to be balanced against the risks of continuing pregnancy and abortion; and notes that the time limit of 24 weeks for abortion, except in the most unusual and adverse circumstances, meets the needs of the woman and shows a respect for the developing humanity of the fetus that is soundly based on anatomical and psychological observations.'
APPENDIX 2

FETAL PAIN: AN UPDATE OF CURRENT SCIENTIFIC KNOWLEDGE.

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Since pain is essentially a subjective experience with strong emotional associations, it is always going to be difficult to assess in the fetus and neonate. However it is possible to ask well-defined questions about the response of the immature nervous system to noxious stimulation and these questions can be directed at a number of different levels: behavioural, physiological or cell neurobiological. The answers have to come from a number of different sources. Studies on human fetuses are inevitably limited but some information can be extrapolated from preterm (from 23 weeks) neonates. Animal models are essential for understanding the neural pathways and the fetal and neonatal rat have proved to be excellent models for the study of pain development.

1) What is the behavioural response of the fetus to a noxious stimulus?

The behavioural response is defined here as body movements such as withdrawal of the affected body region and changed facial expression or other somatic motor event such as vocalization. This is the most common way in which most people judge the reaction to pain in infants (and indeed in domestic animals) and forms the basis of standard pain assessment of neonates in clinical practice. However it is limited by the fact that it relies on the integrity and maturity of the somatic motor system and also assumes that the motor output will reliably reflect the sensory input, neither of which are entirely justified.

Reflex responses to somatic stimuli begin at 7.5 weeks in the human fetus and 15 days, (E15 where gestation is 21.5 days) in the rat fetus. The first area to become sensitive is the perioral region which, when touched, results in contralateral bending of the head. In the human, the palms of the hands are sensitive to stroking at 10.5 weeks; at E16 the rat forepaws are similarly sensitive. By 13.5-14 weeks in the human and E17 in the rat, the sensitive area has spread over the body and down to the hindlimbs. The feet and tail regions are the last to become responsive at E18-19. At the same time as the onset of evoked reflexes, the fetus begins to move spontaneously in the absence of any obvious external stimulation. Real time ultrasound recording of human fetuses in utero has revealed a complex variety of movements including stretching, hand to face contact, startle and sucking which build up over 7.5-15 weeks gestation and continue into postnatal life. Analogous spontaneous movements begin in the rat at E15. It is important to emphasise that movements evoked at this stage are of a reflex or spontaneous nature only, even if they involve extensive body regions and therefore intersegmental and brainstem connections. The cortex is not a functional unit at this stage (see below) and therefore any discussion of ‘perception’ or of ‘conscious’ reaction to stimuli is inappropiate.

A feature of early cutaneous reflexes in the rat, kitten and human is that they are exaggerated compared to the adult. Thresholds are lower and the reflex muscle contractions more synchronised and long-lasting. Repeated skin stimulation results in considerable hyperexcitability or sensitization with generalised movements of all limbs. Flexor reflex thresholds are very low in preterm (24 to 32 weeks) infants and newborn rat pups but increase with postconceptional age (PCA). The somatosensory reflexes that appear in fetal life are still prominent at birth but change considerably over the postnatal period. A prick on the hind foot in a newborn rat or [sic] may bring about a ‘whole body movement’ involving wriggling, rolling, and simultaneous responses from fore and hindlimbs but as it matures the response becomes more individuated and restricted to an isolated leg or foot movement. A similar exaggerated response is observed in response to heel lancing (normal clinical practice for blood sampling) in very preterm infants and this gradually declines with increasing age.

Studies of these reflexes have been very useful in understanding the development of spinal cord pain mechanisms but it would be a mistake to equate them with true pain experience which must involve the cortex and develop postnatally along with memory, anxiety and other cognitive brain functions. In other words, stronger reflexes do not necessarily mean more pain. They are a reflection of the absence of the normal inhibitory control or ‘dampening’ influences that higher brain structures normally exert over spinal reflexes at more mature stages (see below). Indeed it has been argued that exaggerated reflex response to noxious stimulation may be protective and beneficial to an organism that is unable (through cortical immaturity or malfunction) to perceive and organize a more directed response to the pain. Reflexes become disinhibited or released once more in extreme
sensitivity (through cortical degeneration) or spinal injury (where the cortical inputs are cut off). Even fairly sophisticated reactions need not involve the cortex, but result from albeit complex interactions at brainstem level. A rat that has been decerebrated at mid-collicular level displays organized pain reflexes and even vocalization.

Perhaps a better idea of pain experience comes from recent behavioural investigations of infant pain analysing facial actions in response to noxious stimuli. These studies have shown that infants display particular facial expressions associated with tissue insult. Behavioural state and severity of illness influenced these responses but even very low birth weight infants between 26-31 weeks gestational age show a significantly different upper facial action response to painful heel prick versus sham. While these studies were carried out after birth, it is reasonable to assume that these same responses would occur in utero. In contrast to spinal cord reflex responses, younger gestational age is associated with less reactivity in facial expression to heel lance, suggesting that the younger infants experience less pain. However, this could simply be a reflection of immature motor control which is likely to affect the more complex activity patterns of facial motoneurones more than those of lumbar spinal motoneurones.

What are the fetal autonomic and neuroendocrine responses to noxious stimuli?

Other measures of responses evoked by noxious stimulation involve the autonomic nervous system e.g. changes in heart rate or the neuroendocrine system, e.g. release of stress hormones. The same difficulties in interpretation arise here as in the use of somatic motor behaviour, but to a greater extent. Even in adults, the poor ability of autonomic or endocrine responses to reliably respond to noxious stimuli are well known and in addition these systems are very immature in fetal life. It has recently been reported that from 23 weeks gestation fetuses are capable of mounting a hormonal response involving increased cortisol and β-endorphin when needles are inserted into the innervated intrahepatic vein but not when they are inserted into the uninnervated placental cord. This demonstrates that the noxious activation of nerve endings in the fetus is capable of activating central pathways, most likely the fetal hypothalamo-pituitary-adrenal axis to produce a classic stress response. The authors raised the possibility that the fetus feels pain in utero and may benefit from anaesthesia and analgesia for invasive procedures. While this may be so, this study certainly does not demonstrate it. Although pain frequently produces stress, stress does not necessarily indicate pain. The link between reported levels of pain and the hormonal stress response in adults is unpredictable and increasingly questioned. What the fetal stress response does show is exactly the same as the behavioural studies, namely that noxious sensory stimulation can and does produce a clear reaction from the fetal nervous system. In this respect, the most interesting aspect of the stress response is that it is sensitive to analgesics. Preterm infants of 28 weeks show marked changes in hormonal and metabolic variables during and after surgery which can be blunted by the administration of the analgesic opioid intravenous fentanyl. In babies of 27-31 weeks undergoing intensive care treatment, morphine reduces adrenaline levels. However, since little is known about appropriate opioid doses in neonates, it is not clear whether these effects are a result of sedation or of true analgesia.

Autonomic responses have also been used as a measure of pain and some investigators have found significantly different maximum heart rate and respiration to painful heel lance versus sham in very preterm infants, but the effects are variable and compounded by the immaturity of the autonomic system.

How does the fetal somatosensory system respond to noxious stimuli?

In the end, to answer the question of how the fetus experiences pain, we must move away from the use of motor, autonomic or endocrine responses to measure pain reactions and directly investigate the sensory neurons and pathways from peripheral tissues, through to the spinal cord, brainstem, thalamus and finally cortex and evaluate their functional connectivity in fetal life. The possibility of doing this in human infants is, of course, limited but much can be learned from laboratory animals.

There are great differences in neural structure and function of developing compared to adult pain pathways, which can be referred to in detail elsewhere. For example, peripheral sensory receptors that convey information about low threshold, tactile stimuli to the body surface make functional connections in the fetus with spinal cord cells, which in the adult are exclusively reserved for pain inputs. Furthermore fetal spinal cord sensory neurons responding to noxious stimuli respond to relatively larger areas of the body surface (receptive fields) than in the adult. These diffuse central connections and large dorsal horn cell receptive fields are likely to lead to poorer discrimination between noxious and non-noxious events and poorer spatial localization of stimuli in fetuses. Another important feature of fetal pain pathways is that neurotransmitter and receptor function and distribution is quite different from that in adults. Many receptors are in high density but diffusely spread and in some cases neurotransmitters that are inhibitory in the adult may be excitatory in the fetus.
Gradual suppression or inhibition of neural connections is a feature of the developing somatosensory system and has an important influence on the postnatal organization of pain responses. Descending inhibitory pathways travelling from the brainstem via the dorsolateral funiculus of the spinal cord to the dorsal horn do not become functionally effective until postnatal day 10 in the rat. This may in part be due to deficiency of neurotransmitters in this case 5-HT (serotonin) and noradrenaline but may also be due to delayed maturation of crucial interneurones. This lack of descending inhibition has important implications for the function of nociceptive pathways in the neonate because it means that there is no endogenous inhibitory system to ‘dampen’ noxious inputs as they enter the CNS and their effects may therefore be more profound than in the adult. It accounts for the exaggerated reflexes observed in the fetus and neonate.

Much less is known of the maturation of spinal projection pathways, thalamic and cortical connections in relation to pain processing compared to events in the periphery and spinal cord. However, what little we do know suggests that noxious inputs, however strong or weak, would not reach the cortex before 26 weeks in the human fetus. In the rat dorsal horn projection cells begin to grow axons prenatally and afferents reach the thalamus at E19. The earliest thalamic axons reach the cortical plate also at E19 and by PO there is a plexus of growth-cone tipped axons in the cortical plate and a few thalamic axons have reached the marginal zone. In the human, thalamocortical fibres penetrate the cortical plate at 26-34 weeks. These anatomical findings correlate well with functional studies. Evoked potentials from the forepaw develop the adult form in the rat somatosensory cortex by P12 and the equivalent potentials in humans begin to mature at 29 weeks postconceptional age.

Electrophysiological analysis of rat cortical cells at P7 shows them to be organized in columns as in the adult but to have larger receptive fields, suggesting a lack of inhibition as discussed above for the spinal cord. The delayed maturation of inhibitory processes occurring several weeks after excitatory connections have been established has been observed in the neonatal rat hippocampus and may be a general pattern in developing cortex. The rodent cortex remains immature for up to 6 weeks after birth and the human cortex for many years. The complex developmental processes taking place over this period of attention and memory, and the many important cognitive factors contributing to the cortical perception of pain in infants and children are reviewed elsewhere.

Summary and Conclusions

The fetus displays clear reflex responses to peripheral noxious stimuli which continue into the postnatal period. These may be somatic motor, neuroendocrine or autonomic responses. The existing evidence show that little sensory input reaches the developing cortex before 26 weeks and therefore these reactions to noxious stimuli cannot be interpreted as ‘feeling’ or perceiving pain. Furthermore the immaturity of the nervous system means that the reflex responses are not always selective for noxious stimuli and must be interpreted in the context of developing neural connections. Immature spinal reflexes, for example, are exaggerated and the emergence of inhibitory mechanisms, both local, segmental and descending from the brain, play a part in producing specific pain behaviour.

However, despite the lack of evidence for fetal pain, it cannot be denied that the fetal nervous system mounts clear protective responses to tissue injury and this cannot be ignored. The evidence for early exposure to inappropriate sensory stimuli or tissue trauma leading to adverse effects on future neural development is increasing. In other words, noxious stimulation may not need to penetrate the consciousness in order to substantially alter the normal course of sensory development. If a fetus or preterm infant is to survive and mature into an adult, it is essential to consider this issue. The effects of trauma of any kind to the developing nervous system should be minimised as far as possible by whatever means are available to avoid changing the course of normal development.

REFERENCES