FETAL AWARENESS

- *Sentience, pain and the developing fetus.*
- *Implications for medical practice.*

POST note 94 February 1997

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The question at what stage it is possible for a developing fetus to be aware (e.g. of pain) has been kept under review by the Department of Health (DH) as scientific understanding advances. Recently, the question has been raised in Parliament, following the release of a paper prepared by the All-Party Parliamentary Pro-Life Group.

While there are important religious and ethical dimensions to this issue, this POSTnote concerns itself solely with scientific and medical aspects.

BACKGROUND

As medical science sheds more light on human development, more is becoming known of how the various components of the nervous system develop and join together during fetal life. This has led to a renewed discussion over whether the developing fetus is capable of being aware of its state and surroundings; and, if so, when in gestation this can occur. This work is important to all concerned with medical care of the woman and fetus - including medical and surgical interventions for diagnostic and therapeutic purposes, and the effects of analgesics and anaesthesia. In Parliament, a primary interest is in the context of abortion, with some Members arguing that the workings of the Abortion Act should be reviewed.

The question 'can a fetus feel pain' at a given age has a number of scientific components. There are questions of neural development and the integration of the sensory system into the developing brain; and of the development of structures and functions of the brain that are necessary for awareness of pain.

In fetal development, the rudimentary organs or tissues are laid down at an early stage and all exist in their initial primitive form by 8-9 weeks, after which they must grow in size, complexity and organisation until they can work together to support independent life at full term. The nervous system conforms to this general pattern and some key stages are outlined in **Box 1**. The first tissues differentiate when the human embryo is only 2-3 weeks old with the formation of the 'neural tube' from which the nervous system derives. The primitive structures of the brain (fore, mid and hindbrain) are recognisable four weeks after conception. Some peripheral nerves and connections within the spinal cord can be functional by 7 weeks, allowing reflex reactions through the sensory and motor nerves communicating within the spinal cord. As the brain develops, fetal movement increasingly comes under the control of the brain - first manifested (from 17-18 weeks) in the suppression of the automatic reflex actions, but from 6 months on, activity increases again.

Four critical regions start to develop from the forebrain from five weeks onwards - the thalamus, cerebral cortex, hypothalamus and limbic system. The thalamus becomes the reception area for most of the sensory input to the brain travelling up the spinal cord, and relays it to the appropriate region of the cortex via its **projection fibres** (neurons which connect different parts of the brain). These thalamocortical fibres start developing at 17 weeks and penetrate the cortical plate to make permanent connections at 22-34 weeks.

The part of the brain associated with thought, consciousness, emotion etc. is the cerebral cortex which forms the largest part of the developed brain, enveloping the lower structures (Figure B) in two cerebral hemispheres, the first signs of which are visible at 5-6 weeks. The cortex itself starts as a layer of undifferentiated cells (the cortical plate) which grows rapidly in both size and complexity throughout gestation. Eight different cortical layers have developed by 38 weeks, and the characteristic convolutions (these increase the cortex surface area) are displayed towards the last two months (Box 1). The brain continues to develop at the high rates typical of the fetus for a year or so after birth, until the basic physical layout and structures are completed.

Once one moves from a physical description of the operation of the nervous system to end results such as feelings of pain or suffering, other factors may be involved, and there is some discussion of the role of emotional and cognitive (learning) components and the degree of consciousness required in the appreciation of pain. Some thus argue that it may be difficult to characterise this question **solely** in terms of a neural reaction to noxious stimuli (NS).

The DH commissioned in May 1995 an "*update on current scientific knowledge*" by Prof. Maria Fitzgerald of the Dept of Anatomy and Developmental Biology at University College London. This is summarised in **Box 2** and concluded that while the fetal nervous system mounts protective responses to NS from an early age, they cannot be interpreted as feeling or perceiving pain at least until neural connections are established to the cortex - then seen as 26 weeks or more after conception.

Box 1 KEY STAGES IN THE DEVELOPMENT OF THE FETAL NERVOUS SYSTEM AND BRAIN

After fertilisation, the embryo's cells multiply and after about 10 days separate into the ectoderm (precursors of the outer skin, nervous system amd other parts) and endoderm (precursor to the digestive system and lungs), soon separated by the mesoderm (to become muscles, bones, circulatory system etc.). Growth continues apace and by 8-9 weeks, all the basic tissues and organs of the infant exist in their initial form. This represents the start of the fetal period which lasts until birth during which time the fetus' length increases ten-fold (from 30mm to 300mm), its weight one thousand-fold (from 3g to 3500 g) and its proportions change to those of the full-term baby.

At around 17 days, the ectoderm separates a ‘neural plate’ which folds to form a hollow tube (the neural tube) within which the spinal cord and brain will start to develop. After the neural tube has closed (failure to close at the head end leads to anencephaly; at the bottom to spina bifida), the various regions of the nervous system start to develop, and the cells inside the tube proliferate to form the raw materials of the nervous system - the neurons. As these grow in number (at the peak of growth, some million neurons are produced every four minutes), they sort themselves into layers each of which then develops further towards its end tissue (e.g. spinal cord, brain regions). By attaching themselves to architectural cells called glial cells, the neurons start migrating to the positions in the developing nervous system which they need to reach in order to function properly.

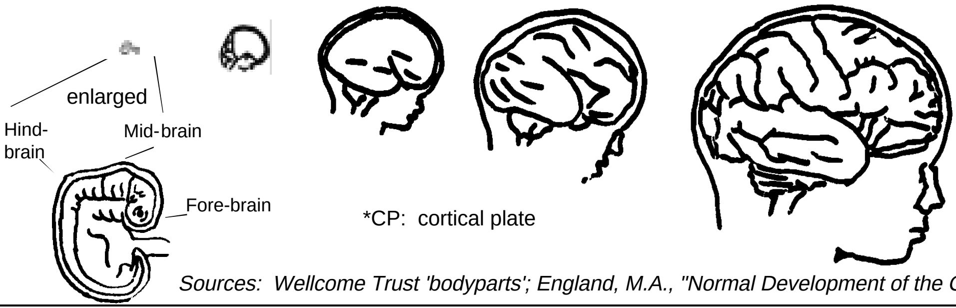
The primitive structures of the brain (forebrain, midbrain and hindbrain) are recognisable by 4-5 weeks after conception and develop and grow into the many different parts of the brain. The first signs of the brain's basic units (thalamus, cortex, etc.) are recognisable from around 6 weeks, and from then grow in size, develop the internal structure necessary to function, and interconnect throughout gestation. Internal structural development is as important as size - for instance the cortical plate starts off as a single undifferentiated layer, but by 38-40 weeks has 8 differentiated layers. The brain’s physical development is only partly complete at birth, and continues at fetal rates for another year before all key areas are built (e.g. the cerebral cortex has over 40 regions which regulate distinct processes). **Figure A** shows an external view of the brain at various fetal ages. **Figure B** shows the location of the various parts in the mature brain.

Development is a continuous process, not one separated by steps or jumps. For instance, the future cerebral hemispheres are just recognisable at 5 weeks (Figure A), from which point they grow rapidly in size (Figure A). In parallel with the development in size (Figure A) goes the development of neural connections between the various parts of the brain and the overall structure (e.g. the cerebral cortex develops its characteristic convolutions in the last trimester). When complete, sensory signals (including noxious stimuli) pass from peripheral nerves to the spinal column, through the brain stem and end principally in the thalamus. Further nerve fibres link the thalamus to the cerebral cortex. Anatomical and biochemical studies suggest that signals may begin to reach the cortex from 22-34 weeks.

As shown in Figure B, the higher functions derive from the forebrain:
The **thalamus** receives most of the sensory input to the brain, and relays it to the appropriate region of the cortex via its projection fibres.
The **hypothalamus** looks after important body processes (e.g. water balance).
The **cerebral cortex** is the outer layer of the brain and comprises 80% of it and is responsible for our consciousness of self, ability to think, plan, perceive, communicate etc.
The **limbic system** is important to emotion, motivation and learning.

Figure A THE DEVELOPING BRAIN (figures one quarter size)

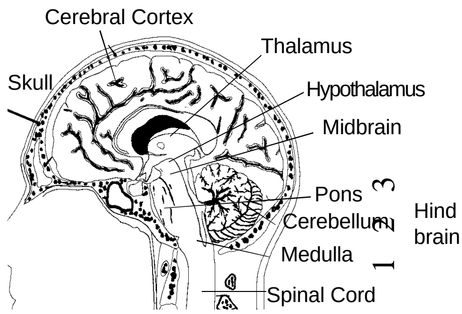
	5-6 weeks	14 weeks	22 weeks	30 weeks	39 weeks
Fetal length (mm)	18	75-90	170-200	280-320	420-460
Cortex thickness(µm)	0	250-400	800-900	1300-1500	1800-2100
Cortical layers	0	VI, CP*	VI,V,IV,IIIC,CP	VI,V,IV,IIIC,IIIB,CP	VI,V,IV,IIIC,IIIB,IIIA,IIB,CP



*CP: cortical plate

Sources: Wellcome Trust 'bodyparts'; England, M.A., "Normal Development of the Central Nervous System" , 1988.

Figure B PARTS OF THE BRAIN



Fetal Movement

The fetus is capable of movement from a very early age. At 7 weeks it can move its head in response to a stimulus around the mouth. At ten weeks, the palms will flex or toes curl if touched. Spontaneus jerks of limbs and squirming movements become routine and towards the end of the fourth month, these are detectable by the woman. These movements are automatic and serve to sort the developing neurons into efficient organisational pathways; without them, limbs would not develop. At 17-18 weeks, they start to subside, as the developing brain regions start to inhibit the primitive activity of the existing central nervous system. Ultimately movements are brought under brain control and from six months onwards, the level of fetal activity increases again. There is evidence that fetuses of gestations 30 weeks or more register certain experiences in the womb and ‘learn’ to recognise reassuring sounds such as maternal heartbeat, or simple repetitive (e.g. 'soap' theme) tunes or words.

The trauma of birth has been looked at by many researchers. Normal birth is associated with fetal stress hormones such as adrenaline, which are thought to protect he fetus from the hazards of birth (pressure on the head and shortage of oxygen) and to stimulate the necessary post-birth processes (increasing metabolic rate, clearance of liquid from the lungs and breathing).

Box 2 ADVICE TO THE DEPARTMENT OF HEALTH

The 1995 review by Professor Fitzgerald looked at the question of fetal pain from three different approaches.

First it considered the **behavioural response** of the fetus to a 'noxious stimulus' (NS). In newborns, reactions such as withdrawal of the affected body region, crying and facial expression (e.g. to a heel prick) are held to indicate pain, although one cannot be sure that the physical response equates to a sensory one. Experience with premature births (down to 26 weeks) suggests that similar responses are encountered, though with less reactivity at the earlier ages. In the fetus, only movement can be detected. This starts at 7.5 weeks when the first movement of the head can be induced, extending over the next 7 weeks until all the body is sensitive to touch. At the same time the fetus moves spontaneously. Professor Fitzgerald points to the cortex not being an integrated functional unit at this stage, with the conclusion that the movements are reflex (i.e. an involuntary response to a stimulus) rather than conscious.

Second, fetuses also respond to NS by **physiological changes** (e.g. heart rate, 'stress' hormones). In adulthood, such releases are not a reliable indicator of response to NS, so using these as a surrogate for pain or sensitivity is especially problematic in the fetus. Nevertheless, from 23 weeks gestation, such hormones are released in response to NS which later in life would clearly be painful. These responses could be because the fetus feels pain but do not demonstrate it. The response is blunted by analgesics, but it is not known whether this is due to true pain suppression or more general sedation.

Third, one can consider the **state of development of the fetal nervous system** to infer whether it is capable of experiencing pain - i.e. at what stage the various component parts may function collectively. The key components are the sensory neurons in peripheral tissues, the connections to the spinal cord, brainstem, thalamus and cortex. Here analogies with adults are not straightforward - for instance, nerves triggered by tactile sensations in the fetus use spinal cord pathways which in the adult are reserved for pain signals; spinal cord neurons in the fetus which carry NS-triggered signals serve larger more diffuse areas than in the adult. The way in which fetal nerve cells work (in terms of neurotransmitter and receptor function) is also quite different. Also 'feedback' mechanisms to dampen response do not develop fully until after birth. Drawing conclusions is thus difficult but one key development may be the penetration of the cortex by the thalamic fibres; without these, messages reaching the thalamus would not proceed to the cortex and be sensed. At the time of the 1995 review this event was placed at 26-34 weeks (post-conception), but more recent information suggests the process may start from 22 weeks.

The review concluded that while the fetal nervous system mounts protective responses to NS from an early age, they cannot be interpreted as feeling or perceiving pain until connections exist to the cortex. The review emphasised however, that even reflex responses to NS may affect future course of sensory development and thus "*the effects of trauma of any kind to the developing nervous system should be minimised..*".

In 1996, the CARE trust established a 'Commission of Inquiry into Fetal Sentience' (CIFS) which called expert witnesses and concluded that "*the fetus may be able to experience suffering from around 11 weeks of development*". The All-Party Parliamentary Pro-Life Group (APPLG) also brought out a paper ("*Human Sentience before Birth*"), which concluded that the anatomical structures in the fetal nervous system necessary for the appreciation of pain are "*present and functional before the tenth week of intrauterine life*".

MAIN AREAS OF CONTENTION

There is some consensus over the main stages and processes in the actual physical development of the nervous system. There is also no dispute that reflexes can be observed from an early age, and that it is also possible to induce (e.g. by needling) hormonal responses to NS at 23 weeks (or detectable shifts in blood flow in the brain during invasive procedures from 18 weeks). The main areas of contention centre on:

- whether reflex actions (or changes in the levels of particular hormones) indicate sensation;
- whether sensations can be brought about by parts of the developing brain before the higher order regions (especially the cortex) have been connected and start to work together;
- whether a minimum level of consciousness is necessary for pain to be experienced.

The existence of **reflex actions** demonstrates that nerve connections to the part of the spinal cord involved, and return motor nerve circuits are functional. The parts of the nervous system responsible for the reflex action (spinal cord to brain stem) differentiate earlier than the higher brain structures and functions in the forebrain, and many medical scientists thus see reflex activity as shedding no light on the question of pain. Reflex and pain circuits are simply separate; one can have a reflex without pain (e.g. knee-jerk), pain without reflex (e.g. headache). APPLG and CIFS authors, however, see reflex action as a measure of neural development overall, and question whether it can be assumed that sensory nerves have not already formed which ascend to parts of the brain able to experience pain.

Stress hormones are released in infants in response to NS which are painful (as well as in other circumstances). They also help (e.g. at birth) the baby to survive. APPLG / CIFS argue that since painful stimuli in infants / adults can release these hormones, their release in a fetus is evidence of pain. The contrary view is that such responses are as automatic as the reflex response and do not need to be associated with pain. However, particularly in view of the greater maturity of the nervous system by the time they can be induced, some paediatricians accept that such hormones could indicate the **possibility** of pain, and advise caution on procedures likely to trigger their release (e.g. after a gestation period of 23 weeks).

Turning to the **development of the nervous system**, the key difference between opposing participants in the debate is whether **existence** of a part of the nervous

Figure 1 ANAESTHETISTS' PRACTICE IN 1988 AND 1995

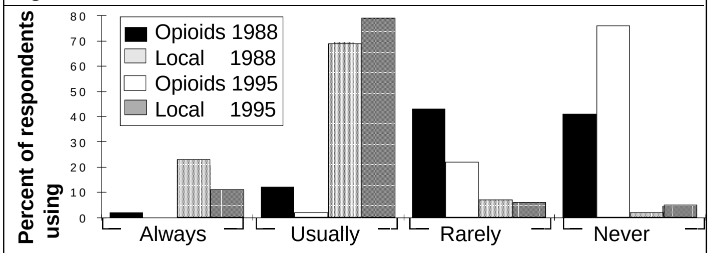
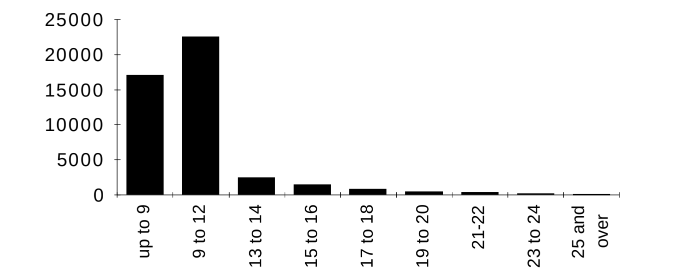


Figure 2 FETAL AGE IN ABORTIONS (Jan to March 1996)



system (particularly at a very immature stage) is evidence of **function**. First, there is the question of how far the cortex can function ahead of its differentiation into the many different layers. Secondly, many experts see the system having to operate as a functional whole, where the different parts of the brain interact integratively to produce sensations and functions. In this context, Prof. Fitzgerald's analysis argues that the lack of established connections from thalamus to cortex until after 22-26 weeks is a strong argument against any ability to feel pain (Box 2) - before that point, signals coming from peripheral nerves cannot reach the cortex and any response (e.g. to touch) will be a result of automatic reactions mediated by the spinal cord and brain stem[1]. CIFS and APPLG, however, argue that sub-cortical units may be sufficient (ahead of their integration into the fully functioning brain) to allow a fetus to be aware of NS via an unpleasant sensation. In support of this hypothesis, they point to evidence of reactions to stimuli in individuals whose cortex has failed to develop (anencephaly) or been damaged; and to 'thalamic syndrome' - a burning pain which can follow damage to the thalamus (e.g. from a burst blood vessel).

The thalamus is the 'switchboard' through which sensory messages flow to the cortex where they are interpreted (as pain, tickling etc.). Whether at an early stage the thalamus (as yet unconnected to the cortex) is capable of creating an unpleasant sensation on its own is impossible to prove or disprove. However, much medical opinion holds that the dissection of the brain into discrete areas with discrete functions is too simplistic and that the different areas need to interact to produce sensations. In this case, the last area of interconnection will be limiting for the sensation as a whole. Suggestions that anencephalic patients feel pain may be more a reflection of a response in the medulla or of the brain's plasticity (ability to adapt and relocate functions following damage) than a general insight into normal functioning. Equally, the fact that pain can follow damage to the thalamus does not mean it is sensed there - the interruption in message flow (or the generation of spurious messages) will affect the cortex.

1. The routine activity of nerve and other cells(e.g. their birth and growth) involves ion changes and electrical activity can first be detected in the fetus at 6 weeks, and in the developing brain region around 10 weeks. By monitoring activity in the developing cortex, research suggests that sensory messages can be first detected reaching the cortex from the lower regions of the brain at 29 weeks.

EVOLVING CLINICAL PRACTICE

Perceptions of how newborn and young infants experience pain have evolved in the last decade. It used to be thought that the ability to feel pain was very limited, and many surgical procedures were undertaken without analgesics. However animal studies suggest that acute stress to fetuses and neonates can have permanent behavioural consequences (in humans for example, neonatal circumcision increases pain responses 6 months later). This, and evidence that neonates can experience pain, has led to changes in practice - recently quantified in a survey among members of the UK Association of Paediatric Anaesthetists. This found that there was almost universal agreement in 1995 that new-borns perceived pain, whereas in 1988, only 64% held this view. The figures also revealed a shift towards routine use of analgesia in major surgery (**Figure 1**).

As already mentioned (Box 2), premature babies respond to 'painful' stimuli such as heel pricks, although the level of response is less in the younger ones. The question of what analgesia to use in surgical intervention thus clearly applies. At present, fetal analgesia *in utero* can present problems and practice varies - in general, it is considered undesirable to use anaesthesia on the fetus unless absolutely necessary for fear of upsetting fetal development - for instance, caesarean deliveries generally attempt to use the minimum anaesthetic consistent with avoidance of pain to the mother.

The Royal College of Obstetricians and Gynaecologists (RCOG) has set up a Working Party to conduct an independent review of fetal awareness. The Committee is expected to report to the Council of the RCOG in April 1997. As well as reviewing scientific evidence since the 1995 DH review and addressing areas of differing interpretation discussed in this note, the working party will consider the implications for abortion practice - a matter raised recently in Parliament. In this context, the gestation period in terminations from Jan.-Mar. 1996 is shown in **Figure 2**; 27 out of 45,385 were later than 24 weeks, and the majority (87%) were in the first trimester. Current guidance by the RCOG is that specific methods to ensure fetal death *in utero* should be taken whenever there is a possibility of the fetus being able to breathe after delivery. Such procedures should be routine at gestations over 21 weeks.